

Nephrol Dial Transplant (2019) 34: 1469–1480

doi: 10.1093/ndt/gfz089

Advance Access publication 14 June 2019



# Nephrology and Public Policy Committee propositions to stimulate research collaboration in adults and children in Europe

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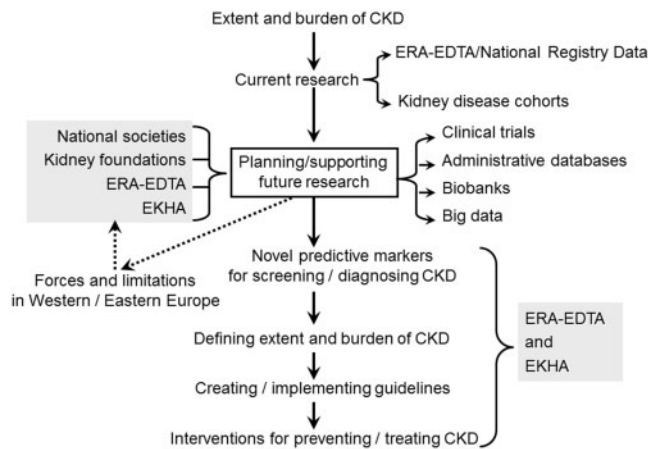
## ABSTRACT

The strengths and the limitations of research activities currently present in Europe are explored in order to outline how to proceed in the near future. Epidemiological and clinical research and public policy in Europe are generally considered to be comprehensive and successful, and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) is playing a key role in the field of nephrology research. The Nephrology and Public Policy Committee (NPPC) aims to improve the current situation and translation into public policy by planning eight research topics to be supported in the coming 5 years by ERA-EDTA.

**Keywords:** acute kidney injury, big data, cohorts, guidelines, registry

## INTRODUCTION

The goals of this article are to present the current state of the art of research in epidemiological and clinical nephrology in adults and children in Europe. It also aims to specify the strengths and the limitations currently present in Europe in order to explore how to proceed in the near future. To this end, the article will also propose a research plan with a few hot topics to be facilitated by the European Renal Association – European Dialysis



**FIGURE 1:** Roadmap for ongoing nephrology research for screening, diagnosing, preventing and treating CKD. Although valuable registry data and cohort studies exist for defining the current burden of CKD, novel studies are certainly needed for screening, diagnosing, preventing and treating this public health problem. Information that may be gained from future research may be useful for establishing novel predictive biomarkers for screening and diagnosing CKD, and thus be useful for creating/implementing guidelines and finally performing interventions for prevention and treatment of CKD. National societies, kidney foundations, ERA-EDTA and EKHA may collaborate and support all parties involved in managing the problems encountered during the planning and the support of these projects.

and Transplant Association (ERA-EDTA) in the coming years through stimulating research collaboration and supporting grant applications to other funding bodies. Finally, it is hoped that there may be an improvement in screening, diagnosing, preventing and treating chronic kidney disease (CKD) (Figure 1).

This article is divided into several sections and written by the following authors who are members of the Nephrology and Public Policy Committee (NPPC), an advisory group recently created to develop the Clinical Nephrology Governance Branch of the ERA-EDTA [1]:

- (i) Kidney disease cohorts in Europe (Kitty Jager, Benedicte Stengel and Ziad Massy);
- (ii) National kidney registries and the ERA-EDTA Registry (Patrik Finne);
- (iii) European paediatric nephrology (Jerome Harambat);
- (iv) European Renal Best Practice (ERBP) (Evi Nagler);
- (v) Important topics related to the European Union (EU) priorities (Raymond Vanholder);
- (vi) Important clinical research topics in Eastern (Mehmet Sukru Sever) and Western Europe (Fergus Caskey); and
- (vii) Summary and research proposals (Ziad Massy).

## KIDNEY DISEASE COHORTS IN EUROPE

Cohort studies are important tools in medical research when it comes to investigating risk factors for disease occurrence in the population and factors related to prognosis in patients. These studies follow large numbers of individuals and typically collect

data over long periods of time, through prospective cohorts (which look ahead in time) and retrospective cohorts (which look back in time). Over the past 15 years, there has been considerable development of cohort studies investigating kidney diseases worldwide, several of them set up in European countries. This paragraph takes into consideration the available large cohorts, though not exhaustively, encouraging future research collaborations to enhance the scientific potential of the data. Table 1 lists examples of such studies, investigating CKD, end-stage kidney disease (ESKD) or, to a lesser extent, acute kidney injury (AKI) in the general population or in the clinical setting, initiated or funded by nephrology researchers in one or more European countries [2–23].

Whereas stand-alone cohort studies are a valuable resource for research, collaboration on innovative research topics may further increase both their scientific quality and impact. Some examples of areas where collaboration may provide added value include (i) the identification of determinants of outcome where exposures or events are rare, and numbers in separate cohort studies may be too small; (ii) the investigation of specific patient subgroups, such as those defined by age, a specific type of nephropathy or an uncommon patient phenotype; (iii) the concurrent development and external validation of biomarkers or prediction models; and (iv) the comparison of prevention strategies, clinical practices, services and costs in kidney disease care.

Although several hurdles would need to be overcome regarding different data definitions and discrepancies among included data, such collaboration may promote further use of data and biobanks and optimize scientific output. Notably, the availability of large biobanks in carefully clinically phenotyped patients is a major strength and provides an opportunity to conduct collaborative research designed to uncover non-invasive diagnostic tests or novel predictive markers of kidney disease complications and to further improve the classification and prognostication of kidney diseases, notably based on large-scale genomic and proteomic data. The identification of the best form of prevention, clinical and therapeutic practices would also be enhanced by developing collaborative outcome research in culturally close populations exposed to different environments and socioeconomic backgrounds. A few cohorts also have access to patient-level claim data and hospitalization records through record linkage with a health administrative database, thus combining the benefit of well-defined patient phenotypes with so-called big data. Whether and how such data can be used for international comparisons would be worth testing. Such initiatives require funding to help build European nephrology research networks and infrastructures where data from various countries can be analysed according to current European data protection rules. This may provide the opportunity to train nephrologists in clinical epidemiology and include the support of PhD students and post-doctoral researchers analysing the collaborative databases. Based on these principles and with the advantages of existing cohorts, the selection process for research projects to be supported by the ERA-EDTA may thus strongly contribute to improve the scientific quality and scope of clinical research in Europe and evidence-based nephrology worldwide.

