Clinic for Pediatric and Adolescent Medicine, General Pediatrics
Univ.-Prof. Dr. med. Heymut Omran – *Director*

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Patient information for participation in the NEOCYST registry

Registry leadership: Univ.-Prof. Dr. med. Martin Konrad

Patient information for participation in the NEOCYST registry

Dear participant,

Your attending doctor has diagnosed you with a cystic kidney disease and informed you about our registry.
We would like to ask you to participate in a scientific study about cystic kidney diseases. The participation is voluntary. If you are deciding against participation, or if you wish to withdraw from the registry at any point in time, there will be no disadvantages.
This information is providing you with an outline of the registry, benefits and potential risks of participating. Please read the following information carefully and clarify any potential questions with your attending physician.

What is known about cystic kidney diseases?

Hereditary cystic kidney diseases are congenital diseases which mainly affect the kidneys but other organs as well. Cystic kidney diseases are rare. Currently about 300-400 children and adolescents are diagnosed in Germany. However cystic kidney diseases are among the main causes for chronic renal failure in childhood. Most common forms are the autosomal recessive polycystic kidney disease (ARPKD), nephronophthisis (NPH), Bardet-Biedl-syndrome (BBS) and HNF1ß nephropathy. Onset and pattern of disease vary strongly in affected patients. In some patients disease manifestation occurs in early childhood, sometimes even before birth. In others first symptoms only appear during late adolescence. Major variability of the individual disease courses – sometimes even within a family - complicates an individual prognosis.

Cystic kidney diseases are caused by alterations (mutations) of so-called „cystic genes“. Currently more than 70 cystic genes are known. The number of known genes has increased

rapidly over the past years due to comprehensive research. Most cystic kidney diseases in childhood are inherited recessively, which means that patients carry two affected copies of the gene while their – usually unaffected – parents carry one healthy and one affected copy of the gene.

Over the past 10-15 years scientists all over the world have made considerable progress in understanding the mechanisms causing cystic kidney diseases. However there still does not exist an effective treatment plan for affected children. In order to predict a patient's disease progression, depending on the individual gene mutation, long-term clinical studies are required.

The purpose of NEOCYST is to increase the knowledge on the epidemiology. We aim to improve the clinical management and thereby the life quality of patients suffering from early onset cystic kidney disease and their families. Sheer diagnosing you or other individuals or exploring individual predispositions is not aim of this study.

What is NEOCYST? Why are we conducting the NEOCYST study?

NEOCYST (Network for Early Onset CYSTic Kidney Diseases) is a multicenter, interdisciplinary network of clinicians and scientists exploring cystic kidney diseases in childhood. In addition to various pediatric nephrologists this network includes geneticists, statisticians and fundamental researcher. The backbone of the network is the NEOCYST registry, combining clinical and genetic data of patients suffering ofARPKD, NPH, BBS and HNF1ß nephropathy.

Cystic kidney diseases are characterized by overlapping symptoms which makes a distinct disease classification difficult. Within the NEOCYST registry we are analyzing the data of all cystic kidney diseases in combined comparative fashion. We aim to identify common disease mechanisms and thereby potentially create therapeutic targets. This standardized systematic approach of analyzing clinical data allows ultimately for a better differentiation between different cystic kidney diseases.

Our goal is to identify individual symptoms and disease patterns that will suggest whether the course of the disease is likely to be mild or severe. We aim to find answers to the following questions:

1) Do different forms of cystic kidney diseases have common causes?
2) Which gene alterations lead to which clinical symptoms?
3) Are there further genes that can affect the course of disease in a positive or negative way (modifier genes)?
4) Can we identify marker proteins in blood or urine samples that allow a prediction of an expected loss of renal function?
5) Will patients benefit from an early treatment?
6) What kind of therapeutic approaches are being pursued so far and which ones are showing a positive effect?

Due to the rarity of cystic kidney diseases each medical center only cares for a small number of patients. In order for us to increase the knowledge on the epidemiology we are required to work closely within a multicenter network. The patient data will be collected and stored anonymized, thus the identification of the individual person is not possible. The study data enables the translation of scientific findings into clinical practice. This research will form the basis for future therapeutic trials.
Because of the imperative need for new therapeutic guidelines the Federal Ministry of Education and Research (BMBF) has decided to fund the NEOCYST network.

