The German Chronic Kidney Disease (GCKD) study: design and methods

Kai-Uwe Eckardt[1], Barbara Bärthlein[2], Seema Baid-Agrawal[3], Andreas Beck[2], Martin Busch[4], Frank Eitner[5], Arif B. Ekici[6], Jürgen Floege[5], Olaf Gefeller[7], Hermann Haller[8], Robert Hilge[9], Karl F. Hilgers[1], Jan T. Kielstein[8], Vera Krane[10], Anna Köttgen[11], Florian Kronenberg[12], Peter Oefner[13], Hans-Ulrich Prokosch[2], André Reis[6], Matthias Schmid[7], Elke Schaeffner[3], Ulla T. Schultheiss[11], Susanne A. Seuchter[1], Thomas Sitter[9], Claudia Sommerer[14], Gerd Walz[11], Christoph Wanner[10], Gunter Wolf[4], Martin Zeier[14] and Stephanie Titze[1]

[1]Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany, [2]Chair of Medical Informatics, University of Erlangen-Nürnberg, Erlangen, Germany, [3]Department of Nephrology and Intensive Care Medicine, Charité, Campus Virchow Clinic, University Medicine, Berlin, Germany, [4]Department of Internal Medicine III, University of Jena, Jena, Germany, [5]Division of Nephrology and Clinical Immunology, RWTH University of Aachen, Aachen Germany, [6]Institute of Human Genetics, University of Erlangen-Nürnberg, Erlangen, Germany, [7]Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nürnberg, Erlangen, Germany, [8]Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany, [9]Department of Nephrology, Ludwig-Maximilians University, Munich, Germany, [10]Division of Nephrology, Department of Internal Medicine I, University of Würzburg, Würzburg, Germany, [11]Division of Nephrology, Department of Medicine, University Hospital Freiburg, Freiburg, Germany, [12]Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria, [13]Institute of Functional Genomics, University of Regensburg, Regensburg, Germany and [14]Divison of Nephrology, Department of Medicine, University of Heidelberg, Heidelberg, Germany

Correspondence and offprint requests to: Kai-Uwe Eckardt; E-mail: kai-uwe.eckardt@uk-erlangen.de

Abstract

Background. Chronic kidney disease (CKD) is increasingly recognized as a global health problem. The conditions leading to CKD, the health impact of CKD and the prognosis differ markedly between affected individuals. In particular, renal failure and cardiovascular mortality are competing risks for CKD patients. Opportunities for targeted intervention are very limited so far and require an improved understanding of the natural course of CKD, of the risk factors associated with various clinical end points and co-morbidities as well as of the underlying pathogenic mechanisms.

Methods. The German Chronic Kidney Disease (GCKD) study is a prospective observational national cohort study. It aims to enrol a total of 5000 patients with CKD of various aetiologies, who are under nephrological care, and to follow them for up to 10 years. At the time of enrolment, male and female patients have an estimated glomerular filtration rate (eGFR) of 30–60 mL/min $\times$ 1.73m^2 or overt proteinuria in the presence of an eGFR >60 mL/min $\times$ 1.73m^2. Standardized collection of biomaterials, including DNA, serum, plasma and urine will allow identification and validation of biomarkers associated with CKD, CKD progression and related complications using hypothesis-driven and hypothesis-free approaches. Patient recruitment and follow-up is organized through a network of academic nephrology centres collaborating with practising nephrologists throughout the country.

Conclusions. The GCKD study will establish one of the largest cohorts to date of CKD patients not requiring renal replacement therapy. Similarities in its design with other observational CKD studies, including cohorts that have already been established in the USA and Japan, will allow comparative and joint analyses to identify important ethnic and geographic differences and to enhance opportunities for identification of relevant risk factors and markers.