**Table 1. Studies investigating CKD, ESKD or AKI in the general population or in the clinical setting, and initiated or funded by nephrology researchers in one or more European countries**

Cohort studies [Ref.]	Country	Target population	Sample size
General population and primary care cohorts			
Berlin Initiative Study [2]	DE	General population	2069
Esther Study [3]	DE	General population	9961
Gubbio Study [4]	IT	General population	5376
Prevention of Renal and Vascular End-stage Disease Study [5]	NL	General population	8592
The Renal Risk in Derby study [6]	UK	Primary care patients with CKD Stage 3	1741
Uppsala Longitudinal Study of Adult Men [7]	SE	Men from the general population	2322
CKD cohorts (adults)			
Cardiovascular and Renal Outcome in CKD Stages 2–4 Patients—The Fourth Homburg evaluation [8]	DE	CKD Stages 2–4	444
Chronic Renal Impairment in Birmingham [9]	UK	CKD Stages 3–5 not on dialysis	382
Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner [10]	NL	CKD Stages 2–4	788
Grampian Laboratory Outcomes, Morbidity and Mortality Studies [10]	UK	CKD Stages 3–5 not on dialysis	3414
Mild to Moderate Kidney Disease Study [12]	DE, AU, IT	Patients with primary kidney disease	227
NephroTest Study [13]	FR	CKD Stages 3–5 not on dialysis	2084
EQUAL study [14]	DE, IT, SE, NL, UK	CKD Stages 4–5 and aged >65 years	3500 (target)
The German Chronic Kidney Disease (GCKD) study [15]	DE	CKD Stages 1–5	5217
Chronic Renal Insufficiency Standards Implementation Study [16]	UK	CKD Stages 3–5 not on dialysis	1325
The Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN) cohort study [17]	FR	CKD Stages 3–5 not on dialysis	3033
MERENA study [18]	ES	CKD Stages 3–4	1129
The Biobank of Nephrological Diseases in the Netherlands cohort: the String of Pearls Initiative [19]	NL	CKD Stages 1–4	2200
CKD cohorts (children)			
4C-Study [20]	TR, DE, FR, IT, PL, UK, AU, RS, PT, CZ, LT, CH	Children ages 6–17 years old—GFR of 10–60 mL/min/1.73 m <sup>2</sup>	688
AKI cohorts			
FINNAKI [21]	FI	ICU patients	2901
PREDICT [22]	FR	ICU patients	1200
OAKS [23]	UK	Adults undergoing gastrointestinal resection, liver resection or reversal of ileostomy or colostomy	6500

DE, Germany; IT, Italy; NL, the Netherlands; SE, Sweden; AU, Austria; FR, France; ES, Spain; TR, Turkey; PL, Poland; RS, Serbia; PT, Portugal; CZ, Czech Republic; LT, Lithuania; CH, Switzerland; FI, Finland; FINNAKI study, Finnish Acute Kidney Injury study; OAKS, Outcomes After Kidney injury in Surgery; GFR, glomerular filtration rate; ICU, intensive care unit.

AKI and related metabolic disorders are increasingly recognized to represent significant causes of morbidity and mortality. Also, AKI is recognized as an important risk factor for CKD as well as ESKD [24]. With this in mind, the International Society of Nephrology (ISN) launched the 0by25 AKI initiative to prevent all avoidable deaths from AKI across the world by 2025 [25]. This initiative seems more directed at developing countries than to European countries. The distinctive features of AKI in Europe are the ageing population, the association with multiple organ failure, the advanced technology available for patient care, the emerging area of onco-nephrology and the financial resources that allow care for almost all patients with AKI [24]. Several cohort studies are presented in Table 1. Since the committee believes that the study of AKI should be part of

ERA-EDTA's missions and objectives, additional proposals should be presented such as the creation of a dedicated nephrology network for AKI at the European level to organize, coordinate and improve the practices, research and education in the field of AKI [24].

### NATIONAL KIDNEY REGISTRIES AND THE ERA-EDTA REGISTRY

Most European countries have their own registries for dialysis and transplantation patients. Many of these registries are of high quality with a virtually complete coverage of the patient population dating back many years. The national and regional registries have an important role in serving the local nephrology

communities by publishing annual reports and, for example, ensuring regional equality of nephrological care within a country. A central task of these local registries is data collection, which would be very difficult to organize in a centralized manner in Europe because it requires close collaboration with the nephrology units, preferably in the local language. On the other hand, the decentralized data collection has led to heterogeneity in the data sets between registries.

### **What data do the national registries provide and what should they provide to the ERA-EDTA Registry?**

Many of the national registries provide the ERA-EDTA Registry with a core dataset with individual patient data, which enables international comparisons on essential epidemiological measures such as incidence and prevalence of kidney replacement therapy (KRT) including kidney transplantation rates and patient outcomes (ERA-EDTA Annual Report, please consult [www.era-edta-reg.org](http://www.era-edta-reg.org)). Some registries provide aggregate data rather than individual patient data, which gives basic information about KRT in the country.

In recent years, some registries have provided the ERA-EDTA Registry with an extended data set on clinical performance indicators, such as blood pressure and various laboratory variables. So far these data have been used in a few research projects [26, 27], but have not been presented in annual benchmarking reports. An aim for the future is that more countries could provide similar data on clinical performance indicators because this would enable comparison of achievements of treatment targets between countries and initially. This could be done in a representative sample of patients in order to enhance feasibility. The collaboration of the ERA-EDTA Registry and the national registries is clearly a necessary imperative to define the requested common parameters and explore the feasibility of such collection.

### **How can the ERA-EDTA Registry support the national registries?**

The ERA-EDTA Registry is dependent on well-functioning national and regional registries, which the ERA-EDTA Registry has supported, mainly by providing know-how. Since 2004, the Registry staff has organized almost 30 courses on clinical epidemiology and statistics in various parts of Europe. In addition, educational articles on epidemiological methods have been published in *Nephrology Dialysis Transplantation*, *Kidney International* and *Nephron Clinical Practice* (please consult [www.era-edta-reg.org](http://www.era-edta-reg.org)), and young researchers have been able to visit the Registry office in Amsterdam to work on research projects. A central aim must be to continue and develop this support to national registries as it helps improve the quality and enhance the conformity of the registries. A large amount of data is available in the national registries and it is important that this are analysed and reported by knowledgeable persons.

### **How to get the most out of the ERA-EDTA Registry data in order to improve nephrology in Europe?**

The data provided to and held by the Registry are needed to produce information to guide decisions about KRT in Europe.

Many fairly large differences have been observed between countries and regions, for example, regarding incidence and prevalence of KRT and regarding outcomes. This indicates that treatment policies are different. Efforts should be made to continue studying international differences and secular trends of KRT in Europe, and to attempt to find the reasons behind, and the consequences of, these differences for patient outcomes.

Registry data are commonly used for observational studies, which have known limitations when comparing effectiveness of treatments. There is a scarcity of high-quality evidence from randomized controlled trials (RCT) to guide treatment of dialysis and transplantation patients. The registry-based RCT is an innovative type of trial that uses registry data to identify the study subjects and to also collect outcome data [28]. For example, randomization protocols could be built into the database systems of renal registries. When a new patient who fulfils pre-specified inclusion criteria is reported to the registry, he would be randomized to an intervention arm and asked for consent. The intervention must carefully be selected and should be safe and inexpensive, for example, comparing two compositions of dialysate. As the inclusion criteria are usually less stringent than in conventional RCTs, the results may be more generalizable. As the follow-up data are obtained from registries, the cost is typically low. One successful example is a Swedish study on thrombus aspiration during myocardial infarction, which utilized a national registry to recruit and follow-up a large number of patients at low cost [29]. Registry-based RCTs could be performed in some national renal registries in collaboration with the ERA-EDTA Registry with especially high-quality data, potentially providing very valuable information that could change treatment policies in nephrology.