Who can participate in NEOCYST? How do I register?

The patient´s data can only be entered into the registry by the attending doctor. Patients do not have to enter any data themselves.
All patients (any age and sex) diagnosed with one of the following cystic kidney diseases are allowed to participate: autosomal recessive polycystic kidney disease (ARPKD), nephronophthisis (NPH), Bardet-Biedl-syndrome (BBS), HNF1ß nephropathy. If further family members are affected we kindly ask you to provide them with information about our study as well. A written declaration of consent by patients or by parents for minors is mandatory before any data can be entered into the registry. Participants can withdraw from the study at any point in time without consequences.

Who cannot participate in NEOCYST?

Patients who have been clinically, genetically or histologically diagnosed with any other form of kidney disease are not allowed to participate in NEOCYST.

What kind of data will be collected? What tests will be done?

We will register and save disease symptoms, patterns, ultrasound test results, lab test results, biopsy test results, genetic test results and information about family history. The data will be anonymized and entered into an online registry.

In case you are already participating in any other pediatric nephrology study (for example the 4C-study: Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study), we kindly ask for your consent to transfer some of the already existing data into our registry. Some of the relevant data are lab test results, age, height and past medical history. All data will be anonymized. Any data collection will be done by medical professionals.

Will I remain anonymous in NEOCYST?

All data will be anonymized. Nobody will be able to draw conclusions about personal patient information from the data stored in the online registry. We are exchanging patient names for ID-Codes. Those codes are a combination of a personalized number and the attending medical centers number (for example Harry Potter, Köln → 01-13). Only the attending physician knows the patient´s personal ID-Code and he will be keeping the identification codes on a separate sheet. Not even the registry management will have access to this information. In some cases special study nurses will be entering patient data into the registry. Please be assured that medical confidentiality is applied to all cases involving your personal data.

Are additional tests required for participation in the study?

No! Please be assured that no additional or unnecessary testing will be required in case you decide to participate in the NEOCYST study.

However, we will be asking for your consent to collect your biological samples. Included in our study are blood, urine and nasal swab samples which we will be using for future research projects.

Important: The consent to provide biological samples is optional and does not interfere with the participation in the NEOCYST registry. A separate written declaration of consent is required for each biological sample.

Information about the handling of biological samples

Examination and analysis of human biological samples is vital for medical research. This is why we kindly ask our patients to give consent for collection of biological samples for future research purposes. The consent to provide biological samples is optional and does not interfere with the participation in the NEOCYST study.

What kind of biological samples will be requested? How will they be obtained?

For our research purposes we require:

- Blood (10-20 ml)
- Urine (100 ml)
- Nasal swabs (1x each of both nostrils)

1) **Blood:** As part of a scheduled routine blood test we would take supplementary vials (10-20 ml) of blood for research purposes. In small children the amount of extra blood is reduced to the minimum. We will not schedule blood tests purely for research purposes.

2) **Urine:** When the patient provides urine at a routine visit we would like to collect 100 ml of this sample. This urine sample will be used to identify marker proteins via the so-called

Urinomics-technology. Additionally we are extracting epithelial cells from the urine which are substantial for future research projects.

3) **Nasal swabs:** We are using a little brush to swab the inside of both nostrils to collect mucosal cells. The procedure is not invasive. Patients may feel discomfort for a short amount of time and may get watery eyes. Very rarely it may cause nasal bleeding. The nasal swabs are providing us with valuable cells. These cells are much easier to cultivate than urine cells and are extremely important for our research.

What happens to the samples?

1) **Blood:** With your consent, we are analyzing your blood samples with the aim to identify new cyst-genes and special gene variants that modify the disease progression (so-called modifier). In detail the genetic material (DNA) will be analyzed with state of the art high-resolution techniques to identify known mutations causing cystic kidney diseases as well as mutations that have not been described so far.
The genetic analysis will be performed in cooperation with our NEOCYST partner:

Medical Genetics Mainz
Prof. Bergmann and Colleagues
Im Breitenspiel 115
69126 Heidelberg, Germany

2) **Urine:** We are obtaining urine samples for two purposes:

a) We are using the Urinomics-technology to detect marker proteins and to analyze protein patterns. The aim is to identify disease specific protein patterns. We would be able to offer a fast, patient friendly and non-invasive method that would allow us to inform patients about their individual disease courses.

b) We will isolate epithelial kidney cells and urinary tract system cells from the patient´s urine sample and cultivate those in the laboratory. These cell culture models will be of great importance for various research projects. In particular we will be analyzing kidney specific intracellular signaling pathways as well as mechanisms of renal cystformations.

