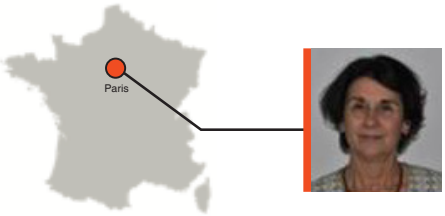
CKD-REIN :
Chronic Kidney Disease
Renal Epidemiology and Information Network

CKD Rein
Préserver la santé rénale



Dr. Bénédicte STENGEL
M.D., Ph.D., Research Director at Inserm

benedicte.stengel@inserm.fr

OVERVIEW

AT A GLANCE

> Nephrology
> Chronic Kidney Disease (CKD)
> CKD patients
> Coordinated by Dr. Bénédicte Stengel
> Inserm sponsorship
> Funded by ANR, PHRC & private funds

KEY FACTS & FIGURES

> Status: Inclusions started in July 2013
> 3,200 expected enrolled patients
> 2,700 included patients
> 5 year follow-up
> Multicentric cohort with 41 clinical sites
> Blood, serum, plasma, DNA and urines biobanking
> Administrative database linkage expected with SNIIRAM databases

CKD-REIN cohort will serve to improve our understanding of the biological, clinical and health care system determinants associated with CKD progression and adverse outcomes as well as of international variations in collaboration with the CKD Outcome and Practice Pattern Study (CKDopps).

CKD-REIN will foster CKD epidemiology and outcomes research and provide evidence to improve health and quality of life of CKD patients and the performances of the healthcare system in this field.

A total of 41 clinical sites participate in the cohort. Stratified selection of clinical sites yields a sample that represents the diversity of settings, *e.g.*, geographic region or public *vs* for-profit and non-for-profit private clinics.

Positioning

> The CKD-REIN project includes the French part of the international study called CKDopps (CKD Outcomes and Practice Patterns Study)

> The CKD-REIN study is the first large (N=3,200) cohort based on a representative sample of adult CKD patients receiving nephrologist-led care

> CKD-REIN has already established a public-private partnership with 6 pharmaceutical companies

LEADERSHIP

CKD-REIN's leadership team, led by Dr. B. Stengel, brings together renown epidemiologists and clinicians who have been committed to the field of CKD study and renal care for more than 20 years.

Dr. Bénédicte Stengel, Epidemiology/CKD, Research Director, Inserm U1018, Villejuif, Paris

- **20 years experience** in the field of CKD epidemiology, principal investigator of many epidemiological studies on determinants and complications of CKD
- **Study coordinator of NephroTest** *(a cohort study of over 2,000 adult patients included from 2000 to 2012 with chronic kidney disease stages 1 to 5)*
- **Membership of international consortia:** CKD Prognosis, CKDopps, IgA Nephropathy and GWAS, Global Network of Chronic Kidney Disease Cohorts
- **Elaboration of the "Renal Epidemiology and Information Network" registry protocol** for renal replacement therapy managed by the Biomedicine Agency
- Member of several scientific committees
- Collaborations with numerous researchers in France and abroad
- **More than 80 peer-reviewed publications**

Prof. Ziad Massy, Nephrology/Head of Nephrology Division, Ambroise Paré Hospital, Versailles Saint-Quentin en Yvelines University (UVSQ)

- **Relevant experience in clinical research** specifically focused on **etiology and slowing of CKD progression,** cardio-vascular complications in CKD, description of uremic toxin impact on CKD, CKD biomarkers and therapeutic trials

SCIENTIFIC NETWORK & MANAGEMENT

CKD-REIN is linked with the international cohort CKDopps (coordination by Arbor Research, USA)

The French "branch" of the CKDopps cohort is coordinated by Prof. C. Combe (CHU Bordeaux) and Dr. B. Stengel.