Keywords: biomarkers; cohort; epidemiology; prognosis; risk factors

Introduction

Uniform criteria for the definition and classification of chronic kidney disease (CKD) were first proposed in 2002 [1]. Since then, a growing body of evidence has established the importance of CKD with respect to both its prevalence and the associated adverse consequences. Most recently, a large meta-analysis initiated by the global organization 'Kidney Disease: Improving Global Outcomes' (KDIGO), which included data from

>1.5 million individuals, has demonstrated a progressive increase in all-cause mortality, cardiovascular mortality, acute kidney injury incidence and kidney disease progression with decreasing glomerular filtration rate (GFR) and increasing albuminuria [2]. These relationships were strikingly consistent across general population-based cohorts [3, 4], high-risk cohorts [5] and CKD cohorts [6]. CKD has also been identified as a strong and independent risk factor for specific cardiovascular events and complications [7].

Despite its public health impact, the underlying mechanisms and the full spectrum of pathophysiological and clinical consequences of CKD are poorly understood (Figure 1). The prognosis of CKD patients is highly variable and the individual risks are not predictable with sufficient precision. In particular, premature death and progression to end-stage renal disease (ESRD) are competing risks and it is unclear to which extent they are the culprits of similar or different disease pathways.

Emerging high-throughput technologies, including genomics, metabolomics and proteomics, offer vast opportunities for identification of novel risk factors and/or risk markers that reflect predisposition to CKD or are associated with the manifestation and progression of CKD and its consequences [8]. The application of these technologies requires biomaterials from well-phenotyped patient cohorts with a prospective evaluation of individual patient courses, in order to allow for an efficient search for discriminative molecular patterns that are associated with different outcomes. So far, the number of observational cohort studies specifically addressing CKD and its risk factors, and the number of patients enrolled in such cohorts worldwide is rather small. Less than 22 000 patients of >1.5 million individuals within the recent KDIGO meta-analysis were participants in CKD cohort studies and in only some of these cohorts, have biomaterials been collected [2]. The Chronic Renal Insufficiency Cohort

(CRIC) has enrolled 3612 patients of diverse ethnicities in the USA [9]. The Chronic Kidney Disease Japan Cohort (CKD-JAC) has used a similar design to enrol 3000 Japanese patients [10]. Given the genetic and environmental heterogeneities, the results of these studies will not necessarily be generalizable to a central European population. In fact, international comparisons between the CKD prevalence and the progression to ESRD suggest important differences between populations [11].

We have therefore established the German Chronic Kidney Disease (GCKD) study, a national prospective observational cohort study, to characterize the burden and the course of CKD patients, to identify and validate novel risk factors and markers for the manifestation, progression and complications of CKD and to improve the understanding of the underlying pathophysiology.

Materials and methods

Study objectives

The main objective of the GCKD study is to establish a large cohort of ~5000 CKD patients with a moderate reduction in GFR and/or overt proteinuria at enrolment, who receive comparable medical care, and are followed prospectively for up to 10 years and in whom biomaterials are collected at baseline and at regular intervals during the course of the study.

The main specific aims of the study are (i) to identify and validate risk factors and markers associated with the progression of CKD and the development of ESRD, (ii) to identify and validate risk factors and markers associated with cardiovascular disease (CVD) events and CVD progression in the setting of CKD, (iii) to assess the interrelationship between risk factors for CKD and CVD progression, (iv) to determine gender-related differences in the risks for CKD and CVD progression and (v) to assess the consequences of CKD for general health, non-CVD morbidity and health-related quality of life (QOL). Additional aims are to contribute to the identification of risk factors and markers for the development of CKD through comparison with general population-based cohorts.

Study organization

The GCKD organizational structure integrates the advantages of a centralized project management and decentralized recruitment centres. The project management centre at the University of Erlangen-Nürnberg hosts the central database, the data coordinating centre and the central biobank. Recruitment is organized through nine regional centres at collaborating academic institutions in Aachen, Berlin, Erlangen, Freiburg, Hannover, Heidelberg, Jena, München and Würzburg. Each centre is anticipated to recruit and follow an average of 550 patients in collaboration with the local practising nephrologists.