Extension of the present national and regional registry databases to include patients in CKD Stages 4–5 at national levels is ongoing. It is of crucial importance to stimulate such registries to collect similar data and use the same definitions so that valid comparisons can be made in the future. The ERA-EDTA Registry could serve as a facilitator in this.

## **EUROPEAN PAEDIATRIC NEPHROLOGY**

### **Past and present situation**

In the field of paediatric CKD, the European collaborative clinical research began 30 years ago with studies conducted by the 'European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood' in 25 centres from 8 different countries. The research done by this group showed that a low-protein diet did not affect growth and CKD progression, in contrast to proteinuria and blood pressure, which were strongly associated with disease progression [30]. The network then expanded to cover a wider clinical research area, especially in cardiorenal research. In 2009, the trial entitled 'Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Paediatric Patients' (ESCAPE) showed that strict blood pressure control under the 50th percentile slows down CKD progression during the 5-year follow-up [31]. The initial antiproteinuric response to the angiotensin-converting enzyme inhibitor therapy was predictive of a long-term renal survival

despite the occurrence of proteinuria rebound in half of the patients [32]. The ESCAPE Network now involves more than 55 centres in 16 European countries and serves as a collaborative platform for major ongoing paediatric projects, such as the ‘Cardiovascular Comorbidity in Children with Chronic kidney disease’ (4C) study [20, 33], the ‘HDF, Heart and Height’ (3H) study [34] and the ‘Antibiotic Prophylaxis and Renal Damage in Congenital Abnormalities of the Kidney and Urinary Tract’ (PREDICT) trial [ClinicalTrials.gov. Antibiotic Prophylaxis and Renal Damage In Congenital Abnormalities of the Kidney and Urinary Tract (PREDICT). Accessed at: <https://clinicaltrials.gov/ct2/show/NCT02021006>]. The findings of these projects concerning the management of how to improve the outcome of CKD have often been translated into clinical practice guidelines and implemented in routine clinical settings.

ESKD in children is a specific and extremely challenging condition that requires large-scale, prospective and cohort studies. In 2007, a new European registry of paediatric KRT, the European Society for Paediatric Nephrology (ESPN)/ERA-EDTA Registry, was launched. Since then, there has been a progressive increase in the number of European countries providing individual patient data to the Registry, with 38 countries—the whole of Europe—currently participating, covering a general population of more than 100 million children  $\leq 15$  years old. In recent years, the ESPN/ERA-EDTA Registry has successfully provided epidemiological data on incidence, prevalence, patient characteristics, KRT modalities and mortality in paediatric ESKD, along with relevant insights on cardiovascular risk, anaemia, nutrition and growth, dialysis and transplantation outcomes and rare kidney diseases [35]. The Registry has yielded several research findings directly relevant to patients, physicians and healthcare policy makers. For instance, among more than 6000 children who started dialysis in Europe in the period between 2000 and 2013, the mortality rate was 28 deaths per 1000 patients a year [36], more than 50 times higher than in the general paediatric population without kidney disease. The mortality rate in Europe is approximately half that reported in the USA by the United States Renal Data System (USRDS). Along with other international registries, the ESPN/ERA-EDTA Registry provided information on the largest cohort of children starting chronic dialysis in the neonatal period to date [37]. Given the medical and ethical challenges that arise from this rare clinical situation, this study provided data of critical importance showing much improved survival rates. This study will thus help clinicians to provide reliable prognoses and counselling to families. Another population-based Registry study on mortality of children on KRT in 32 European countries showed considerable variation in the country-specific mortality rate and demonstrated that most of this variance could be explained through disparities in public health expenditure, which was inversely associated with mortality risk [38]. In contrast to data for adult ESKD, increased healthcare spending promotes patient survival for the vulnerable population of children on KRT. Other relevant European collaborative efforts in paediatric ESKD include the ‘Cooperative European Paediatric Renal Transplant Initiative’ registry, a multinational paediatric kidney transplantation network [38], and the ‘European Paediatric

Dialysis Working Group’ [39]. In addition, many European paediatric nephrology centres participate in the global ‘International Paediatric Dialysis Network’ [40].

The main causes of CKD in children are Congenital Anomalies of Kidney and Urinary Tract and hereditary nephropathies. Continuous advances in cell and molecular biology techniques have revolutionized the knowledge, diagnosis and sometimes even prognosis of many inherited kidney diseases. As the rarity of these diseases creates a barrier for clinical research, several European networks, registries, disease-specific databases and bio-repositories have been created to overcome this issue, with major clinical inputs in genetic counselling, phenotypic refinement or genotype–phenotype association, prognostic value and eventually mechanistic insights leading to therapeutic approaches [41–44]. Furthermore, the European Rare Kidney Disease Reference Network, a consortium of 38 centres in 12 European countries, has been implemented to promote dissemination of knowledge, research and healthcare of rare kidney diseases (ERKNet. The European Rare Kidney Disease Reference Network. Accessed at: <https://www.erknet.org/index.php?id=home>).

### Future epidemiological and clinical research directions

There remain, however, many challenges and areas in which further epidemiological and clinical research is needed. There is an increasing emphasis on patient-centred outcome research in kidney disease but this remains an understudied area of paediatric nephrology (e.g. growth, pubertal development, fatigue, schooling, absenteeism, familial stress, quality of life and cognitive function). Accurate evaluation of social determinants of kidney health and integration of social aspects into clinical care to assist vulnerable families with broad social needs will represent an important step towards optimization of renal care and long-term outcomes for children with kidney diseases.

There is unmet need for new drug developments and high-quality clinical trials in paediatric nephrology research. Recently, the ‘connect4forchildren’ (C4C) initiative, a new paediatric multidisciplinary public–private consortium that includes academic and industry partners from 20 European countries, has been launched. This network, in which paediatric nephrology is represented, is a sustainable infrastructure created to facilitate the delivery of multinational clinical trials in children.

Finally, further studies are needed to improve patient outcomes after transitioning from paediatric to adult care. This is a key issue that should include standardized outcome measures and time intervals in order to evaluate successful transition processes during this high-risk period. This essential research will require active collaboration between paediatric and adult nephrologists and cohorts/registries that allow tracking lifelong psychosocial and medical outcomes of patients with kidney disease.