Prof. Christian Combe, Nephrology/Head of Nephrology Division, CHU Bordeaux

- **Relevant expertise in etiology and slowing of CKD progression, hemodialysis, nutrition and psychology**

Prof. Denis Fouque, Nephrology/Head of Nephrology Division, C. Bernard, Lyon University

- **Relevant experience in slowing of CKD progression, bone quality in CKD, nutrition, hemodialysis and peritoneal dialysis**

Prof. Serge Briançon, Epidemiology/Patient-Reported Outcomes, Head of Public Health Division, CHU Nancy

- **Relevant experience in the study of Chronic Diseases, Patient-Reported outcomes through epidemiologic and psychological approaches**

Prof. Luc Frimat, Nephrology/Head of Nephrology Division, CHU Nancy

- **Relevant experience in clinical research specifically focused on descriptive and analytical epidemiology of CKD, impact of CKD on patient quality of life, patient satisfaction, hemodialysis and peritoneal dialysis**

Yves-Edouard Herpe, Operational manager of the Picardie Biobank, CHU Amiens

- **Picardie Biobank: relevant expertise in both "systematic" biobanking and "project-driven" biobanking**

Dr. Joost Schanstra, Inserm U1048, I2MC, Toulouse

- **Relevant expertise, at international level, in renal fibrosis and in urinary proteomics**

Jean-François Deleuze, Head of CEA-CNG, Évry

- **Relevant expertise of the CEA-CNG in whole genome association studies (GWAS), pan-genomic expression profiling, epigenetic studies (DNA methylation, chromatin structure studies) and whole genome sequencing**

Bruce Robinson, CKDopps coordinator, Arbor Research, Ann Arbor, Michigan, USA

- **Relevant expertise in nephrology, biostatistical analyses, clinical practice, collection and management of large data sets, economics, and public policy to inform health care practitioners and policy makers. B. Robinson scientific work has contributed to improved CKD patient care and revisions of public policy in the USA and internationally**

Pascal Morel, Head of Etablissement Français du Sang Bourgogne Franche-Comté, Besançon

- **Relevant expertise in collection of blood, plasma and platelet donations, in processing, screening and distribution of labile blood products (LBPs) to health-care establishments**

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

The primary objective of the CKD-REIN cohort study is to develop a research platform to address key questions regarding various patient-level factors and biomarkers associated with CKD outcomes and to assess clinical practices and healthcare system-level determinants of CKD outcomes

Secondary objectives such as:

> Assess the associations of a set of **psychosocial, environmental, biological, and genetic factors** and their interactions with several renal and non-renal outcomes

> Assess the value of new **biomarkers to predict CKD progression and outcomes**

> Evaluate the associations of a set of healthcare providers regarding **CKD management, healthcare organization and clinic services** offered to CKD patients with end-points such as **survival, ESRD* incidence, hospital admissions, patient-reported outcomes** and achievement of **clinical practice guidelines** at both national and international (CKDopps) levels

> Identify and quantify net costs of different treatment strategies and combine these with estimated practice effects on patient outcomes to provide estimation of incremental **cost-effectiveness ratios at both national and international levels**

*ESRD : End-Stage Renal Disease

INNOVATIVE SCIENTIFIC FEATURES

Nationally representative sample of CKD patients

Will provide **an unbiased view of routine CKD** care in a wide variety of settings while collecting standardized data

The CKD-REIN research platform can serve for ancillary studies, in that prospect, **innovative projects** and broad use of data by external research groups will be encouraged

METHODOLOGY QUALITY

A web-based data collection system was developed for CKD-REIN using the same **secured web portal and patient identification module** as the REIN registry

Confidentiality, security and the integrity of data are covered by the Biomedicine Agency

Serum, plasma, DNA and RNA are stored at ultra-low temperature at the **Picardie Biobank, an ISO 9001 and NFS 96900 certified biological resources center**

Setting up by the EFS (Etablissement Français du Sang) of a **standardized protocol for the biological sample treatment**

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	3,200 patients CKD stage 3-4 receiving nephrologist-led care 1,600 stage-3 and 1,600 stage-4 patients
Sites:	41 nephrology clinics. Clinical center selection followed a stratification (*e.g.*, based on survey data) to yield a sample that approximately represents the diversity of community-based nephrology clinics across the country
Inclusion criteria:	eGFR between 15 and 60 ml/min/1.73m^2 for at least 1 month and no prior dialysis or transplantation Confirmed CKD
Exclusion criteria:	<18 years old, prior dialysis or transplantation, pregnant, institutionalized, unable to give inform consent, decline participation

INCLUSION COLLECTION
Database: Clinical, biological, treatment, environmental and social data integrated through clinician/CRTs and self-reporting
Biobank: Blood, serum and urine sampling

