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GeNepher data- and biobank for patients with (suspected) genetic kidney disease: Rationale, design and status update

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ABSTRACT

Background: Clinical research on monogenic kidney disease (MKD) is thriving and the need for large cohorts, prospective data collection and biobanking is increasing. We aim to create a sustainable large MKD biobank with a vast amount of uniformly collected high-quality data that is readily available for future research, with an infrastructure that allows for recontacting participants.

Methods: The GeNepher data- and biobank is an ongoing data- and sample collection that includes patients and family members with known and/or suspected MKD. With a tiered approach participants can give broad consent for including their 1) available medical data (including genetic testing results), 2) inclusion of massively parallel sequencing data for add-on analysis, and 3) additional biobank sampling (e.g. urine for tubuloids, skin biopsy for fibroblasts). Recontacting is possible for additional data collection, novel research opportunities and return of relevant findings.

Discussion: The GeNepher data- and biobank collects prospective and retrospective data from kidney disease patients and their relatives. The broad consent allows for research that extends beyond one specific research question. Herewith, this biobank aims to 1) increase the scientific knowledge based on disease mechanisms including (novel) monogenic causes, 2) study modifiers, 3) improve care, including reproduction related research questions. Furthermore, it facilitates recontacting for opportunities in treatment development or when diagnose specific trials are started or specific treatment is approved.

Conclusion: The GeNepher biobank is designed to support a wide range of research projects by providing access to a diverse population of patients with (suspected) MKD and has the potential to make a significant contribution to the field of rare kidney disease research.

1. Introduction

Chronic kidney disease (CKD) affects 10–15 % of the population worldwide and can have a big impact on quality of life [1,2]. Understanding the etiology of CKD is important for personalized treatment and prevention. A substantial proportion of patients with CKD has an (undiscovered) monogenic cause [3,4]. Monogenic kidney diseases (MKD) form a heterogeneous group of disorders, which are individually

Abbreviations: ACMG, American College of Medical Genetics and Genomics; BRP, Personal Records Database; CBS, Central Agency of Statistics; CKD, Chronic kidney disease; EDC, Electronic Data Capture; EHRs, electronic health records; ERKNet, European Reference Network for Rare Kidney Diseases; MKD, monogenic kidney disease; NVN, Dutch Kidney Patients Association; TCBio, Biobank Research Ethics Committee; UMCU, University Medical Center Utrecht; VUS, variant of unknown significance.

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often rare, but as a group frequent and important diagnoses to establish [4-6]. The timely identification of a potential genetic etiology in CKD patients has profound implications 1) for diagnosis and subsequent care, including personalized treatment and (extra-renal) follow-up, 2) for family members (e.g. in presymptomatic testing and family donation) and 3) for lifecycle medical care, for instance around reproductive options (e.g. preimplantation genetic diagnosis) and pregnancy care [4,7]. Having a genetic diagnosis can also end or prevent a "diagnostic odyssey" that is often invasive, time consuming and distressing. Additionally, genetic stratification in clinical trials can prevent exposure to unnecessary risks and reduce confounders.

Biobanks, which collect detailed medical data and human biological material from large groups of patients, aim to enhance knowledge and improve patient care [8,9,10]. To improve care for patients with known or suspected MKD, making optimal use of genetic data generated in diagnostics, we have established the GeNepher data- and biobank. Being a biobank with broad consent, GeNepher is primarily a repository of data and samples that can be used for (yet-to-be-specified) research projects in the realm of MKD. In this paper we highlight the general objectives, showcase the biobank set-up and discuss current and future opportunities and challenges.

1.1. Objective 1: gene finding

Currently, only one-third of the coding genes in our DNA have a known function, with 500–600 of these genes known to be involved in kidney function and disease (https://panelapp.genomicsengland.co.uk; https://www.umcutrecht.nl/genpanel) [11]. Since not all genes involved in MKD are known, genetic testing in kidney disease patients may yield a false negative result. GeNepher's objective is to facilitate further exploration of known and new genetic causes of renal disease by collecting data and biological material from patients and family members with (suspected) MKD. First, the dataset of consented exomes can be used to identify candidate genes, either in individually highly suspect cases or through internal and external matches with patients with variants in the same candidate genes [12]. Secondly, the dataset can be used for advanced prioritization methods like for instance with KidneyNetwork [13]. Third, the human biological materials available can be used for functional evaluation of genes potentially underlying MKD.