3) **Nasal swabs:** We are collecting mucosal cells from the inside of the patient's nose and cultivate those in the laboratory. The obtained samples can be analyzed with high-resolution microscopes. Of special interest are cell components called "cilia" which can be found in large numbers on mucosal cells. Most cystic kidney diseases show abnormal cilia structure and function. We aim to develop a patient friendly, non-invasive method to diagnose cystic kidney diseases as replacement for more aggressive methods like biopsies.

4) **Tissue samples:** In case your attending doctor requires a biopsy from you or you require a transplantation of organs we would kindly ask for your consent to take a small part of

those tissues and use those for further molecular, genetic and immunological testing. The medically required procedure will not be amended, prolonged or extended if you give your consent to provide tissue samples for research purposes.

The patient will be informed by the study coordinator in case any medical findings will arise from analyzing the bio samples. If you do not wish to be informed of any results affecting the patient´s health you are free to express your concern on the declaration for consent.

All samples will be anonymized and stored in a Biobank at the Hannover Medical School. With your given consent to provide biological samples to the Biobank they automatically become property of the Biobank and you agree that the Biobank analyzes the obtained data. The Biobank stores the biological samples under donor protection rights. Samples can be requested for use in approved research projects. Your participation in the study will support future research projects and the development of new therapies. Under no circumstances will any samples or data be sold, the Biobank will only charge fees to cover any handling and delivery fees. The Biobank at the Hannover Medical School is a cooperating partner from the NEOCYST network and is under the leadership of:

Prof. Dr. Thomas Illig
Pediatric Research Center
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany

Safety and right of access to biological samples:

The patient´s biological samples are being used for cystic kidney disease research only. Genetic testing results are being stored anonymized. Only the patient´s attending doctor will be able to match the results to the patient. Access to the anonymized samples and medical data will be granted for research purposes only. Any study centers requesting access are required to do so in writing to the research network committee. Requests are being reviewed by an ethics committee first. Upon positive evaluation the research network committee will decide if the request will be granted.
It is possible that the samples stored in Hannover are being sent to research centers worldwide after access has been granted. It is the patient´s right to restrict the use of his samples. The patient has the right to request for his samples to be destroyed at any point in time. Evaluated data will remain part of the study unless the patient requests otherwise.
Cystic kidney diseases are very rare and the patient´s samples are of high value. This is why patient´s samples are being stored indefinitely unless otherwise requested.

What risks are associated with the participation in NEOCYST?

NEOCYST is a registry-based study. Already existing data will be collected and stored. There will be no change in therapy or additional testing because of participation in NEOCYST. When the attending doctor is taking a routine blood sample he is able to take a little bit more for the NEOCYST study. There will be no physical, medical or financial disadvantages when participating in the NEOCYST study.

Please be aware that there are risks associated with the collection, storage and transmission of patient´s data. Any risk in terms of breach of data confidentiality is being kept at an absolute minimum through the process of anonymizing patient´s information and samples. State of the art technical security is being put in place at any time however the risk of data leakage cannot be eliminated entirely. The risk of data leakage will be increased significantly if the patient decides to publish any medical data on the internet (for example for ancestry research).
The NEOCYST committee wants to reassure all participants that all data will be handled with the highest of care to ensure data confidentiality at all times. Any external research centers requesting patient data and samples are required to have the highest possible data privacy and protection laws in place.

What benefits are associated with the participation in NEOCYST? Will the participant be reimbursed?

The participation in NEOCYST will most likely not lead to any personal gain. Samples and data are being analyzed for research purposes only. Participants and attending doctor won´t be financially reimbursement for their participation in NEOCYST. Patients that have not yet been genetically analyzed will be genetically tested as part of the study at no charge. The participation will provide valuable new insights to cystic kidney disease and results from this study may lead to the development of new treatment options and thus to better patient care in the future.