FOLLOW-UP : ONCE A YEAR
Database: Combination of systematic follow-up visit with using a variety of different national administrative databases and sources to ascertain death and other health-related information (RNIPP, SNIIR-AM)
Biobank: Sampling follow-ups will be at 2nd, 4th and 5th years

DATABASE & BIOBANK CONTENTS

DATABASE

Patient-Level Variables

> **Medical Questionnaire (MQ), Interval Summary (IS), & Termination Form (TF)**
>> Patient characteristics: Demographics, cause of CKD… (MQ)
>> Medication categories: RAS antagonists, statins, phosphate binders, ESAs therapy… (MQ/IS)
>> Clinical measures: Blood pressure, weight, height, urine protein, biochemical measures…(MQ/IS)
>> Nutrition: Prescribed restrictions of protein, potassium, sodium and phosphorus (MQ/IS)
>> RRT planning: Vascular access referral, placement & procedures, services used (education programs, social worker, dietician), timing of decision about RRT modality, transplant wait-listing (MQ/IS)
>> Dialysis data: eGFR at dialysis initiation, clinical measures & dialysis dose (IS)
>> Clinical outcomes: Hospitalizations (IS), death (TF), study departure (TF)

> **Patient Questionnaire (PQ)**
>> Patient-reported data: QoL (KDQoL…), burden of kidney disease, functional status, self-reported depression (CESD), satisfaction with care, involvement in decision-making, using validated instruments when possible

Provider-Level Variables from Clinician Surveys (CS)

> Medical Director Survey: Clinic protocols for achieving practice guidelines (*e.g.*, vascular access, kidney transplantation)
> Physician practices not covered by protocol: Preferences for levels to initiate therapy and target for blood pressure, hemoglobine, phosphate, proteinuria - Treatment preferences, use of single *vs.* dual RAS antagonists…
> Surveys of other health care providers: Nutrition, social work, vascular access, ESRD education programs; staffing levels; integration of care (multidisciplinary care clinic); palliative care services

Expected linkage of the database with others databases such as SNIIRAM, RNIPP...

BIOBANK

Originality

> **A large scale biobank with 3,000 patients sampled, nationwide;** serum, plasma, DNA and urines; with a conservation of 1/3 of the samples in liquid nitrogen for long-term conservation and 2/3 at -80°C
> CKD-REIN is member of an **international cohort network,** Global Network-CKD including 14 cohorts, 12 with a biobank. The coordination of this network is performed by the International Society of Nephrology

Scientific objective

> Biobanks aims to carry out future studies of uremic toxins, progression, inflammation and oxidative stress biomarkers, mineralization products, genetics and proteomics, and cardiovascular risk markers and factors
> No current research project using the biobank

Samples

> Plasma, Serum and Urine. DNA is extracted from blood samples
> Number of samples per patient at the inclusion and during the follow-up:
>> Plasma: 19 aliquots (500 µL)
>> Buffy coat: 2 aliquots (500 µL) only at baseline
>> Serum: 8 aliquots (500 µL)
>> Urine: 8 aliquots (5 mL)

> **At baseline**, **3,000 patients** are expected to be sampled, 1,200 during the 2 and 4 year-follow-up and 2,400 at the 5 year-follow-up
> Total number of samples expected: **178,200 blood** (plasma, serum, buffy coat) and **62,400 urines samples**

Associated resources

> The CKD-REIN cohort owns the know-how, the required **equipment and the human resources** to exploit the biological samples through **GWAS and Proteomic analysis,** in collaboration with the CEA-CNG platform (JF. Deleuze) and the Inserm Laboratory at Toulouse (J. Schanstra), respectively; both of them are partners of the CKD-REIN project

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- **Picardie Biobank centralizes the CKD-REIN biological samples** and is responsible for all the biobank quality procedures
- Biological samples collection, treatment, short-time **storage and transfer to Picardie Biobank** is organized and **performed by ESF** in most sites for procedure harmonization
- Picardie Biobank ensures the long-term conservation in liquid nitrogen for 1/3 of all the CKD-REIN biological samples, **2/3 being stored at -80°C**
- Each biological sample is identified with an identical 2D and 1D barcode. Theses IDs are different from the patient ID and only the Biomedecine Agency (CKD-REIN partner) has the correspondence between both