1.2. Objective 2: identification and validation of modifiers of (genetic) kidney disease

While huge progress has been made in the past years in the methods to diagnose MKD, there is still a large gap in knowledge in predicting disease course [14,15]. For many kidney diseases, there is inter- and/or intrafamilial variability in penetrance and expression [16-18]. Modifying factors can be genetic, in the same gene (i.e. genotype-phenotype correlations) or elsewhere in the genome (coding or non-coding), or non-genetic (i.e. environmental/life style factors). GeNepher aims to facilitate investigation of genetic data from large numbers of patients to identify genetic modifiers and study them across diseases.

1.3. Objective 3: improving care for patients with (suspected) MKD

The data collected by the GeNepher biobank can also be used to improve care for patients with (suspected) MKD. Given the rarity of individual diseases, the data collection can be used to inform doctors and patients about patient-related objectives such as disease specific prognosis, genotype-phenotype correlations and pregnancy outcomes [19-22]. This same data can be used to evaluate standard patient care practices [23,24]. As an expert center for genetic and congenital kidney disease and urinary tract anomalies we are affiliated with ERKNet, the European Reference Network for rare kidney disease. Therefore, patients with an established diagnosis are also asked to participate in ERKReg, ERKNet's own registry. ERKReg's main objectives are to generate epidemiological information, identify current patient cohorts for clinical research, explore diagnostic and therapeutic management practices, and monitor treatment performance and patient outcomes [23]. ERKReg and GeNepher overlap in the medical data collection. The GeNepher biobank complements ERKReg in collecting biological materials and broad genetic data, and includes suspect cases with unknown etiology.

1.4. Objective 4: treatment research

In this era with emerging compound identification which target specific disease etiology [25-27], a dataset with patients with rare kidney disease diagnoses, from whom biological materials can be requested (for instance for ex vivo research) is of great value for translational research. Biological materials can also be used for high throughput drug testing and for individualization of drugs: in vitro testing specific (approved) drugs to see which drug works for an individual patient / variant. Furthermore, the GeNepher biobank will be a source for contacting patients (and/or family members) who might be eligible for targeted clinical trials, including N of 1 trials, of specific treatments.

1.5. Overall objective: the importance of "findability"

The broad consent enables future research questions not yet captured by the abovementioned objectives. For innovative translational research and care for patients with rare kidney disease it is of utmost importance that these patients can be found, their data can be studied and they can be recontacted. Unsurprisingly, the rare disease field is investing in creating (international) registries [23,28-30]. Biobank GeNepher is a valuable addition to these registries, as it is a prospective biobank often with DNA and sequencing data available.

The GeNepher biobank is a valuable resource for improving care and advancing knowledge in the field of MKD through gene finding, identification and validation of modifiers, and improving care for patients with suspected MKD, as well as treatment development. In the following, we describe the GeNepher biobank in detail.

2. Methods

2.1. Biobank design and protocol

Biobank GeNepher, designed and implemented under the protocol approved by the Biobank Research Ethics Committee (TCBio) of the University Medical Center Utrecht (UMCU) in July 2021 (TCBio 20–305), is a comprehensive collection of data and biological material from patients with suspected or confirmed MKD and their family members. The GeNepher biobank is a sub-biobank of the Central Biobank of the UMCU (bbmri-eric:ID:NL_CBB:collection:32). Data and biological material are collected at the UMCU, but patients from all medical centers within the Netherlands and potentially from other countries are eligible for inclusion, provided that such inclusion is in compliance with the applicable laws and regulations of the respective country. Patients can also be eligible for inclusion when they have consented to recontacting in a previously conducted study. The Dutch Kidney Patients Association has been consulted to incorporate the patient perspective in the design and implementation of the biobank.

2.2. Study population

The study population for this research includes patients who meet at least one of the following criteria (as depicted in Fig. 1):

1. Patients diagnosed with MKD, as established by genetic testing results and/or clinical phenotype.
2. Patients who present with suspected MKD.