Fig. 1. Schematic presentation of the topic areas addressed in the GCKD study. CKD is known to be associated with various outcomes, of which progressive loss of kidney function and cardiovascular complications have major importance; ESRD requiring renal replacement therapy and premature death from cardiovascular cause are competing risks. However, the individual risks in patients with CKD are poorly defined and how the risk of progression of kidney disease or CVD are related to each other is largely unknown, as are the molecular pathways promoting both end points. Assessing course, risk factors and markers of CVD (A) and progressive loss of renal function (B) are therefore the main goals of the study. In addition, careful survey and long-term follow-up will also define other risks associated with CKD and the impact of CKD on health-related QOL (C). Comparisons between the GCKD cohort and other cohorts will also allow to explore factors associated with the manifestation of CKD in the presence of known predisposing factors, such as diabetes mellitus (D) and yet unknown factors increasing the risk for development of CKD (E).

Cohort participants

The GCKD study is enrolling male and female Caucasian patients who have been previously referred to a nephrologist providing outpatient care in a nephrology practice setting or in outpatient clinics of the participating university hospitals. Inclusion criteria include an age range of 18–74 years and moderately reduced estimated glomerular filtration rate (eGFR) (30–60 ml/min $\times$ 1.73m^2, corresponding to CKD Stage 3) or 'overt' proteinuria, defined as an albumin excretion of >300 mg/g creatinine or a protein excretion of >500 mg/g creatinine or corresponding values of 24-h urinary excretion, in the presence of an GFR >60 mL/min $\times$ 1.73m^2 (Table 1). The eGFR defining eligibility is estimated from a locally measured serum creatinine value using different assays, which are not necessarily isotope dilution mass spectrometry (IDMS) traceable and the 4-variable MDRD formula [12]. Albumin or protein excretion rate defining eligibility is taken from patient records using locally determined values. Exclusion criteria are active malignancy, NYHA IV heart failure, renal or any other transplantation, non-Caucasian origin and legal attendance. In contrast to the CRIC Study in the
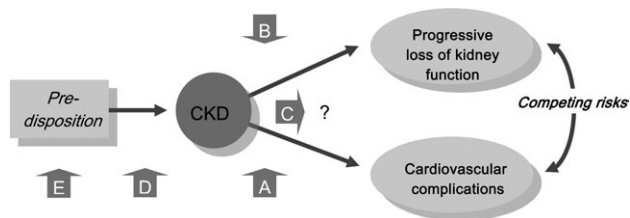
USA, enrolment is not stratified for age, cause of disease or presence of diabetes mellitus [13].

Enrolment and study design

The regional centres inform practising nephrologists in their region about the GCKD Study. If they agree to collaborate, they screen incident and prevalent patients under their care for eligibility. Eligible patients are then contacted by their nephrologists, receive detailed information about the study and are asked about their willingness to participate. Following informed consent, patients are invited to meet members of the GCKD study team in the nephrologist's practice or the outpatient clinic where they are under routine care. Flexibility is allowed to either combine the GCKD study visit with a routine visit or to make a special appointment according to physician and patient preferences.

Baseline phenotyping of patients

Baseline assessment includes anthropometric measures, three measurements of resting blood pressure using a standardized device, heart rate and single-lead ECG. Information is collected on socio-demographic factors, medical and family history and the use of prescription drugs and over the counter medications. In addition, patient questionnaires are used to assess health-related QOL [14], life-style factors and symp-

Table 1. Inclusion and exclusion criteria in the GCKD study

Inclusion criteria
Age: 18–74 years
eGFR: 30–60 mL/min/1.73m^2 or
eGFR: > 60 mL/min/1.73m^2 and 'overt' albuminuria/proteinuria as
defined by any of the following:
Albuminuria >300 mg/g creatinine
Albuminuria >300 mg/day
Proteinuria >500 mg/g creatinine
Proteinuria >500 mg/day
Exclusion criteria
Non-Caucasian race
Solid organ transplantation or bone marrow transplantation
Active malignancy within 24 months prior to screening
Heart failure NYHA IV
Patients under legal attendance or unwilling to provide consent

