

# Common Elements in Rare Kidney Diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference



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Rare kidney diseases encompass at least 150 different conditions, most of which are inherited. Although individual rare kidney diseases raise specific issues, as a group these rare diseases can have overlapping challenges in diagnosis and treatment. These challenges include small numbers of affected patients, unidentified causes of disease, lack of biomarkers for monitoring disease progression, and need for complex care. To address common clinical and patient issues among rare kidney diseases, the KDIGO Controversies Conference entitled, *Common Elements in Rare Kidney Diseases*, brought together a panel of multidisciplinary clinical providers and patient advocates to address five central issues for rare kidney diseases. These issues encompassed diagnostic challenges, management of kidney functional decline and progression of chronic kidney disease, challenges in clinical study design, translation of advances in research to clinical care, and provision of practical and integrated patient support. Thus, by a process of consensus, guidance for

addressing these challenges was developed and is presented here.

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The definition of rare diseases varies across the world. In Europe, a disease or disorder is defined as rare when the prevalence is <1 in 2000 individuals; whereas in the USA, the designation of rare disorder applies when <200,000 Americans are affected. Rare kidney diseases encompass ≥ 150 different conditions. The majority are inherited,<sup>1</sup> while others, such as the primary glomerulonephritides, have complex etiologies. For inherited kidney disorders, diagnosis, management, and treatment are complex, especially when they are associated with multisystem complications. Patients often spend years visiting multiple health care providers before receiving an accurate diagnosis. Advances in kidney replacement therapy and its increased access allow prolonged patient survival, yet often with a poor quality of life. In particular, children born with severe congenital nephropathies face a high likelihood of altered physical, cognitive, and psychosocial development.<sup>2</sup>

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Therapeutic advances in rare kidney diseases have been hindered by several factors, including unresolved genetic defects, lack of biomarkers to monitor disease progression, heterogeneous clinical phenotypes, and outdated diagnostic classifications that do not reflect underlying pathophysiological mechanisms.<sup>1,3</sup> Many initiatives have focused on rare kidney diseases, and regulations have been created to promote the development of therapies, organize optimal health care systems, and encourage research. Patient organizations have also taken a leading role in these matters. Together, technological advances and organized advocacy have helped enhance understanding of the clinical, genetic, and mechanistic issues in many inherited kidney disorders.

To address common clinical and patient issues among rare kidney diseases, Kidney Disease: Improving Global Outcomes (KDIGO) convened a global, multidisciplinary Controversies Conference to address 5 central issues in rare kidney diseases: diagnostic challenges, management of kidney functional decline and progression of chronic kidney disease (CKD), challenges in clinical study design, translation of advances in research to clinical care, and provision of practical and integrated patient support. The deliberations from this conference are now summarized here with additional ancillary information available online at <http://kdigo.org/conferences/common-elements/>.

## DIAGNOSTIC CHALLENGES

The growing use of next-generation sequencing techniques is expected to increase diagnostic accuracy for rare kidney diseases, help decipher the molecular mechanism of disease, facilitate genetic counseling, and offer possibilities for carrier testing.<sup>4</sup> The burgeoning wealth of genetic and molecular information has evoked new challenges, such as the need for more sophisticated bioinformatic analytic tools and algorithms. Additionally, the changes in molecular techniques and interpretations are creating novel ethical, legal, and social challenges.<sup>5,6</sup> Even for well-defined disorders, barriers to generalized use of genetic testing may persist due to high cost and long turnaround times, insufficient genetic literacy, assumptions that establishing a genetic diagnosis will impact (or not) clinical management, and differences in accessibility and insurance coverage.<sup>7</sup> These factors are particularly challenging in settings with limited resources. Policies to promote clinically relevant genetic testing and adequate integration of genetic information are needed.<sup>8</sup>