### ERBP

Clinical practice guidelines are designed to aid medical decision-making with the aim of improving care. In theory, their primary relevance and their quality rely on the rigour of the underlying development process. During the past decade,

**Table 2. EKHA actions**

Organization of an Annual European Kidney Forum in the European Parliament
Participation in the European Commission Conference on chronic diseases (2014)
Participation at the ASN 2015 Kidney Week stakeholder meeting to present EKHA as a possible model for collaboration across US kidney organizations
Participation in the European Commission Conference on food product improvement (2016)
Contribution to the event 'Improving organ donation and transplant across the EU: A cross-condition campaign' (2016)
Successful advocacy towards EU support of 'The Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes' project (2017–19)
Organization of multi-country survey on patient information (2017)
Contribution to EU Health Policy Platform (2017)
Development of a European Commission Thematic Network on the Employment of Patients with Chronic Diseases
Collaboration with the EU Joint Action CHRODIS on prevention and treatment of chronic diseases
Co-drafting of position statements calling for EU action on risk factors (salt, trans fatty acids, tobacco)
Participation in the drafting of a position statement of the European ADPKD Federation
Participation in the drafting of the EU Roadmap for Action on Food Product Improvement
Development of a thematic network on Improving Organ Donation and Transplantation in the EU for the EU Health policy Platform, resulting in practical recommendations on how to proceed for the European Commission (2019)

ADPKD, autosomal dominant polycystic kidney disease; CHRODIS, Chronic Diseases platform.

ERBP has substantially contributed to raising the standards for guideline developments in nephrology [45]. For every guideline, an extensive scoping process ensures overlap with other guideline bodies is avoided and important questions are addressed [46]. Decision-making is based on core outcomes that are critically important to all stakeholders, including patients, their clinicians and policymakers [46]. Evidence is comprehensively collected and critically appraised using Cochrane systematic review methodology [47]. Results are subsequently fed into an evidence-to-statement framework using grading of recommendations assessment, development and evaluation methodology, which requires guideline developers to carefully consider the anticipated effects of the options being considered, the certainty of the evidence for those effects and the costs and feasibility of options [48]. Patient involvement is encouraged throughout the development process and every step is executed transparently with clear documentation of judgements made. Guidelines are primarily published in *Nephrology Dialysis Transplantation*, but co-publication has occurred, depending on the topic [49], to reach a wider audience. National societies are involved in translating short versions of the guidelines into various languages, and dissemination is supported through presentations during national and international conferences.

In order for guideline development efforts to have significance, guideline recommendations must be correctly implemented. Unfortunately, merely developing and disseminating

clinical practice guidelines *per se* does not ensure their use in daily renal practice [50]. Several factors related to knowledge, attitude and behaviour affect their uptake. While ERBP has invested much effort in producing and disseminating trustworthy guidelines over the years, little is known about their implementation in practice and any resulting changes in the quality or outcomes of care.

International and European cohorts and registries with centre-level data could offer an opportunity for monitoring the downstream effects of guideline implementation on a national, European and international scale. Meaningful initiatives would require informed determination of quality indicators, covering structure, process and outcome [51, 52]. Such indicators may overlap with existing quality of care measures, already captured by existing datasets. One key future goal may require inclusion of new indicators as part of prospectively collected datasets in different cohorts and particularly in the ERA-EDTA Registry. To this end, the QUality European STUDies initiative [53]—taken over by the Registry almost 15 years ago—may be revitalized. For any such exercises to be informative, long-term involvement of experts in implementation science will be needed. Moreover, the promotion for a further and close collaboration between the two ERA-EDTA entities, the ERBP experts and the ERA-EDTA Registry staff, should become a key goal in the future.

## IMPORTANT TOPICS RELATED TO THE EU PRIORITIES

### Actions of European kidney health alliance (EKHA) in the last few years

The constantly rising number of patients with CKD and ESKD throughout Europe [54] consumes a considerable portion of healthcare budgets [55]. To maintain high-quality care, a coordinated European approach is needed, which implies organizational, educational and clinical action, as well as research planning.

The EKHA (<http://ekha.eu/>) unites all key European stakeholders in kidney care (patients, nurses, foundations and physicians), and proposes solutions at the EU policy level for the challenges posed by CKD, given that both the European Commission (EC) and European Parliament play vital roles in assisting national governments via a top-down approach. EKHA's work at the EU level is complemented by its contacts with kidney stakeholder groups at a national level.

With these aims in mind, in 2015, EKHA published its Recommendations for Sustainable Kidney Care (<http://www.renal.org/news-item/2015/05/26/ekha-recommendations-for-sustainable-kidney-care#sthash.331yWFTZ.dpbs>), which are centred around four main goals: (i) early detection and prevention of CKD and its progression; (ii) patient education and free choice of treatment; (iii) increasing access to transplantation; and (iv) treatment reimbursement strategies.

From 2016 on, EKHA undertook various initiatives to reach these aims (Table 2) and also organized yearly stakeholder for a in the European Parliament on these topics, in order to streamline activities, draw the attention of European and national

**Table 3. Preliminary results of the patient information questionnaire: percentage of patients perceiving that they did not receive enough information about a given approach**

Kidney Replacement or Conservative Therapies	FR	NL	SP	GR	SL	LI
Peritoneal dialysis	40	13	36	56	51	41
Home haemodialysis	56	50	48	74	79	65
Overnight haemodialysis	70	50	60	78	71	68
Kidney transplantation	15	17	35	44	30	14
Conservative care	77	64	70	56	90	33

Data are presented as percentage of total responders per country; FR: France; NL: the Netherlands; SP: Spain; GR: Greece; SL: Slovenia; LI: Lithuania. Data are preliminary and need more detailed analysis.

policy makers to these themes and include the involvement of Members of European Parliament to advance kidney-related matters.

Prevention is one of the cornerstones of good outcomes and quality of life, but it is underused. Current CKD cohorts and population-based cohorts will play a key role in identifying modifiable risk factors for disease onset and progression, as well as the best clinical practices. They also have the potential to point out barriers for successful implementation of primary and secondary prevention strategies. However, on average in Member States, only 3% of the health budget is spent on prevention. If part of healthcare financing were shifted from therapy to prevention, this would have a positive impact on total health expenditure [55]. CKD is linked to many other non-communicable diseases (NCDs), including diabetes mellitus, hypertension, cardiovascular disease, cancer and liver disease [55, 56]. Modifiable measures to reduce incidence of these NCDs are often related to lifestyle, diet and environment. Since the same risk factors are common to many chronic diseases, they require broader action than from the kidney community alone. In this context, EKHA also has a leading role in the European Chronic Diseases Alliance, an umbrella consortium representing 11 chronic disease organizations (<http://www.alliancechronicdiseases.org/home/>).

Not all renal replacement strategies are available to all valid candidates in all EU countries, and many patients are not well informed about their options, especially regarding home dialysis (both home haemodialysis and peritoneal dialysis), transplantation and comprehensive conservative (palliative) care [57]. EKHA confirmed this shortcoming via a recent survey among patients from several European countries (Table 3).