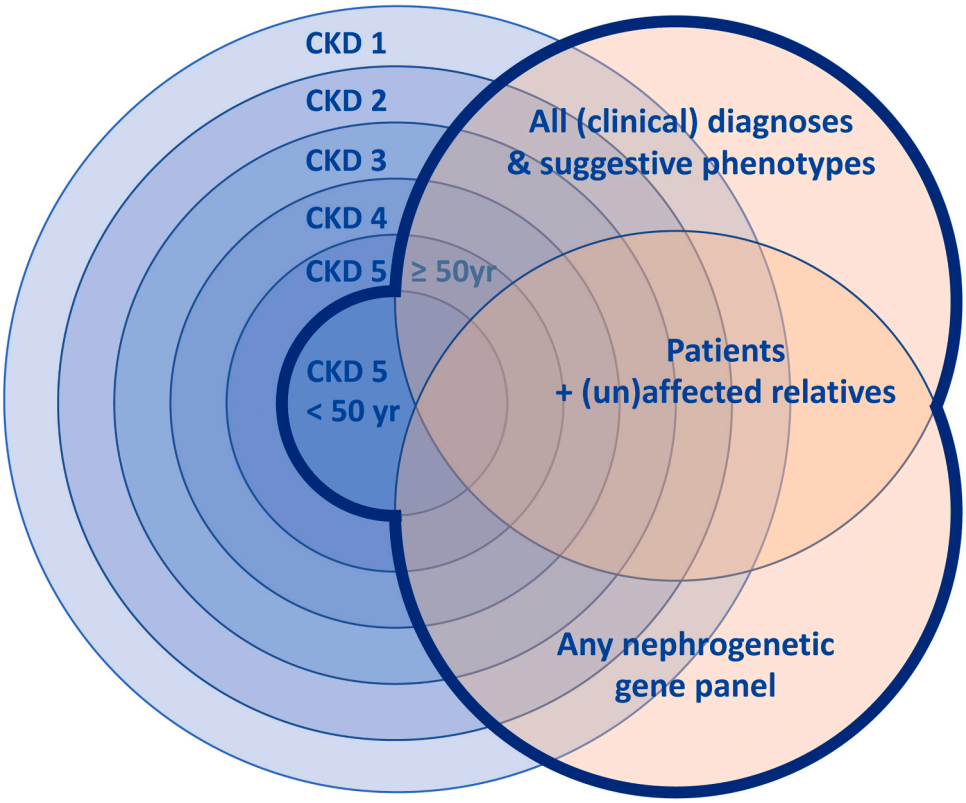

Fig. 1. Patients and family members eligible for inclusion in GeNepher Data- and Biobank. | CKD = chronic kidney disease.

3. Patients who have undergone a nephrogenetic gene panel.
4. Patients with CKD stage 5, diagnosed prior to the age of 50 years.
5. Family members of patients who meet any of the aforementioned criteria 1–4. Any family member can be contacted.
6. Prenatal cases (i.e. fetal DNA and or specimens) may also be included if they meet any of the criteria 1–4 for patients.

2.3. Tiered broad consent

The informed consent process for this data- and biobank is based on a tiered broad consent model, which allows for use of collected data and samples in unspecified (future) research studies pertaining to genetic kidney disease. Eligible participants are provided with information about the objectives of the biobank and the potential use of their data. Inclusion in the study is contingent upon consent for being informed about clinically relevant findings (including unsolicited findings, for which a review committee is in place). A tiered approach is utilized, as depicted in Fig. 2, where all participants are asked for inclusion of their medical data. Additional consent options include the inclusion of already available DNA / massively parallel sequencing data (MPS) for supplementary analyses and/or the collection of biological materials (such as blood, saliva, buccal swab, skin biopsy and/or residual materials from diagnostic procedures or treatment). The collection of additional material is only pursued when it could contribute to a specific