### Genetic testing in diagnosis

In diagnosing rare kidney diseases, careful phenotyping encompassing physical examination, patient history, biochemical analysis, and pathology, is essential. However, genetic testing has an increasing role in the diagnostic armamentarium:<sup>9</sup> for example, confirming clinical diagnosis, establishing inheritance patterns, differentiating heterogeneous disorders, determining appropriate treatment, guiding decisions about family planning, determining the cause of unexplained familial renal disorders, identifying risk factors

for recurrence in kidney transplantation, evaluating family members' suitability for kidney donation, and prompting evaluation for extrarenal features (Table 1).<sup>10–12</sup>

Genetic testing can play an essential role in evaluating children and young adults and thus should be considered when the clinical phenotype does not suggest a clear diagnosis.<sup>9</sup> The role of genetic testing in adults is generally more limited. However, for those suspected to have a genetic disease, such as X-linked Alport syndrome, testing can confirm diagnosis and establish inheritance patterns.<sup>13</sup> In addition, some patients view genetic testing as important for family planning, understanding their disease, and contributing personally to disease research. Therefore, practitioners who treat adults with rare kidney diseases should be knowledgeable about the modalities of genetic testing, and all patients should be informed that genetic testing is available when applicable.

For some patients, such as those with nephrotic syndrome and urogenital malformations, genetic testing can be justified based on minimal phenotypic information. Testing should be considered when the index of suspicion for a given disease is high and the patient would otherwise be exposed to invasive procedures, or to ineffective or costly treatment with side effects (e.g., children with steroid-resistant nephrotic syndrome).<sup>14</sup> The decision to perform genetic testing should be collaborative, with input from the nephrologist, clinical geneticist, genetic counselor, genetic lab specialist, the primary care physician, the patient, and his or her caregivers. With decreasing turnaround times, genetic testing is increasingly becoming an important contributor to clinical decision making.<sup>9</sup>

### Presymptomatic genetic screening

In the context of genetic disorders, nephrologists should serve as advocates for patients and their children, always respecting each patient's religious beliefs, cultural perspectives, and autonomy in decision making. Patients with any genetic diagnosis should be counseled about reproductive options, including germ cell donation, prenatal diagnosis, and preimplantation genetic diagnosis.<sup>15</sup> Nephrologists should collaborate with trained clinical geneticists and genetic counselors to provide information and recommendations. In children at risk for a dominantly transmitted disorder, such as autosomal dominant polycystic kidney disease, presymptomatic genetic testing should be considered only if obtaining the information has potential benefits for managing emergent symptoms or preventing complications.<sup>12</sup> When there are no prevention or treatment options available, many factors should be considered before proceeding with testing, including type of disease, age and maturity of the child, and family's cultural background and resources. All patients should be counseled regarding the ways in which a genetic diagnosis could hinder their ability to obtain health or other types of insurance.<sup>16</sup>

### Implementing access to diagnostic services in low-income regions

Access to clinical expertise and genetic testing in resource-poor countries may be limited. However, telemedicine can

**Table 1 | Sample case vignettes****Diagnostic challenges: Usefulness of genetic testing**

An 8-month-old girl presents with failure to thrive, polyuria, polydipsia, and frequent vomiting. She is clinically dehydrated. Her height is at the 5th percentile. Normal birth weight is mentioned. Blood analysis reveals hypokalemia, metabolic acidosis, hypophosphatemia, and hypocalcemia. Urinalysis reveals loss of amino acids, potassium, bicarbonate, calcium, phosphate, glucose, and  $\beta_2$ -microglobulin. There is no family history of kidney disease.

The most frequent cause of renal Fanconi syndrome in children is cystinosis. However, other metabolic diseases (tyrosinemia, galactosemia, glycogen storage diseases), Wilson disease, Dent disease and Lowe syndrome should also be considered in the differential diagnosis of the renal Fanconi syndrome. Some cystinosis patients initially present with atypical manifestations, such as metabolic alkalosis, and are initially diagnosed as Bartter syndrome or nephrogenic diabetes insipidus. An early start of cysteamine therapy, which acts by lowering the intracellular accumulation of cystine, has an important impact on the clinical outcome of patients with cystinosis, justifying an early diagnosis. The current gold standard for the diagnosis of cystinosis is the detection of elevated cystine levels in white blood cells. Molecular testing of the *CTNS* gene is well-established and reveals 95% of disease-causing mutations. (See Langman et al.<sup>10</sup>)