In addition, the Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes project, advocated by EKHA at EU level and funded by the Third Health Programme of the EU, started to assess KRT option availability and patient information at the beginning of 2017 [58]. Although Europe is one of the leading continents in transplantation [59], the differences in transplant rate and number of KRT patients living with a functioning transplant among countries suggests that there is room for improvement [59]. Likewise, the differences across Europe between living and deceased donation show that few countries are strong in both,

and that action should be undertaken to increase by country the types of donations that occur less [59].

### Future actions of the EKHA

Between 2009 and 2015 the EC ran an Action Plan to stimulate transplant activities throughout Europe. The plan was partially successful, but more work remains to be done. EKHA suggests that a second EU Action Plan could further boost European transplant activity, benefitting from the experience accumulated during the first programme. EKHA intends to become one of the catalysers for this, drawing from the EKHA ‘gift of life’ campaign launched in 2018 and the EC Thematic Network on transplantation, which will be developed by EKHA starting in 2019 ([https://www.eurekaalert.org/pub\\_releases/2018-12/e-epo121718.php](https://www.eurekaalert.org/pub_releases/2018-12/e-epo121718.php)).

The reimbursement of KRT is a matter of concern. There are substantial discrepancies in reimbursement of dialysis among Member States. The strategies that are least expensive to the health system (transplantation and home dialysis) are counterintuitively underrepresented throughout Europe. An additional matter of concern is the appearance of insufficiently evidenced but costly therapies for rare kidney disorders. All these factors need further research to guide policy action. Although the EU has funded several research projects where kidney disease was the main or an ancillary focus, it is time for a more coordinated action, in analogy with the ‘Kidney Innovation Accelerator (KidneyX)’ project run by the US Department of Health and Human Services, in collaboration with the American Society of Nephrology (<http://www.kidneyx.org/>).

The approach outlined by several Dutch stakeholder groups (‘Combating Kidney Disease—Nierziekte de baas’) may be taken as an example for the development of an action plan outline ([https://www.nierstichting.nl/media/filer\\_public/14/ef/14ef1c2a-73f9-40f6-b833-afbc940dbd41/onderzoeksagenda\\_nierziekte\\_de\\_baas\\_-\\_gezamenlijke\\_agenda\\_oi\\_2017.pdf](https://www.nierstichting.nl/media/filer_public/14/ef/14ef1c2a-73f9-40f6-b833-afbc940dbd41/onderzoeksagenda_nierziekte_de_baas_-_gezamenlijke_agenda_oi_2017.pdf)). This framework has four major foci: the much neglected prevention and quality of life aspects of kidney disease, and the innovatory fields of personalized and regenerative medicine. This research framework strives for more sustainable and less costly solutions, while also considering the scarcity of evidence-based and health-economic analyses in nephrology [60, 61].

Personalized medicine covers not only tailored treatment for specific disorders or mechanisms (e.g. the multiple diverging factors at play in kidney fibrosis and progression of CKD) or targeted drug administration depending on the individual sensitivity, but also, as health illiteracy is frequent among CKD patients [62], education (with specific approaches and attention for the less educated or low income groups as well as ethnic minorities).

Regenerative medicine programmes focus on bioartificial organs (the combination of polymers and cells), organoids and stem cells [63]. Research might also be guided towards often neglected but troublesome problems for patients, such as itching, cognitive dysfunction or pain, focusing on patient-centred outcomes, such as those defined by the Standardised Outcomes in Nephrology (SONG) initiative (<http://songinitiative.org/>).

Programmes supporting KRT strategies, which favour better quality of life, are encouraged with focus on projects promoting and improving transplantation and home therapies. EKHA will target the hot topics that should be supported in the future by nephrologists according to the EU needs and will work in collaboration with ERA-EDTA to reach these goals.

## IMPORTANT CLINICAL RESEARCH TOPICS IN EUROPE

### Western Europe

Beyond registries and cohort studies, there are broadly speaking three types of health services research—clinical trials, big data and qualitative (exploratory) research. While there is a great deal of interesting and important qualitative research going on to explore ‘why’ things happen using non-numeric data in Western Europe, qualitative research groups in nephrology in Western Europe and indeed globally are less well established than in other research areas. Furthermore, results tend to be more hypothesis/logic generating and more context-specific than from other research areas. The committee therefore agreed that the potential for qualitative research to be world leading, practice changing and with high impact is less clear at the moment, and for that reason prefers focusing on existing strengths and opportunities in clinical trials and big data research.

The conclusions below are based on responses to the following questions from four to six experts in each of these two research areas in Western Europe:

Q1. In what way do you think the region covered by ERA-EDTA is in a unique position to lead the world in (clinical trials/big data research) (e.g. existing healthcare infrastructure, information governance and existing research networks)?

Q2. Can you give 2–3 examples of world-leading (clinical trials/big data research) conducted in the region covered by the ERA-EDTA in the last 5 years?

Q3. What do you think would be the key 2–3 things that the ERA-EDTA could do to promote world-leading (clinical trials/big data research) in Europe?

**Clinical trials.** A number of major, practice-changing, investigator-initiated trials have been led by researchers in Western Europe in recent years. These have been in the areas of vasculitis, membranous glomerulopathy, renal vascular disease and cholesterol lowering, and demonstrate that it is possible to create a network of renal units across Europe to recruit sufficient numbers to trials. On the contrary, respondents raised concerns about Western Europe’s ability to recruit to trials and especially industry-led trials.

Existing collaborations and cultural similarities, along with the harmonized regulatory process, should facilitate delivery of large trials across the continent. It was felt that the role of the ERA-EDTA should be ‘concertation’, that is, bringing academics and other partners together to define the best questions, methodology and clinical trial processes. This could be achieved in a number of ways:

- establishing a network of centres willing to do clinical trials and provide methodological support;

- creating registers of patients willing to be contacted about clinical trials relevant to them;
- providing educational courses that train investigators to design and execute trials;
- funding clinical trial fellowships to attach research leaders of the future to developing projects to help grow the expertise;
- improving the management/presentation/discussion of trial results at the ERA-EDTA annual conference;
- arranging standalone workshops to examine specific topics such as end-point design;
- interfacing with regulatory agencies, research funders, industry and patients to design and deliver trials that are needed to inform clinical practice;
- fostering closer working with other specialities to reduce working in a condition-specific silo—some of the future drugs for kidney diseases are likely to come from developments in oncology;
- creating a culture of offering patients RCT where evidence is lacking (similar to oncology); and
- using the ERBP to encourage inclusion in clinical trials, for example, avoiding expert recommendations when a clinical trial could be done.

It was felt that the ISN had successfully established a clinical trials infrastructure Advancing Clinical Trials (ACT), and those lessons could be learned from that while avoiding duplication.

**Big data.** Traditionally, Scandinavian countries and those with nationalized healthcare systems provide an excellent opportunity to use routine health and social care records to describe associations between practices and outcomes in general, un-selected, populations. There are also, however, some potentially useful general population-level linked datasets in Spain, France and Switzerland. The new general data protection regulation makes the rules clearer and more consistent and makes it less difficult to establish a lawful basis for academics to process personal data for clinical research. There is also heterogeneity in clinical practice within Western Europe that provides an excellent opportunity to use observational data to explore the consistency of associations and even the causal nature of relationships.