SPECIFICATIONS

- Male and Female patients, >18 years, CKD stage 3 and 4, no prior dialysis or transplantation
- Date of the first sampling: 07/01/2013
- **Sampling frequency:** At baseline, and at 2nd, 4th and 5th year follow-ups
- Responsible: Picardie Biobank (Y.E. Herpe)
- Protocol for the biological sample collection exists but confidential
- **A minimum dataset** for each CKD-REIN biological sample **is available on databiotec server** managed at the Picardie Biobank whereas the main database is managed and hosted at the Biomedecine Agency
- **Label of quality:** CKD-REIN biobank received a bio-collection authorization from the French Ministry of Research, CODECOH n° AC-2012-1624 based on the **Picardie Biobank quality standard**
- Biobank procedures were developed by the CKD-REIN coordination team in order to **apply standardized methods for sample collection, treatment and conservation** (Standard Operating Procedure)
- CKD-REIN biological samples will be **available in Q3 2016**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	Origin	Quantity / concentration available	No. of aliquots	No. of subjects who have been/will be sampled (ongoing/ expected)	Storage conditions
At Baseline (date of the first sampling): 7th January 2013					
Plasma	Blood	500 µg	14	3,000 expected	-80°C
Plasma	Blood	500 µg	5	3,000 expected	Liquid nitrogen
Serum	Blood	500 µg	6	3,000 expected	-80°C
Serum	Blood	500 µg	2	3,000 expected	Liquid nitrogen
Buffy coat	Blood	500 µg	2	3,000 expected	-80°C
Urines	Urines	5 mL	5	3,000 expected	-80°C
Urines	Urines	5 mL	3	3,000 expected	Liquid nitrogen
During the follow-up : 2nd, 4th and 5th year follow-ups					
Plasma	Blood	500 µg	14	1,200 / 2,400	-80°C
Plasma	Blood	500 µg	5	1,200 / 2,400	Liquid nitrogen
Serum	Blood	500 µg	6	1,200 / 2,400	-80°C
Serum	Blood	500 µg	2	1,200 / 2,400	Liquid nitrogen
Urines	Urines	5 mL	5	1,200 / 2,400	-80°C
Urines	Urines	5 mL	3	1,200 / 2,400	Liquid nitrogen

BIOBANK SAMPLE ACCESS MODALITIES

- A **document** specifying **the CKD-REIN resources access has been drawn**
- Biological samples, including DNA **are accessible** to academic as well as to industrial research teams
- Specific biological samples **access** will be granted on the **acceptation of the research project proposal submitted to the steering committee**
- To access biological samples, **the industrial research company needs to become a CKD-REIN partner and then to submit its specific research project through a proposal to the Steering and Scientific Committees for review**
- Biological sample **transfer is not allowed**
- Biological samples **are not shareable with a foreign company**

BIOLOGICAL SAMPLE ANALYSES

- The CKD-REIN protocol stipulates GWAS and proteomic analysis as studies conducted upon CKD-REIN biobank
- The collected samples are planned to be used for the validation of the CKD disease diagnosis
  - > The **identification of new biomarkers** to predict CKD progression and metabolic complications
  - > The **validation of the CKD disease** diagnosis

COST

- Access to biospecimens is under condition: Private companies need to sign a partnership with already defined modalities to access to biobank and associated data
- **A financial estimation** of the CKD-REIN biological samples is **in progress**
- A price list of the cost of each biological sample is not yet available

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

Translational research

> **Identification of new biomarkers** to predict CKD progression and metabolic complications

> **Pharmaco-genomic studies** to characterize **patient profile resistant to treatment**

Clinical development

> **Validation of prognosis value of biomarkers** in various sub-populations defined by age, gender and diabetes status

> **Optimization of clinical studies** (variations in the prevalence and distribution of patient clinical and biological characteristics…)

> **Epidemiological studies** (prevalence and incidence of CKD-related outcomes and co-morbidities) to support market access

Outcomes research

> **Pharmaco-epidemiological studies:** drug safety, "real-world" use, effectiveness, practice patterns, compliance, risk/benefit, adverse drug events of anti-hypertensive, lipid-lowering and antidiabetic drugs and of CKD-specific drugs (EPO...)

> **Pharmaco-economic studies:** cost/benefit, health economic outcomes related to end-stage renal disease treatment (dialysis, transplantation, conservative management)

> **Quality of life and patient satisfaction studies**

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