**Challenges of transitioning children**

A 16-year-old patient with a diagnosis of classic Bartter syndrome (mutations in *CLCNKB*) presents with cramps and muscle weakness. He is clinically dehydrated. Kidney function is normal, but potassium level is at 2.0 mmol/l, magnesium is 0.4 mmol/l, bicarbonate 35 mmol/l. The patient was followed at the tertiary hospital until age 13 years, but he was then lost for follow-up. He is now living with his mother and has difficulties in school. He knows about the potassium and magnesium supplements, but he does not like to take so many pills. Indomethacin and spironolactone were used in the past but they were stopped a few years ago. The patient feels generally fine and does not understand why he is so weak.

Individual management of patients with salt-losing tubulopathies has been advocated, with particular emphasis on education about the disease mechanism and importance of salt repletion and supplemental therapy. Side effects should be discussed, in particular abdominal pain and diarrhea induced by magnesium salts and gastric irritation from potassium chloride. Physicians should also be attentive to other factors that could hamper adherence to the supplements, including socioeconomic difficulties, lack of reimbursement, transition period to adulthood, work conditions, and such. The transition phase between pediatric and adult care is particularly important. (See Blanchard et al.<sup>11</sup>)

**Utility of Specialized Centers**

An 8-month-old child presents to the emergency department with seizures. The clinical exam shows patches of light-colored skin on the trunk. Computed tomographic scanning reveals multiple calcified subependymal nodules in the brain. A diagnosis of tuberous sclerosis is made. Subsequent investigations involve specialized neurology, dermatology, nephrology, ophthalmology, cardiology, and pulmonary consultations. The father had a history of childhood seizures. He also presented adenoma sebaceum lesions along the nose, an ungula fibroma on the left foot, an area of pigmented, thick leathery skin on the lower back, and subependymal nodules on the brain computed tomographic scan.

Current consensus supports the value of a multidisciplinary team approach to care, with all relevant specialties provided in 1 center or clinic to patients presenting with multisystemic disorders, including tuberous sclerosis and autosomal dominant polycystic kidney disease. These benefits include access to educational material about clinical manifestations, the opportunity to meet other patients with the same rare conditions, information about current research studies, and, most importantly, substantial shortening of the odyssey incurred by multiple clinic appointments and fragmented care. (See Chapman et al.<sup>12</sup>)

connect physicians from low-income countries with experts in rare kidney diseases. Local strategies for genetic testing can include mini-gene panels for a set of disorders, for example, focal and segmental glomerulosclerosis, or direct tests for population-specific variants or founder mutations. These approaches can reduce costs associated with genetic testing and the requisite bioinformatic analyses.

**MANAGING DECLINE IN KIDNEY FUNCTION****Measurement and treatment**

Glomerular filtration rate (GFR) should be assessed in accordance to the 2012 KDIGO CKD Guideline and in pediatric settings, with age-appropriate equations.<sup>17–20</sup> GFR estimation by creatinine (e.g., Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine, Schwartz, full-age-spectrum equation) may be misleading in patients with abnormal body mass. In rare diseases with reduced muscle mass or altered body habitus, the use of other formulas (e.g., CKD in Children [CKiD], Filler, CKD-EPI cystatin-C) or actual measurement of GFR may be advisable.<sup>21–23</sup> Currently there is inadequate information regarding the ability of GFR estimating equations to capture actual GFR during the transition from adolescence to adulthood.