Information on data protection

As legal foundation for processing personal data serves the consent for processing personal data from the data subject, Art.6 (1) letter a) of the EU General Data Protection Regulation *EU-DSGVO (EU-Datenschutzgrundverordnung)*.

Data storage:

Personal and medical data will be collected, analyzed and stored in a web-based databank on a server. Patient samples and data will be anonymized. The patients name will be replaced with a patient-ID which is composed of a personal ID and the participating center (for example Harry Potter in Köln → 01-13). The patient´s address and the exact date of birth aren´t listed. Only the birth months and year will be listed to determine the patients age. The anonymized data are being stored indefinitely unless otherwise requested.

The attending doctor will enter the patient data into the database via a password protected area of an SSL- website (SSL: Secure Sockets Layer, an encrypting protocol for secure online data transmission). The data will be stored on a separate server to the data entry server. All data is being stored on two different servers at the Medical Informatics Group, University of Frankfurt (. The highest possible data security guidelines in Germany are being followed. There are back up copies of all stored data in case of technical difficulties. Special IT employers will be able to restore lost data, however they won´t be able to access or change the data. Participants have the right to be informed about their stored data and the right for correction of falsely stored data.

Responsible for processing of personal data is:

Klinik für Kinder- und Jugendmedizin – Allgemeine Pädiatrie-
Pädiatrische Nephrologie
Prof. Dr. med. Martin Konrad
Waldeyer Straße 22
48149 Münster
E-Mail: Martin.Konrad@ukmuenster.de

Data protection official:
Universitätsklinikum Münster
Datenschutzbeauftragter UKM
Albert-Schweizer-Campus 1
48149 Münster
Phone: 0049 (0) 251- 83-49694
E-Mail: datenschutz@ukmuenster.de

Data subject Art. 13II b der Datenschutzgrundverordnung provides participants with the right to:

- Disclosure (Art 15 DSGVO und §34 BDSG)
- Objection (Art 21 DSGVO und §36 BDSG)
- Data transfer (Art 20 DSGVO)
- Deletion (Art 17 DSGVO und §35 BDSG)
- Restriction of processing (Art 18 DSGVO)
- Correction (Art 16 DSGVO)

Please make usage of forms provided on the internet in case of enforcement of any rights:

www.betroffenenrechte.ukmuenster.de

Alternatively please collect a paper form from:

Geschäftsbereich Recht und Drittmittel
Albert-Schweizer-Campus 1
Gebäude D 5

Participants have the right to make complaints to the surveillance authority:

Landesbeauftragte für Datenschutz und Informationsfreiheit
Nordrhein-Westfalen
Postfach 20 04 44
40102 Düsseldorf
Phone: 0211/38424-0

All bio samples will be processed and stored anonymized. Data is being coded twice which reflects the highest possible data safety protocol. Samples and data will only be forwarded in its encrypted state.

Publications:

Results from this study may be published in scientific magazines and presented on scientific conferences. Under no circumstances will any publication contain personal patient information. Study results may lead to a commercial benefit (for example a patent). Please be aware that participants won´t profit from any financial gain.

What happens if I decide to withdraw my consent?

The participation in NEOCYST is voluntary. The participant and the guardians are free to withdraw from the NEOCYST study at any point in time without consequences. You are able to withdraw your consent for the entire study or for parts of the study. If you decide to withdraw from the study please contact your attending doctor. If specified all data will be deleted and no conclusion can be drawn to the patient's identity. Samples can either be destroyed or handed over to the patient. Data and samples already collected can remain part of the study with your consent.

Changes in eligibility requirements:

In case of fundamental changes to the NEOCYST study and the scientific targets you will be given information from your attending doctor. The ethics committee provided advice to the initiators for the establishment of the NEOCYST network. NEOCYST received positive appraisal by the ethics committee as required by law.

Who is your contact person?

Primary contact person for participants is the attending doctor.

Attending doctor:

Name: _____

Institution: _____

Phone: _____

Further questions?

Please do not hesitate to contact us for further questions.

Coordinating office of NEOCYST:
Dr. Jens König
Waldeyerstr. 22
48149 Münster
Phon: 0251-83 56213