Table 2. Synopsis of data obtained in the GCKD study

GCKD data	Instruments
Demographics	
Anthropometric data	
Renal and cardiovascular	
history, renal biopsy history	
Comorbidities	
Medication, life style	
Family history	
Heart failure	Modified Gothenburg scale
Angina pectoris/dyspnoea	Rose questionnaire
Intermittent claudication	Edinburgh claudication questionnaire
QOL	KDQOL 36
Core laboratory parameters	
Serum	Creatinine, cystatin C, urea, sodium, calcium, phosphate, albumin, C-reactive protein, total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, uric acid, haemoglobin, haemoglobin A$_{1C}$[a]
Urine	Albumin, creatinine

[a]Since all samples are shipped frozen, the haemoglobin concentration and the concentration of haemoglobin A1C are determined in thawed whole blood.

toms of heart failure [15], angina pectoris [16] and claudication [17] (Table 2). A core set of laboratory parameters is determined centrally (Table 2).

Follow-up visits

Follow-up visits are planned in 2-year intervals. One year after each follow-up visit, structured phone interviews are conducted with patients enrolled in the study to assess their disease course and new-onset complications and hospitalization episodes during the past 12 months. In addition, the patient's nephrologist is contacted annually to assess key information on patient health and the latest serum creatinine value. Patients will be followed until death, the end of the study or withdrawal of consent. Follow-up with an adjusted protocol will continue after the initiation of renal replacement therapy.

Collection of biological material for biobanking

Blood samples are collected at baseline for DNA extraction. At each visit, plasma, serum and spot-urine samples are collected, processed and shipped frozen to a central laboratory for routine clinical chemistry (Table 2) and to the central biobank for future analyses. Workflows to track sample processing, sample transportation and sample storage are quality assured and supported by a dedicated biobank management system [18].

Study outcomes

The main study end points are (i) mortality, (ii) decline in renal function, including doubling of serum creatinine and need for regular renal replacement therapy and (iii) cardiovascular events, including cardiac death, non-fatal myocardial infarction, hospitalization due to angina or heart failure, cardiac surgery and stroke. Additional clinically relevant events recorded include development of malignancies and hospitalization due to infection. Written reports on all hospitalizations will be collected and adjudication will be performed according to a standardized protocol.

Data protection

The GCKD study has implemented a data protection concept according to the data protection recommendations of the platform for technology and methods for networked medical research (TMF; www.tmf-ev.de), supported by the German Ministry of Education and Research (www.bmbf.de). The study protocol was approved by local institutional review boards at each participating academic institution and the data protection concept was reviewed by the data protection officer of the State of Hessen. A core component is that each patient is assigned a unique pseudonym. Personal identification data are stored in regional centres only and are strictly separated from medical and research data, which are stored centrally. Biosamples are identified only with their unique sample identifier and no patient identification is stored within the biobank management system. A 2D-barcode system is used for tracking, storage and retrieval of all biosamples.

Statistical considerations

The sample size of the GCKD cohort of 5000 patients was chosen as a realistically attainable cohort size based on feasibility considerations. This sample size ensures adequate statistical power to differentiate subgroups showing different behaviours with respect to the primary end points. For example, even when focussing only on the expected 2700 patients who will stay under observation for the entire study, we will be able to differentiate between two equally sized subgroups according to a standardized difference in yearly GFR decline of 0.11 mL/min/1.73m^2 with a power of 80%. The sample size allows for detection of a hazard ratio of 1.2 in time-to-event analyses with at least 80% power over a wide range of plausible scenarios with different occurrence rates in two equally sized subgroups (assuming a constant hazard ratio over time). In event-based analyses, e.g. comparing the proportion of patients requiring chronic renal replacement therapy or developing cardiovascular complications between two subgroups, a similar effect size, i.e. a relative risk of 1.2, can be detected with a power of 80% in all plausible settings.