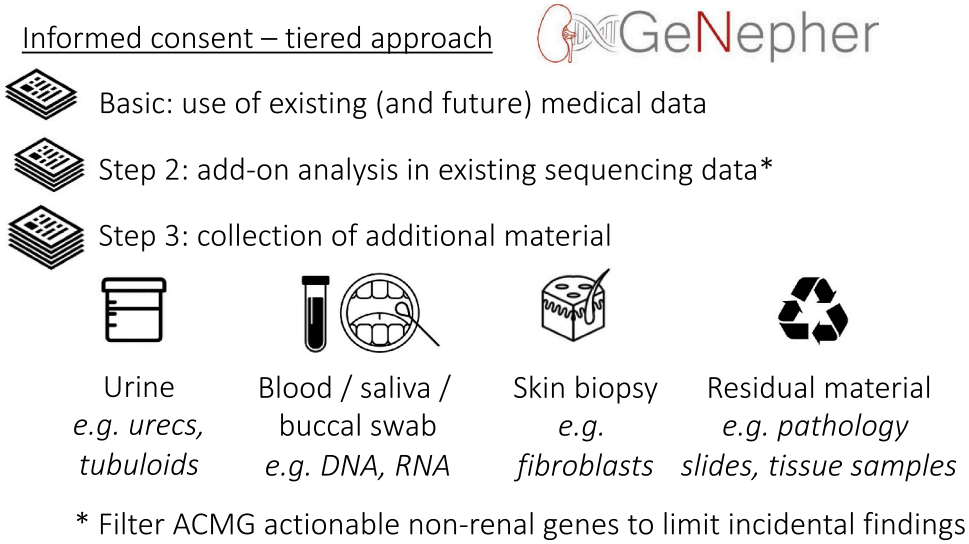

Fig. 2. Informed consent with tiered approach.

research project, to ensure that participants are not unnecessarily burdened. Any participant (e.g. adults, children, both unaffected and affected individuals) that opted in for possible additional sample collection, may be contacted. After receiving information about the specific collection, they can decide whether to consent to it. Whenever feasible, we prioritize using residual materials from (future) diagnostics/treatment or opt for the least invasive collection method, especially when dealing with children.

2.3.1. Basic consent

All participants who provide consent will:

- Allow for the storage and use of their current and future medical data for the objectives of the biobank.
- Grant permission for medical information to be requested from their general practitioner and hospitals where they have been treated.
- Allow for this consent to remain valid until they indicate otherwise.
- Agree to filling out a 30-min questionnaire.
- Be informed about findings that are of direct relevance to their health or the health of their family members.
- Allow for encrypted data to be linked to family members who are also included in the biobank.

Participants can opt to

- Be contacted about:
  - The collection of additional medical and/or family data if this is needed for a particular research project.
  - The collection of additional biological materials. After they are informed about which material is requested, they can decide whether they agree to this.
  - Relevant research projects that require new consent.
- Give permission to the research team to request:
  - Updated contact details from the "Personal Records Database" (BRP in Dutch)
  - Cause of death from "Central Agency of Statistics" (CBS in Dutch).
- Allow for forwarding encrypted data to countries outside the EU.
- Allow for the use of encrypted data in collaboration with commercial companies.
- Allow for the use of relevant medical data for diagnostic genetic testing of family members.
- Provide contact details for a family member who can be reached regarding relevant findings after the participant's passing. If this is not provided, the general practitioner will be contacted to try to reach the family.

2.3.2. Additional consent

When participants provide additional consent for biological materials, including already available DNA/RNA/MPS, they will also consent to:

- Collection and use of the relevant biological materials for the objectives of the biobank.
- Storage of their biological materials is indefinite, unless indicated otherwise.

In addition, these participants may also choose to opt-in for:

- Use of their DNA/RNA/MPS for add-on analyses like whole exome analysis or whole genome analysis, with the application of a filter based on the ACMG 59 gene list except for genes known to cause renal disease [31].
- Use of their biological materials for cell culturing, including organoids. Organoids, more specifically tubuloids, can be urine-derived or made from residual material [32].
- Allow for forwarding biological materials to countries outside the EU.
- Allow for the use of biological materials in collaboration with commercial companies.
- Allow for the use of biological materials for genetic testing of family members.