It should also be recognized that big data research extends far beyond linking health and social care records for research; it can include data from scans, free text and wearable devices, genomics, proteomics, metabolomics and exposomics.

Both types of big data research can involve the use of prior hypotheses and statistical models or agnostic approaches such as machine learning and artificial intelligence. There is certainly world-leading statistical expertise in Western Europe with considerable potential to apply novel methods of analysis to nephrology if interesting research questions and datasets can be presented to them. There is less of a track record of machine learning and artificial intelligence in nephrology in Western Europe, but the methodological expertise undoubtedly exists.

It was felt that the ERA-EDTA could support the development of world-leading big data research in a number of ways:

- establishing a network of researchers with awareness of and access to routine healthcare databases in different



**Table 4. Research plan with eight hot topics to stimulate research collaboration and grant applications in Europe**

(i)	To conduct collaborative research designed to uncover non-invasive diagnostic tests or new predictive markers for kidney disease complications, aimed to further improve the classification and prognosis of kidney diseases based on large-scale omics data using available European patient cohorts
(ii)	To review the feasibility and relevance of the development of CKD Stages 4–5 registries based on on-going experiences at national level and explore if and how these can be brought together for quality assurance and research at the European level
(iii)	To plan a successful transition process from paediatric to adult care of CKD by active collaboration between paediatric and adult nephrologists and cohorts/registries
(iv)	To reinforce the collaboration between the ERBP experts and ERA-EDTA Registry staff in order to extend the number of indicators to include the thresholds of the ERBP recommendations as part of prospectively collected datasets stemming from different national or regional cohorts and from the ERA-EDTA Registry and to adapt those as new recommendations are published
(v)	To continue supporting EKHA with its established links with the EU, allowing it to target key nephrological topics prioritized by patients and professionals, such as better quality of life in KRT patients and improving kidney transplantation and home treatment modalities, which also include regenerative and personalized medicine
(vi)	To support the development of world-leading big data research in a number of ways including the creation of data networks and the development of educational programmes
(vii)	To help the Eastern European nephrology community to optimize patient care and patient-oriented research in their countries by increasing public awareness, encouraging/supporting clinical nephrology and epidemiology studies and improving training in nephrology
(viii)	To create a European network of kidney units in order to extend our understanding of AKI progression and complications, including transition of AKI to CKD

countries to facilitate international studies that validate findings and mine heterogeneity;

- arranging standalone workshops that bring together nephrologists and methodologists to examine specific topics;
- facilitating the training of the future big data researchers through this network and statistical/epidemiological training courses that take things beyond the introductory level;
- encouraging the adoption of information standards as part of renal IT systems to improve data quality for clinical care and research;
- educating the public, policy makers and funders on the importance of kidney disease and in particular the personal and societal burden of ESKD, which often gets overlooked due to its infrequent occurrence;
- dedicating a session at the ERA-EDTA conference to innovations in big data analysis;
- working out recommendations for which parameters would be essential to be included in kidney big databases; and
- stimulating health-economically oriented kidney research (nephrology traditionally being not being keen to invest in this area, whereas nephrology is consuming proportionally large chunks of health care budgets).

### Eastern Europe

The problems cited below and suggestions for solutions improvements to these problems are not specific to the Eastern European countries. However, these problems may be more prominent in this region of Europe.

- Unique features of nephrological problems in Eastern Europe. Overall, Eastern Europe includes 10 countries (Belarus, Bulgaria, Czech Republic, Hungary, Moldova, Poland, Romania, the Russian Federation, Slovakia and Ukraine). According to some other sources, additional countries [Albania, Bosnia-Herzegovina, Croatia, Estonia,

Latvia, Lithuania, Montenegro, Serbia, Former Yugoslav Republic of Macedonia (FYROM), Georgia, Armenia, Azerbaijan and Turkey] are also classified as being a part of Eastern Europe. To the best of our knowledge, extensive epidemiologic data on the prevalence of CKD stage in Eastern Europe in the ERA-EDTA Registry are available only on CKD Stages 5D and 5T [64]. Only limited data are available on the prevalence of CKD Stages 3–5 not yet on dialysis, which was considered to be higher than in Western Europe [65]. Although there are no comparative trials, it may be speculated, or largely accepted, that this part of Europe may differ from the western part in:

- limited funds for both healthcare services and projects;
- less public awareness about chronic diseases, which also means less attention paid to CKD;
- difficult cooperation with health care authorities;
- country-specific health problems (i.e. Balkan nephropathy, more frequent obesity and diabetes, possibly worse control of diabetes and hypertension, air pollution and deviations from recommended diet);
- low transplantation rates in many, but not all, of these countries [59]; and
- targets/feasibility of these targets.

Since all of the above-mentioned difficulties have potential negative effects on various aspects (identification, prevention and treatment) of CKD, actions to be taken may or should target to improve each of these items. Some of these actions are more easily achievable (i.e. increasing public awareness, encouraging-supporting studies on clinical nephrology and epidemiology, improving nephrology training), whereas others are more difficult to achieve (i.e. limited funds and lower standards for healthcare and problematic cooperation with authorities). Suggestions by ERA-EDTA and/or EKHA may help contribute to convincing authorities to make changes, at least in some countries.

**Target population.** Since CKD is very frequent (mostly affecting 13–15% of the population of the whole country) and a major cause of morbidity and mortality in addition to having a huge economic burden, it should be very well understood by:

- healthcare authorities;
- the public; and
- medical professionals, including general practitioners and specialists with a high probability of seeing CKD patients (i.e. general internists, cardiologists, diabetologists, endocrinologists, urologists, oncologists, hepatologists, vascular and cardiac surgeons and neurologists).

Thus, the first step should be increasing awareness, and convincing these parties of the importance of CKD.

**Detection of CKD.** The extent of this problem may differ across countries; therefore, epidemiologic studies for each of these countries should be encouraged by healthcare authorities, national nephrology societies and ERA-EDTA. Conducting studies on the economic burden of CKD (by medical professionals as well as economists) may help convince authorities to pay more attention to CKD. Therefore, obtaining current official statistics from governmental bodies on both medical and economical aspects of CKD may be useful to identify the extent of the problem.

**Prevention and treatment.** Authorities should be convinced of the importance of CKD and informed that treatment of ESKD is extremely expensive, whereas prevention is relatively inexpensive and simple.

Pilot and inexpensive projects concerning conservative management of CKD [such as decreasing salt intake, adopting a healthy lifestyle, adequate treatment of diabetes and hypertension, preferably using angiotensin-converting-enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs)] might be initiated in small areas of the region. Based on early experience and lessons learned from these pilot initiatives, major country-wide long-term projects could then be conducted. Close collaboration with ERA-EDTA may be useful for better defining policies to address these problems.