Baseline characteristics will be described using standard descriptive methods such as summary statistics and frequency tables. Parametric and non-parametric statistical approaches (such as contingency table analysis regression and analysis of variance) will be used to compare subgroups at baseline. Because the intention of the GCKD Study is to analyse

all patients recruited for the study (including patients with incomplete data and/or early drop out), focus will be given to statistical methods addressing the problem of missing data [19].

Kaplan–Meier analysis and Cox regression [20, 21] will be the principal approaches to analyse end points such as mortality and cardiovascular end points. Changes in serum creatinine levels will be analysed using mixed-effects models and generalized estimation equations [22, 23]. The latter approaches are able to handle repeated measurements and the heterogeneity of individual creatinine levels. Subgroup analyses will be carried out for diabetic and non-diabetic patients, across sex- and age-strata, for patients with specific aetiologies of CKD and for different cardiovascular comorbidities and outcomes.

Quality assurance

A quality management concept was developed and is constantly controlled by an internal and an external quality management board. Measures to ensure high quality standards include the development of data entry and data management systems, training, certification and recertification of all personnel involved in data collection and testing of data collection procedures. A special tool was developed to control specific data sets by selected experts from the internal quality management board during the complete survey. A web-based Patient Interview Audit (PIA)-Tool (Seuchter SA, Schmid M, Titze S et al., unpublished data) is used to monitor if patient interviews are carried out according to the instructions to ensure accuracy and avoid information bias. The tool also allows for the detection of data entry errors. Continuous data cleaning is used to analyse routinely for missing, extreme or inconsistent values. Biosamples are collected, processed and stored by certified personnel according to standardized protocols.

Enrolment to date

Current enrolment (25 July 2011) comprises a total number of 3291 patients in 158 outpatient sites. It is anticipated that the recruitment period will end in 2012.

Discussion

The GCKD study is planned as one of the largest prospective observational cohort studies to date of CKD patients not requiring renal replacement therapy at the time of recruitment. Recruitment in collaboration with practising nephrologists across the country reflects the organization of nephrology care in Germany: the majority of patients under the supervision of a nephrologist are not being treated in large centres, but in decentralized practices, which are usually run in conjunction with dialysis facilities. Recruitment of patients already referred to a nephrologist is likely to impact on patient characteristics. Thus, we anticipate that the GCKD cohort as compared to the general population and patient populations under non-nephrological care or with undiagnosed CKD will be enriched with individuals with more advanced and more progressive disease, a greater level of complications and symptoms, a higher degree of proteinuria, a higher proportion of specific renal diseases causing CKD and an increased awareness and compliance. Further bias is possibly introduced by the voluntary non-random collaboration of nephrologists. While the selection process will limit the ability to generalize findings to other patient populations, it will minimize the known influence of different levels of care on patient outcomes. In fact, there is considerable evidence indicating that long-term outcome of CKD patients varies depending on whether they do or do not receive medical care guided by nephrologists [24–26]. Mitigation of this variable should therefore facilitate detection of patient-related variables that impact outcomes.

Within this given setting of patient care, we aimed to minimize further selection bias by choosing broad and non-restrictive inclusion criteria. The entry criterion of a GFR of 30–60 mL/min/1.73m^2 corresponds to the current definition of CKD Stage 3 [27], which is known to be the most prevalent stage of CKD in the general population [28]. The study of a common and relatively early stage of CKD may identify risk factors relatively early during the course of the disease and ultimately enable disease prevention in a large at-risk population. In addition, patients with overt proteinuria are also being enrolled if their eGFR is >60 mL/min/1.73m^2, in order to investigate the emerging evidence for the high incidence of adverse outcomes in this subpopulation of CKD patients [3].