Furthermore, when participants are included as children, they will be recontacted at age 16 (the age they reach "medical adulthood" in the Netherlands) to determine if they wish to remain included in the GeNepher biobank. They will need to actively opt-out to discontinue their contribution to the biobank.

2.4. Data collection

2.4.1. Medical data

Following the acquisition of informed consent, a thorough collection of clinical data is performed utilizing both the patients' electronic health records (EHRs) and a standardized questionnaire. The gathered medical information is subsequently entered into a secure electronic case report file using Castor Electronic Data Capture (EDC) software [33]. Basic data entry encompasses the participants' informed consent choices, medical history relevant to their kidney disease, and genetic testing results including interpretations. Within the EDC system, participants are linked to their respective family members through the use of unique study identification numbers. The questionnaire is sent-out to collect additional data on family history, medical history, and pregnancies. The data is directly included in the EDC, unless participants opt for a paper questionnaire.

2.4.2. DNA/RNA/MPS

DNA/RNA is stored at the clinical genome diagnostics department of the UMCU. This allows for verification of research findings in a diagnostic (accredited) setting and for DNA to be available for genetic testing of family members. Sequencing data that is already available from diagnostic testing is shared with the GeNepher research team using a coded study ID.

2.4.3. Collection and storage of additional biological materials

Materials are acquired following the standard diagnostic operating procedures of the UMCU, with the exception of the collection of urine for URECs and tubuloids, for which protocols have been previously published [32,34,35]. The materials are stored within the Central Biobank of the UMCU as described in their annual rapport [37], except for fibroblasts which are stored at the genome diagnostics department, and residual material that is already routinely stored at the pathology department.

2.5. Research projects

Approval from the TCBio via a release review is necessary prior to use of data and biological material from the GeNepher biobank. The TCBio reviews the intended use based on the release criteria of the Biobank Regulations of UMCU (Article 10) and whether this is in line with the signed broad consent. We received approval for use of the collected data and biological material for research projects related to objectives 1–3 as described above (TCBio 22–076). Additional release reviews can be requested for future (yet-to-be-specified) research projects.

3. Study status

Inclusion of participants started in August 2021 and is ongoing. As of March 26th, 2024, 552 probands have received written information about the GeNepher biobank, and 265 of them have provided informed consent. All eligible participants are contacted by phone to inquire about

their interest in participating and to address any questions they may have. To date, 120 probands have indicated that they do not wish to be included in the biobank, and responses are still pending from 167 probands.

3.1. Overview of included participants

An overview of all participants included in the biobank shows that a total of 341 have been enrolled. These include 265 probands and 76 (un) affected family members. Of these 187 are male and 154 are female. The current cohort includes 32 children (< 16 years old) and 309 adults. From 341 participants 314 gave consent for add-on analyses including whole exome/genome analysis. Patient from the UMCU with an established diagnoses for MKD were simultaneously approached for inclusion in ERKReg. Among the patients who provided informed consent for the GeNepher biobank, 135 were also approached for ERKReg, and 92 of them gave consent.

Data has currently been entered in the Castor database from 308 out of 341 included participants, with 263 of these participants having kidney disease. Fig. 3 presents an overview of the phenotype groups and the number of solved and unsolved cases. We have included patients from all phenotype groups and approximately 25 % of our cohort has CKD of unknown origin (Fig. 3A). The genetic testing results of these 263 included participants are displayed in Fig. 3B. About one-third of the participants had a genetic diagnosis explaining their phenotype, with the involved genes listed in Fig. 3B. Approximately 17 % of participants had abnormal test results that only partially explain their phenotype or a variant that requires further investigation (e.g. a variant of unknown significance (VUS) requiring segregation or functional studies). Finally, one-third of the participants had no abnormalities or no genetic test performed (e.g. patient or their family chose not to undergo testing, or another family member was being tested first).

Biomaterials that have been collected to date include skin biopsies, urine samples and kidney tissue (residual material) for tubuloids from over 30 participants (including healthy family members) with a ciliopahty, glomerulopathy, tubulopathy and mitochondrial DNA variant.