Rare genetic disorders typically require specific therapies targeted to the specific disease pathophysiology. For instance, renin-angiotensin-aldosterone system therapeutic blockade, which is commonly used when there is proteinuria in the context of progressive decline in GFR,<sup>24,25</sup> is not applicable in proximal tubular disorders, where albuminuria results from impaired tubular albumin uptake rather than glomerular injury. Moreover, in salt-wasting disorders, renin-angiotensin-aldosterone system blockade may be harmful by compounding hypovolemia and low blood pressure. Contrary to common CKD management, use of nonsteroidal anti-inflammatory drugs in certain polyuric tubular disorders may be indicated and may even be renoprotective. Similarly, dietary salt restriction, while advised in hypertensive disorders, is likely harmful in salt-wasting disorders. There is no evidence that protein restriction should be different in rare versus more common kidney diseases. Protein restriction is not recommended in young children as it may affect growth.<sup>26</sup>

**Monitoring patients for complications**

Algorithms to monitor patients for the development of renal and extrarenal complications are specific to each rare disease, based on the nature of the pathology, and the rate of CKD

progression. Health care providers must have knowledge of the potential specific complications and be able to discuss them with patients and their caregivers. A multidisciplinary approach, ideally with assistance from “Specialized Centers” (also designated as Centers of Excellence/Expertise/Reference in some jurisdictions, see Table 2)<sup>27</sup> may optimize monitoring and treatment of extrarenal complications. Finally, the decision about whether to monitor for complications that have no bearing on clinical management (e.g., uterine abnormalities that occur in patients with *HNF1B* mutations) should be jointly considered by patients and their caregivers.

### Improving standardization and access of optimal care

For rare diseases that lack treatment guidelines, establishing clear protocols based on available publications or expert

opinion can provide a basis for standardizing care. Treatment guidelines should be developed by disease experts in partnership with patient organizations and modified as additional data become available. Retrospective analysis of databases or prospective trials or both can aid in determining the effectiveness of various approaches to treatment. Specialized Centers and networks linking these centers can accelerate the development of treatment protocols.<sup>28,29</sup> Developing practical biomarkers for specific diseases could also improve standardization of care.

Access to optimal care is critical for the best possible outcomes in patients affected by rare diseases. Governments, other payers, and industry should ensure that all effective treatments are available to patients worldwide. Patient organizations have an important role in advocating for access to affordable,

**Table 2 | Standards and quality criteria for Specialized Centers (also known as “Centers of Excellence/Expertise/Reference” in some regions)**

Standard	Metrics for assessment
<b>Comprehensive care</b>	
Renal and extrarenal care specific for the disorder	Availability of ancillary services and nonrenal specialties needed for the specific disorder
Genetics, including genetic testing	
Dietetics	
Psychosocial support	
Coordinated by dedicated team leader	
<b>Expertise</b>	
Care is coordinated by a multidisciplinary team with relevant expertise in the disorder	Publication record, number of patients with specific disease treated
<b>Clinical trials</b>	
Patients should be offered the opportunity to participate in clinical trials relevant to the specific disorder	Involvement in clinical trials for the specific disorder (if any)
<b>Education</b>	
Creation and distribution of information material for patients, families, and professionals, as well as education and training	Availability of informational material, courses, lectures, and training
<b>Patient involvement</b>	
Direct patient involvement to ensure center serves the needs of the patient	Involvement of patients and patient organizations in establishing and managing the center
Facilitate transition from pediatric to adult care	Provision of multidisciplinary age-appropriate support services
<b>Quality criteria</b>	<b>Desired goals</b>
Established through a formal and transparent process based on defined criteria	Access to centers should be facilitated for every patient with the established or suspected specific diagnosis
Should directly involve relevant patient organizations	Referral should be timely and may require changes in existing medical care models
	Care should be provided in cooperation with—rather than in place of—the patient’s local medical team
Performance metrics should be made easily and publicly available so patients can identify the best available center for their condition	Health economic and patient-reported outcomes should be developed
Improvement in care through standardized assessment and treatment	Promoted by patient organizations
	Increased empowerment of individual patients
	Creation of online communities
Financial implications	Up-front financing versus long-term cost reduction

For additional information, see European Union Committee of Experts on Rare Diseases.<sup>27</sup>

evidence-based care and ideally, universal access to Specialized Centers. In geographic regions or countries without such centers, partnerships between local practitioners and center specialists in other regions or countries should be developed.

### Transitioning from pediatric to adult care

A well-designed process of transition from pediatric to adult nephrology health care systems is crucial.<sup>30–33</sup> Psychosocial support, management of potential extrarenal complications, and genetic and reproductive counseling are all potential areas of need for children maturing into adulthood. Specialized Centers may be the optimal vehicle to provide the relevant support and guidance during the transition period (Table 1).