## SUMMARY AND RESEARCH PROPOSALS

Epidemiological and clinical research and public policy is generally considered to be comprehensive and successful in Europe, in terms of prosperity and broad coverage. ERA-EDTA is playing a key role in the field of nephrology research. However, the NPPC members feel that additional efforts can help to further improve the current situation and translate into public policy. The NPPC reached the conclusion that a research plan with restricted key topics is needed. This project would be supported by ERA-EDTA in the coming 5 years. Beyond the support to build RCTs, which is currently operated by ERA-EDTA, after internal discussion and external consultation of the ERA-EDTA council, eight projects were selected (Table 4).

## CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format. Dr.

Stevens reports personal fees from Vifor Pharma, grants from Alexion, Vifor Pharma, Chiesi, LNC Medical, personal fees from Alexion, outside the submitted work. Dr Bruchfeld reports grants from Astra-Zeneca, honoraria from Chemocentryx, MSD/Merck, participation in a company sponsored speaker's bureau for AbbVie, MSD/Merck, Sanofi-Genzyme, outside the submitted work. The other authors have no financial interest to declare relevant to this work.

## REFERENCES

1. Zoccali C, Arici M, Blankestijn PJ *et al.* The ERA-EDTA today and tomorrow: a progress document by the ERA-EDTA Council. *Nephrol Dial Transplant* 2018; 33: 1077–1082
2. 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
3. Raum E, Rothenbacher D, Low M *et al.* Changes of cardiovascular risk factors and their implications in subsequent birth cohorts of older adults in Germany: a life course approach. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 809–814
4. Cirillo M, Terradura-Vagnarelli O, Mancini M *et al.* Cohort profile: The Gubbio Population Study. *Int J Epidemiol* 2014; 43: 713–720
5. Diercks GF, Janssen WM, van Boven AJ *et al.* Rationale, design, and baseline characteristics of a trial of prevention of cardiovascular and renal disease with fasinopril and pravastatin in nonhypertensive, nonhypercholesterolemic subjects with microalbuminuria (the Prevention of Renal and Vascular Endstage Disease Intervention Trial [PREVEND IT]). *Am J Cardiol* 2000; 86: 635–638
6. McIntyre NJ, Fluck RJ, McIntyre CW *et al.* Risk profile in chronic kidney disease stage 3: older versus younger patients. *Nephron Clin Pract* 2011; 119: c269–c276
7. Dunder K, Lind L, Zethelius B *et al.* Evaluation of a scoring scheme, including proinsulin and the apolipoprotein B/apolipoprotein A1 ratio, for the risk of acute coronary events in middle-aged men: Uppsala Longitudinal Study of Adult Men (ULSAM). *Am Heart J* 2004; 148: 596–601
8. Seiler S, Rogacev KS, Roth HJ *et al.* Associations of FGF-23 and sKlotho with cardiovascular outcomes among patients with CKD stages 2–4. *Clin J Am Soc Nephrol* 2014; 9: 1049–1058
9. Landray MJ, Thambyrajah J, McGlynn FJ *et al.* Epidemiological evaluation of known and suspected cardiovascular risk factors in chronic renal impairment. *Am J Kidney Dis* 2001; 38: 537–546
10. van Zuilen AD, van der Tweel I, Blankestijn PJ *et al.* Multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners. Design of The MASTERPLAN Study [ISRCTN73187232]. *Trials* 2006; 7: 8
11. Marks A, Fluck N, Prescott GJ *et al.* Definitions of progression in chronic kidney disease—predictors and relationship to renal replacement therapy in a population cohort with a 6 year follow-up. *Nephrol Dial Transplant* 2014; 29: 333–341
12. Kronenberg F, Kuen E, Ritz E *et al.* Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. *J Am Soc Nephrol* 2000; 11: 105–115
13. Moranne O, Froissart M, Rossert J *et al.* Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009; 20: 164–171
14. Jager KJ, Ocal G, Drechsler C *et al.* The EQUAL study: a European study in chronic kidney disease stage 4 patients. *Nephrol Dial Transplant* 2012; 27 (Suppl 3): iii27–iii31
15. Eckardt KU, Barthlein B, Baid-Agrawal S *et al.* The German Chronic Kidney Disease (GCKD) study: design and methods. *Nephrol Dial Transplant* 2012; 27: 1454–1460
16. Hoefield RA, Kalra PA, Baker P *et al.* Factors associated with kidney disease progression and mortality in a referred CKD population. *Am J Kidney Dis* 2010; 56: 1072–1081
17. Stengel B, Combe C, Jacquelinet C *et al.* The French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study. *Nephrol Dial Transplant* 2014; 29: 1500–1507