3.2. Eligible participants

As an expert center, we see a large number of eligible patients annually. The genome diagnostic department has performed nearly 4000 genetic tests for MKD, comprising both internal and external requests, since 2014. Our center implemented exome-based gene panel sequencing as standard practice early 2018. We currently have whole exome sequencing data stored for over 2000 patients with kidney disease. We will transition to whole genome sequencing for diagnostic

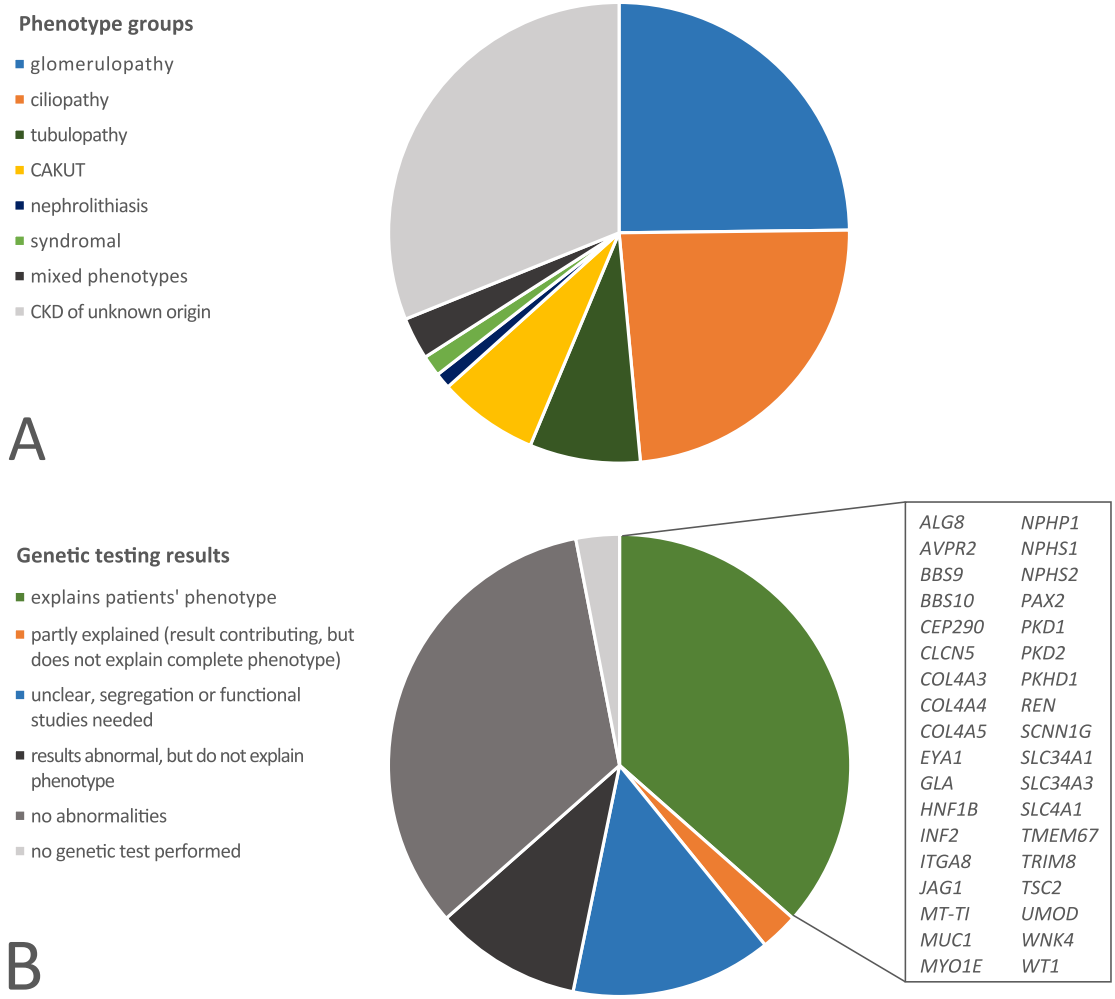

Fig. 3. A. Phenotype groups for included participants (n = 263). Data has currently been collected for 308/341 included participants. 263/308 have a kidney disease themselves. B. Genetic testing results. Genetic testing was performed in 255/263 participants. Whether genetic testing results explain patients' phenotype is shown in the pie chart. Genes explaining patients' phenotypes are displayed on the right.

testing in 2025. The utilization of this genetic data for research purposes is now enabled by the GeNepher biobank, which ensures proper informed consent is obtained from participants.