Despite the decentralized organization of the study, trained and certified study personnel travel to the physicians' practices to enrol the patients. They conduct patient interviews and perform physical assessment in a standardized way to decrease the intra- and inter-observer variability. Moreover, a particular emphasis is put on standardized biomaterial collection and analysis. Thus, a set of standard clinical chemistry variables is analysed in all patients at each visit in a central laboratory. Fresh serum, plasma and urine samples are frozen on dry ice within 2 h after collection and shipped frozen to a central biobank for storage at −80°C. The established procedures have proved to work well, with not a single set of samples lost or thawed prior to arrival at the biobank thus far. The drawback of this standardized procedure is that study resources do not allow for in-person investigation intervals <2 years. However, yearly standardized telephone interviews with patients and doctors performed between two visits capture important information on patient course and possible end points.

A variety of possible risk factors and markers for CKD progression and the manifestation of CVD and mortality in patients with CKD have been identified in recent years [8], and the GCKD cohort will allow validation of many of those factors. In addition, we aim to apply hypothesis-generating approaches to search for molecular patterns that discriminate different courses of disease in serum and urine. We will not routinely collect 24-h urine, which is a limitation for some analysis, but would increase the pre-processing variability. In addition, applying discriminatory methodology to spot urine samples will focus the profile identification on patterns that are less sensitive to sample timing and thus possibly have a higher utility in routine care.

Despite the diversity of causes leading to CKD, recent data suggest that there is a common genetic predisposition for the development of CKD [29, 30] apart from the predisposition to develop specific kidney diseases, such as e.g. polycystic kidney disease [31], IgA nephropathy [32], membranous nephropathy [33], diabetic [34] or hypertensive [35] nephropathy. Genetic analysis will therefore be another important cornerstone of the GCKD Study, using candidate gene approaches, genome-wide association studies in the entire patient group and whole-genome sequencing in selected patients. While the GCKD cohort itself has the potential to contribute to identification of yet unknown genetic factors associated with the future

course and complications of established CKD, comparisons with general populations, non-CKD populations and other high-risk populations have the potential to identify and/or confirm genetic variants predisposing to CKD. This goal can only be achieved in the context of large international consortia, as recently demonstrated [36, 37].

Conceptually, the GCKD cohort is intended as an open network and scaffold for ancillary studies addressing specific characteristics of CKD patients in subgroups of the main cohort. Planned and ongoing studies include an in-depth characterization of the cardiac, micro- and macro-vascular structure and function, analysis of physical activity and analysis of circulating immune cell patterns.

The GCKD study will also greatly benefit from and foster (inter)national collaboration. Comparison of patient characteristics and biomarker profiles between different cohorts will identify not only differences but also similarities and thereby lead to hypotheses regarding their importance. Candidate biomarkers or profiles identified in one cohort can be validated in other cohorts. Moreover, meta-analyses across studies result in an increased statistical power, which is of particular importance to identify risk factors of low effect size, including specific gene variants. To capitalize on existing expertise and facilitate comparative and joint analysis, design, parameter sets and definitions of the GCKD study were chosen in collaboration with the investigators of the CRIC study [9, 13]. CRIC has previously provided guidance for establishment of the Japanese CKD cohort study [10] and we envisage sustained benefits from multinational collaborative approaches in this area. In addition, core data sets from other recently established prospective cohort studies with a nephrological focus in Germany, receiving funding from a source which also supports the GCKD study (KfH Foundation), have been sychronized to facilitate future cross-population comparisons. These studies include a diabetes cohort and CKD studies in an elderly population [38] and in children [39].

In conclusion, the GCKD study will assemble a large well-characterized clinical cohort of CKD patients to better define the disease characteristics, to validate established and to identify novel risk factors and markers. The study aims to advance the understanding of CKD aetiology, manifestation, progression and complications, to identify novel molecular targets and to provide a basis for improved prevention as well as—ultimately—personalized therapy of CKD.

Conflict of interest statement. None declared.