The age at which a patient makes the transition from pediatric to adult care varies between and within countries. For example, in Singapore, the age of transition is 12 years, whereas in the USA, patients in their 20s can still be in the transition process. Transitioning patients between the pediatric and adult centers should allow sufficient time to prepare patients and caregivers and include overlap between the care teams through the transition to minimize the risk of non-adherence to treatment that increases during adolescence and young adulthood.<sup>34,35</sup> Decisions about transition timing should be predicated on patient-specific factors, such as growth and maturity, rather than at a universally applied age. Transition readiness should also be assessed as low transition readiness predicts negative health outcomes.<sup>36</sup> For patients with cognitive impairment, ongoing special support may be necessary.

It is also important to educate patients about kidney replacement therapies (e.g., dialysis, transplantation) early in the disease course. Family members who wish to serve as potential kidney donors may need to undergo genetic and clinical screening, and patients and their families should be made aware of recurrence risk after transplantation.

## CHALLENGES IN CLINICAL STUDY DESIGN

Research in rare kidney diseases is difficult for several reasons, including limited sample sizes, the need for long duration of follow-up, and the paucity of outcome measures.

### Study design considerations

Although rare diseases by definition involve small numbers of patients, applying good statistical methods in study design should be independent of disease prevalence. Therefore, design and sample size for rare disease studies should use methods driven by the disease pathophysiology and natural history, the outcomes measured, and the mechanism of action and anticipated effect size of any intervention. New strategies have been developed for maximizing information obtained from a limited number of patients by using innovative trial designs.<sup>37–40</sup> Table 3 presents a variety of possible trial designs along with a summary of their advantages and disadvantages.<sup>40</sup> Offering children the opportunity to participate in clinical trial programs and entering both pediatric and adult patients into studies that evaluate the mechanism of drug action or an age-independent outcome measure or both may

be more efficient than performing 2 studies would be. If children are to participate in studies that include adults, age-dependent toxicities should be considered.

Recruiting incident patients with rare diseases can be particularly challenging. Prognostic and predictive enrichment strategies employing clinical, biomarker, or genetic information can inform study design.<sup>41</sup>

Drug approval studies in patients with rare diseases should address disease entities defined by common pathophysiological mechanisms, and extrapolation within a given disease across age groups may be acceptable under strictly defined circumstances.<sup>42</sup>

Although observational data cannot replace randomized controlled trials, such studies can provide helpful natural history and safety information valuable for designing future studies.

### Ethical accountability in trial design and reporting

Patient insights and input are essential for designing clinical trials. Patients should be fully and independently informed of trial options and should be made aware of trial registries such as [ClinicalTrials.gov](http://ClinicalTrials.gov) to search for ongoing trials.

In studies of new treatments for rare diseases, placebos are only justified for addressing safety and efficacy, for example, when there is no existing treatment or if the novel treatment is being added-on to an existing treatment (e.g., Patti *et al.*<sup>43</sup>). Participants who receive successful treatment in clinical trials should be offered the opportunity to continue the treatment after the trial has concluded, at least until it becomes commercially available. Clinical trials results should be made available publically and to all participants.

### Outcome measures

There is a paucity of data about whether measured GFR (mGFR) and estimated GFR (eGFR) are comparable in capturing longitudinal changes in GFR. Due to small population sizes in rare kidney diseases, mGFR is ideal.<sup>44,45</sup> However, estimating rather than measuring GFR is generally more practical, given the logistical challenges related to the small number of patients per site. In choosing between eGFR and mGFR, the range of GFR in the patients to be studied should be taken into account. eGFR is less accurate in determining GFR changes in CKD stages G1 and G2 versus stages G3a/G3b and G4. This limited accuracy may be partially compensated for by frequent measurement and use of data-smoothing technologies (Supplementary Figure S1).<sup>46–48</sup>

While the start of kidney replacement therapy is an appropriate hard endpoint for kidney disease populations, the lack of standardized criteria for starting kidney replacement therapy is an issue for clinical research both in common and rare kidney diseases.