18. Martinez-Castelao A, Gorriz JL, Portoles JM *et al.* Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. *BMC Nephrol* 2011; 12: 53
19. Navis GJ, Blankestijn PJ, Deegens J *et al.* The Biobank of Nephrological Diseases in the Netherlands cohort: the String of Pearls Initiative collaboration on chronic kidney disease in the university medical centers in the Netherlands. *Nephrol Dial Transplant* 2014; 29: 1145–1150
20. Schaefer F, Doyon A, Azukaitis K *et al.* Cardiovascular phenotypes in children with CKD: the 4C study. *Clin J Am Soc Nephrol* 2017; 12: 19–28
21. Nisula S, Kaukonen KM, Vaara ST *et al.* Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. *Intensive Care Med* 2013; 39: 420–428
22. Geri G, Stengel B, Jacquelinet C *et al.* Prediction of chronic kidney disease after acute kidney injury in ICU patients: study protocol for the PREDICT multicenter prospective observational study. *Ann Intensive Care* 2018; 8: 77
23. Collaborative ST. Outcomes After Kidney injury in Surgery (OAKS): protocol for a multicentre, observational cohort study of acute kidney injury following major gastrointestinal and liver surgery. *BMJ Open* 2016; 6: e009812
24. Rondeau E, Faguer S, Robert T. Advocacy for a European network of renal intensive care units. *Nephrol Dial Transplant* 2019; doi: 10.1093/ndt/gfy398
25. Mehta RL, Cerdá J, Burdmann EA *et al.* International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* 2015; 385: 2616–2643
26. Helve J, Kramer A, Abad-Diez JM *et al.* Factors associating with differences in the incidence of renal replacement therapy among elderly: data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2018; 33: 1428–1435
27. Ceretta ML, Noordzij M, Luxardo R *et al.* Changes in co-morbidity pattern in patients starting renal replacement therapy in Europe-data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2018; 33: 1794–1804
28. Li G, Sajobi TT, Menon BK *et al.* Registry-based randomized controlled trials – what are the advantages, challenges, and areas for future research? *J Clin Epidemiol* 2016; 80: 16–24
29. Fröberg O, Lagerqvist B, Olivecrona G *et al.* Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013; 369: 1587–1597
30. Wingen AM, Fabian-Bach C, Schaefer F *et al.*; European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. *Lancet* 1997; 349: 1117–1123
31. ESCAPE Trial Group, Wühl E, Trivelli A, Picca S *et al.* Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009; 361: 1639–1650
32. van den Belt SM, Heerspink HJL, Gracchi V *et al.*; ESCAPE Trial Group. Early proteinuria lowering by angiotensin-converting enzyme inhibition predicts renal survival in children with CKD. *J Am Soc Nephrol* 2018; 29: 2225–2233
33. Harambat J, Kunzmann K, Azukaitis K *et al.* Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease. *Kidney Int* 2017; 92: 1507–1514
34. Shroff R, Bayazit A, Stefanidis CJ *et al.* Effect of haemodiafiltration vs conventional haemodialysis on growth and cardiovascular outcomes in children – the HDF, heart and height (3H) study. *BMC Nephrol* 2018; 19: 199
35. Harambat J, Bonthuis M, Groothoff JW *et al.* Lessons learned from the ESPN/ERA-EDTA Registry. *Pediatr Nephrol* 2016; 31: 2055–2064
36. Chesnaye NC, Schaefer F, Groothoff JW *et al.* Mortality risk in European children with end-stage renal disease on dialysis. *Kidney Int* 2016; 89: 1355–1362
37. van Stralen KJ, Borzych-Duzalka D, Hataya H *et al.* Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. *Kidney Int* 2014; 86: 168–174
38. Höcker B, Schneble L, Murer L *et al.* Epidemiology of and risk factors for BK polyomavirus replication and nephropathy in pediatric renal transplant recipients: an international CERTAIN Registry study. *Transplantation* 2018; doi: 10.1097/TP.0000000000002414
39. Shroff R, Stefanidis CJ, Askiti V *et al.* Encapsulating peritoneal sclerosis in children on chronic PD: a survey from the European Paediatric Dialysis Working Group. *Nephrol Dial Transplant* 2013; 28: 1908–1914
40. Rees L, Azocar M, Borzych D *et al.* Growth in very young children undergoing chronic peritoneal dialysis. *J Am Soc Nephrol* 2011; 22: 2303–2312
41. Ashton EJ, Legrand A, Benoit V *et al.* Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies. *Kidney Int* 2018; 93: 961–967
42. Trautmann A, Schnaidt S, Lipska-Ziętkiewicz BS *et al.* Long-term outcome of steroid-resistant nephrotic syndrome in children. *J Am Soc Nephrol* 2017; 28: 3055–3065
43. Mandrile G, van Woerden CS, Berchiolla P *et al.* Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. *Kidney Int* 2014; 86: 1197–1204
44. Ebner K, Feldkoetter M, Ariceta G *et al.* Rationale, design and objectives of ARegPKD, a European ARPKD registry study. *BMC Nephrol* 2015; 16: 22
45. Nagler EV, Webster AC, Bolognani D *et al.* European Renal Best Practice (ERBP) Guideline development methodology: towards the best possible guidelines. *Nephrol Dial Transplant* 2014; 29: 731–738
46. Van der Veer SN, Haller MC, Pittens C *et al.* Setting priorities for optimizing vascular access decision making – an international survey of patients and clinicians. *PLoS ONE* 2015; 10: e0128228
47. Tong A, Craig JC, Nagler EV *et al.*; for the SONG Executive Committee and the European Renal Best Practice Advisory Board, SONG Executive Committee. Composing a new song for trials: the Standardized Outcomes in Nephrology (SONG) initiative. *Nephrol Dial Transplant* 2017; 32: 1963–1966
48. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2011. <https://training.cochrane.org/handbook> (19 April 2019, date last accessed)
49. Spasovski G, Vanholder R, Allolio B *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 2014; 170: G1–47
50. Van der Veer S, Tomson CRV, Jager KJ *et al.* Bridging the gap between what is known and what we do in renal medicine: improving implementability of the European Renal Best Practice guidelines. *Nephrol Dial Transplant* 2014; 29: 951–957
51. Van der Veer SN, Van Biesen W, Couchoud C *et al.* Measuring the quality of renal care: things to keep in mind when selecting and using quality indicators. *Nephrol Dial Transplant* 2014; 29: 1460–1467
52. Liabeuf S, Van Stralen KJ, Caskey F *et al.* Attainment of guideline targets in EURODOPPS haemodialysis patients: are differences related to a country's healthcare expenditure and nephrologist workforce? *Nephrol Dial Transplant* 2017; 32: 1737–1749
53. Jager KJ, Zoccali C. QUality European STudies (QUEST)—a step forward in the quality of RRT care. *Nephrol Dial Transplant* 2005; 20: 2005–2006
54. Pippas M, Jager KJ, Kramer A *et al.* The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2016; 31: 831–841
55. Vanholder R, Annemans L, Brown E *et al.* Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol* 2017; 13: 393–409
56. Kerr M, Bray B, Medcalf J *et al.* Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant* 2012; 27: iii73–iii80
57. Van Biesen W, van der Veer SN, Murphey M *et al.* Patients' perceptions of information and education for renal replacement therapy: an independent survey by the European Kidney Patients' Federation on information and support on renal replacement therapy. *PLoS ONE* 2014; 9: e103914
58. Jager KJ, Stel VS, Branger P *et al.* The effect of differing kidney disease treatment modalities and organ donation and transplantation practices on health expenditure and patient outcomes. *Nephrol Dial Transplant* 2018; 33: 560–562
59. Vanholder R, Stel VS, Jager KJ *et al.* How to increase kidney transplant activity throughout Europe – an advocacy review by the European Kidney Health Alliance. *Nephrol Dial Transplant* 2019; doi: 10.1093/ndt/gfy390
60. Maini R, Wong DB, Addison D *et al.* Persistent underrepresentation of kidney disease in randomized, controlled trials of cardiovascular disease in the contemporary era. *J Am Soc Nephrol* 2018; 29: 2782–2786

61. Vanholder R, Van Laecke S, Glorieux G *et al.* Deleting death and dialysis: conservative care of cardio-vascular risk and kidney function loss in chronic kidney disease (CKD). *Toxins* 2018; 10: pii: E237
62. Taylor DM, Fraser SDS, Bradley JA *et al.* A systematic review of the prevalence and associations of limited health literacy in CKD. *Clin J Am Soc Nephrol* 2017; 12: 1070–1084
63. van Gelder MK, Mihaila SM, Jansen J *et al.* From portable dialysis to a bio-engineered kidney. *Expert Rev Med Devices* 2018; 15: 323–336
64. Kramer A, Pippias M, Noordzij M *et al.* The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. *Clin Kidney J* 2018; 11: 108–122
65. Süleymanlar G, Utaş C, Arinsoy T *et al.* A population-based survey of Chronic Renal Disease In Turkey—the CREDIT study. *Nephrol Dial Transplant* 2011; 26: 1862–1871

Received: 1.4.2019; Editorial decision: 4.4.2019