4. Discussion

In conclusion, we have described the design and current status of the GeNepher biobank, which aims to provide a valuable resource for studying genetic kidney disease. The biobank's approach of obtaining broad, tiered consent and its focus on involving patients in the set-up are strengths that enable collection of high-quality data from a diverse study population. These features make it a valuable resource for initiating research and being a partner for a broad range of research consortia.

However, like all biobanks, we face certain challenges. One of the main challenges is securing continuous funding, which is essential for the long-term sustainability of the biobank [10]. The fact that the biobank is embedded in a large academic center with a strong focus on rare diseases and is a member of 17 out of 24 European Reference Networks, provides assurance that the biobank will have a lasting impact. Additionally, the consent forms required for participation in the biobank can be complex due to legal requirements and may still be daunting for patients, despite efforts to simplify them. However, this is somewhat mitigated by the fact that each patient is personally contacted by a member of the research team and help is offered. Finally, sharing data and biological materials across international borders has become increasingly common in recent years, leading to significant advances in research. However, there are challenges associated with legal policies that regulate the sharing of data and biological materials internationally.

Our study status demonstrates that we included a limited number of patients per phenotype group so far. For research concerning a specific phenotype group, more patients are likely needed. However, small numbers can already be relevant for individually interesting cases – for instance for gene finding in unknown CKD cases highly suspect for a genetic origin – or individuals with (specific) variants in (specific) genes for whom material is collected for tubuloids, or for contributing patients to (inter)national efforts. The big advantage of a broad biobank lies in the fact that we do not need to set-up a separate registry / biobank / study for each individual phenotype group. For research focusing on modifiers the broad phenotype groups and sequencing data from a large number patients will be of great value for different disease groups and make it possible to also study modifier across diseases.

Since we have a large number of exomes available in the UMCU from diagnostics, and because inclusion of such a large number of eligible patients takes time, we have implemented a protocol for anonymous exome sequencing which was approved by the Biobank Research Ethics Committee of the UMCU (TCBio 20–306). This protocol allows us to aggregate sequencing data from patients that were tested with a MKD gene panel. We can use and query it for novel candidate genes and link this to some basic phenotype information. The aggregation of sequencing data together with the removal of any patient identifiable data characteristics allows for an anonymous approach. We will continue building the GeNepher biobank and continue moving inclusions to a national level.

Despite the challenges of securing funding and simplifying the consent process, the GeNepher biobank has the potential to make a significant contribution to the field of genetic kidney disease research. In summary, the GeNepher biobank aims to enhance scientific knowledge about genetic kidney disease by investigating disease mechanisms, including novel monogenic causes, studying modifiers, and improving patient care through current and future research projects. Additionally, the biobank will facilitate re-contacting patients for opportunities in treatment development or participation in specific trials and treatments.

Ethics approval and consent to participate

The protocol for the GeNepher biobank was approved by the Biobank Research Ethics Committee of the University Medical Center Utrecht (UMCU) in July 2021 (TCBio 20–305) and use of the collected data and biological material for research projects related to objectives 1–3 was approved (TCBio 22–076) by the same committee. The TCBio reviewed these protocols based on the criteria of UMC Utrecht's Biobank Regulations which are in compliance with the applicable national and international laws and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

Consent for publication was approved under TCBio 22-076.

Authors' contributions

LRC and AMvE designed the biobank protocol, drafted and revised the paper. IL is currently managing biobank inclusions. Authors from GeNepher Biobank Consortium advised during the design phase of the biobank and/or contributed patients or will contribute patients in the future. All authors assessed this manuscript and approved the final version.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (https://chat.openai.com/chat) in order to enhance the legibility of the near-final manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available as most of the MPS is generated as part of diagnostic procedures and the biobank informed consent does not cover making that data publicly available. The corresponding author can be contacted directly or via the Central Biobank for collaborative research opportunities with this dataset. Standard operating procedures for collection and storage are available on request.

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