Proteinuria reduction may be an appropriate surrogate endpoint, depending on the pathophysiology and predominant clinical manifestations of a specific disease (e.g., hereditary podocytopathies). In tubulopathies, effects on losses of water, electrolyte, and tubular proteins could be considered as endpoints. Measurements of such losses should be

**Table 3 | Examples of study designs and their applications in rare kidney diseases**

Design type/subtype <sup>a</sup>	Short description	Key advantages	Key disadvantages
<b>Single arm</b>	All patients receive the same treatment; no control arm	All patients receive treatment; no risk to get placebo; can help with recruitment	No concurrent (or randomized) control subjects; risks of various forms of bias
Cohort study	Follow a group of patients "exposed" to an agent (treatment) and monitor their subsequent health outcomes; possibly compare with historical control subjects	Could be useful when a treatment has become accepted as standard of care, but no formal evaluation has taken place	High chance of selection and recall bias; generally more useful for following up adverse effects, rather than efficacy effects
Stepped-wedge design	Groups of patients are all given a new treatment at different points in time (e.g., a new group added once a month or once a year)	All patients receive treatment; no risk to get placebo	Possibly a long wait for some patients to get treatment; some ambiguity over quality of control data
<b>Multicenter trials</b>	Studies where >1 treatment (or 1 treatment and a control/placebo) are studied and compared	Usually randomized and concurrent control data, so avoiding many forms of bias	Few disadvantages, unless inefficient because better alternatives exist
Crossover	Patients receive >1 treatment, one after the other	Within-subject variability usually less than between-subject variability, so studies can be smaller; every patient has a chance to get multiple treatments	Not useful for treatments that change the course of disease; not useful for treatments that cure; not useful in mortality studies; not suited for drugs with very long half-lives; each patient has to commit to being in the trial longer than most other designs
AB/BA design	The most common type of crossover design; patients either receive treatment "A" followed by treatment "B", or treatment "B" followed by treatment "A"	Simple design; easy to understand and implement; generally allows smaller sample size than many other designs	As with crossover designs in general
Latin square	Design for $\geq 3$ treatments to be tested in a crossover design	Can compare multiple treatments in relatively few patients	As with crossover designs in general Risks confounding treatment effects with order in which they are given
Youden square	Design for $\geq 3$ treatments to be tested in a crossover design	Can compare multiple treatments in relatively few patients; each patient in the study for less time than Latin square because not all treatments are tested in all patients	As with crossover designs in general; randomization and analysis can be complex
Williams square	Design for $\geq 3$ treatments to be tested in a crossover design; it is balanced for carryover effects from one treatment to the next	Can compare multiple treatments in relatively few patients	As with crossover designs in general; randomization, analysis and interpretation can be complex
Before–after design	Patients are monitored (in a trial setting) while off treatment and then switched to be on treatment and followed up further	Every patient knows they will receive treatment; helps with recruitment; simple to implement	Risk of bias if disease changes naturally over time
N-of-1	Each patient serves as their own control and is randomized to receive different treatments	Highly applicable to find the "best" treatment for a particular patient	Lacks generalizability of conclusions from one patient to another
<b>Parallel groups</b>	Patients are randomized to receive only 1 of $\geq 2$ treatments	Very simple design; fewer potential pitfalls than many of the crossover designs; generally good at avoiding bias	Can be less efficient than many of the alternative options
Factorial	More than 1 treatment, and combinations of treatments are tested in 1 trial	Very efficient; "2 (or more) trials for the price of 1"	Every patient must be eligible to receive any of the treatments (and combinations of them); risks and difficulties of analysis when unexpected interactions appear

(Continued on next page)