Appendix: The GCKD Study Group

Regional Study Centres

Technical University of Aachen
Frank Eitner, MD
Katharina Kehl, MD MPH
Elfriede Ahrweiler, MPH
Sabine Ernst
Mario Unger, RN
Jürgen Floege, MD

Charité, Humboldt-University of Berlin
Elke Schaeffner, MD, MSc
Seema Baid-Agrawal, MD
Kerstin Petzold, RN
Ralf Schindler, MD

University of Erlangen-Nürnberg
Karl F. Hilgers, MD
Silvia Hübner, MD
Susanne Avendano, RN
Dinah Becker-Grosspietsch, RN

University of Freiburg
Anna Köttgen, MD, MPH
Ulla Schultheiß, MD
Simone Meder, RN
Erna Mitsch, RN
Gerd Walz, MD

Hannover Medical School
Jan T. Kielstein, MD
Petra Otto, RN
Hermann Haller, MD
University of Heidelberg
Claudia Sommerer, MD
Claudia Föllinger, RN
Tanja Löschner, RN
Martin Zeier, MD

University of Jena
Martin Busch, MD
Katharina Paul, MSc
Lisett Dittrich
Gunter Wolf, MD, MHBA

Ludwig-Maximilians University of München
Thomas Sitter, MD
Robert Hilge, MD
Claudia Blank

University of Würzburg
Vera Krane, MD
Daniel Schmiedeke, MD
Sebastian Toncar, MD
Daniela Cavitt, RN
Christoph Wanner, MD

Study and data coordinating center

University of Erlangen-Nürnberg
Kai-Uwe Eckardt, MD (PI)

Stephanie Titze, MD
Nina Hauck, MSc
Susanne A. Seuchter, BSc
Birgit Hausknecht
Marion Rittmeier
Anke Weigel

Hans-Ulrich Prokosch, PhD
Barbara Bärthlein, BSc
Andreas Beck, MSc
Thomas Ganslandt, MD
Stefanie Stefan, MSc
Sabine Knispel, PhD
Thomas Dressel, MSc

Olaf Gefeller, PhD
Matthias Schmid, PhD
Martina Malzer, BSc

Analytical centres

University of Erlangen-Nürnberg
Institute of Human Genetics
André Reis, MD
Arif B. Ekici, PhD

Innsbruck Medical University
Division of Genetic Epidemiology
Florian Kronenberg, MD
Barbara Kollerits, PhD
Hansi Weißensteiner, MSc
Lukas Forer, MSc

University of Regensburg
Institute of Functional Genomics
Peter Oefner, PhD

A list of nephrologists currently collaborating with the GCKD study is available at www.gckd.org

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39: S1–S266

2. Levey AS, de Jong PE, Coresh J *et al.* The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2010; 80: 17–28

3. Chronic kidney disease prognosis consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause mortality and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–2081

4. Gansevoort RT, Matsushita K, van der Velde M *et al.* Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 2011; 80: 93–104

5. van der Velde M, Matsushita K, Coresh J *et al.* Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; 79: 1341–1352

6. Astor BC, Matsushita K, Gansevoort RT *et al.* Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011; 79: 1331–1340

7. Herzog CA, Asinger RW, Berger AK *et al.* Cardiovascular disease in chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes. *Kidney Int* 2011 (epub ahead of print)

8. Kronenberg F. Emerging risk factors and markers of chronic kidney disease progression. *Nat Rev Nephrol* 2009; 5: 677–689

9. Lash JP, Go AS, Appel LJ *et al.* Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 2009; 4: 1302–1311

10. Imai E, Matsuo S, Makino H *et al.* Chronic kidney disease Japan cohort (CKD-JAC) study: design and methods. *Hypertens Res* 2008; 31: 1101–1107

11. Hallan SI, Coresh J, Astor BC *et al.* International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006; 17: 2275–2284

12. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470

13. Feldman HI, Appel LJ, Chertow GM *et al.* The chronic renal insufficiency cohort (CRIC) study: design and methods. *J Am Soc Nephrol* 2003; 14 (7 Suppl 2): S148–S153

14. Soni RK, Weisbord SD, Unruh ML. Health-related quality of life outcomes in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2010; 19: 153–159

15. Avery CL, Mills KT, Chambless LE *et al.* Long-term association between self-reported signs and symptoms and heart failure hospitalizations: the Atherosclerosis Risk In Communities (ARIC) Study. *Eur J Heart Fail* 2010; 12: 232–238

16. Lallukka T, Manderbakka K, Keskimaki I *et al.* Angina pectoris: relation of epidemiological survey to registry data. *Eur J Cardiovasc Prev Rehabil* 2011; 18: 621–628

17. Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. *Int J Epidemiol* 1988; 17: 248–254

18. Prokosch HU, Ganslandt T, Hummel M *et al.* IT Infrastructure Components for Biobanking. *Appl Clin Inf* 2010; 1: 419–429

19. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. 2nd edition. New York, NY: Wiley, 2002

20. Klein JP, Moeschberger ML. *Survival Analysis—Techniques for Censored and Truncated Data*. New York, NY: Springer, 2003

21. Therneau TM, Grambsch PM. *Modeling Survival Data—Extending the Cox Model*. New York, NY: Springer, 2000

22. Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. New York, NY: Springer, 2000

23. Diggle P, Heagerty PJ, Liang KY *et al. Analysis of Longitudinal Data*, 2nd edition. Oxford, UK: Oxford Science Publications, Clarendon Press, 2002

24. Winkelmayer WC, Owen WF Jr, Levin R *et al.* A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003; 14: 486–492

25. Wavamunno MD, Harris DC. The need for early nephrology referral. *Kidney Int Suppl* 2005; S128–S132

26. Rucker D, Hemmelgarn BR, Lin M *et al.* Quality of care and mortality are worse in chronic kidney disease patients living in remote areas. *Kidney Int* 2011; 79: 210–217

27. Levey AS, Eckardt KU, Tsukamoto Y *et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67: 2089–2100

28. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–2047

29. Kottgen A. Genome-wide association studies in nephrology research. *Am J Kidney Dis* 2010; 56: 743–758

30. Estrella MM, Sperati CJ, Kao WH *et al.* Genetic epidemiology of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2010; 19: 283–291

31. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007; 369: 1287–1301

32. Feehally J, Farall M, Boland A *et al.* HLA has strongest association with IgA nephropathy in genome-wide analysis. *J Am Soc Nephrol* 2010; 21: 1791–1797

33. Stanescu HC, Arcos-Borgos M, Medlar A *et al.* Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011; 364: 616–626

34. Mooyaart AL, Valk EJ, van Es LA *et al.* Genetic associations in diabetic nephropathy: a meta-analysis. *Diabetologia* 2011; 54: 544–553

35. Freedman BI, Hicks PJ, Bostrom MA *et al.* Polymorphisms in the non-muscle myosin heavy chain 9 gene (MYH9) are strongly associated with end-stage renal disease historically attributed to hypertension in African Americans. *Kidney Int* 2009; 75: 736–745

36. Kottgen A, Pattaro C, Boger CA *et al.* New loci associated with kidney function and chronic kidney disease. *Nat Genet* 2010; 42: 376–384

37. Boger CA, Chen MH, Tin A *et al.* CUBN is a gene locus for albuminuria. *J Am Soc Nephrol* 2011; 22: 555–570

38. Schaeffner ES, van der Giet M, Gaedeke J *et al.* The Berlin initiative study: the methodology of exploring kidney function in the elderly by combining a longitudinal and cross-sectional approach. *Eur J Epidemiol* 2010; 25: 203–210

39. Querfeld U, Anarat A, Bayazit AK *et al.* The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) study: objectives, design, and methodology. *Clin J Am Soc Nephrol* 2010; 5: 1642–1648