**Table 3 | Examples of study designs and their applications in rare kidney diseases** (Continued)

Design type/subtype <sup>a</sup>	Short description	Key advantages	Key disadvantages
Basket study	Multiple treatment options are compared for 1 patient population (1 condition)	Very efficient; “multiple trials for the price of 1”; new treatments can enter the trial at any time, and treatments shown to be ineffective can be dropped at any time	Uncertainties about appropriate control data and possible changes in types of patients over time
Umbrella study	A single treatment is tested in multiple conditions	Efficient for trial logistics; single infrastructure established	Potentially complex protocol unless all conditions being considered need treating in a very similar way
Covariate-adaptive	A method to balance treatment groups for baseline demographic and prognostic factors	Excellent at maintaining balanced groups, particularly when there are too many to use simple stratification	Controversial in terms of validity and analysis
Response-adaptive	A method to skew allocation to treatments toward the treatment showing most promise of superiority	Ethically very attractive; ensures most patients receive what is expected to be the best treatment	Complex to manage and analyze; requires relatively short-term endpoints
Randomized withdrawal	A randomized trial where all patients receive active treatment, then some of the “responders” are randomized to continue that treatment and some are randomized to stop	Ensures as many patients as possible can benefit from the treatment	Not applicable for treatments that change the course of disease; not applicable for treatments that cure disease, or if mortality is the endpoint
<b>Adaptive designs</b>	A wide variety of possible designs where some (potentially any) aspect of the design can be changed part way through the study	Extremely flexible in terms of what can be changed—almost no limits	Complex to design and analyze; often difficult to eliminate bias
Sequential design	Usually a parallel group design where interim analyses are included to potentially stop the trial early if convincing evidence of efficacy or harm are established	Prevents trial running “too long” when sufficient evidence (usually of efficacy) is established	Adds complexity and need for data monitoring committee; not useful for trials with fast recruitment and slow-to-reach efficacy endpoints
Interim analysis	Usually meant as an efficacy analysis in a sequential trial	Allows trial to be stopped early when evidence of efficacy or futility is established	As with sequential designs in general
Futility analysis	An interim analysis designed with the intent to establish whether or not a trial can potentially meet its objectives	Allows early stopping if a trial is very unlikely to meet objectives; saves resources	As with sequential designs in general
Sample size reassessment	Recalculating how many patients are needed in a study while the study is ongoing. Usually done on blinded data	Allows check on original sample size assumptions and correction (if necessary); if done on blinded data, no data monitoring committee is needed	Planning (timelines and budget) cannot be fixed in advance
<b>Superiority design</b>	A trial where the objective is to show one treatment is better (in efficacy terms) than another, or better than placebo	Clear interpretation of results; obvious benefit in terms of patient outcomes	Can require very large number of patients when established treatments already exist
<b>Equivalence design</b>	A trial where the objective is to show one treatment has the same level of efficacy (within a small tolerance) as another	Usually only of interest to expedite regulatory approval of different dosage forms of an established medicine	Often need very large sample sizes; difficulty in agreeing on an accepted margin of tolerance to define “equivalent”; ambiguity of interpretation if no placebo group is included

**Table 3** | (Continued)

Design type/subtype <sup>a</sup>	Short description	Key advantages	Key disadvantages
<b>Noninferiority design</b>	A trial where the objective is to show one treatment is no worse than another (within a small tolerance) but usually in the context of having some other benefit (e.g., better safety or ease of use)	Usually needs fewer patients than a similar superiority trial; obvious ethical preference of not using a placebo control	Difficulty in agreeing on an accepted margin of tolerance to define “inferiority”; sometimes ambiguity of interpretation if no placebo group is included
<b>Enrichment design</b>	A study that uses a run-in period to select patients most likely to respond to treatment and then randomizes those to treatment or control	Needs fewer patients randomized than a similar study not using enrichment	Limited applicability of results to a wider population
<b>Cluster randomized design</b>	A randomized trial where individual patients are not randomized, but groups of patients (e.g., households or villages) are randomized	Good for infectious diseases and public health policy trials	Ethical problems of informed consent; while relatively few clusters may be needed, total sample size (= no. of clusters × average cluster size) can be very large
<b>Repeated measurements design</b>	A study where patient efficacy outcomes are recorded and analyzed at multiple time points	More efficient use of patients; more data collected per patient can allow some reduction in number of patients needed	Analyses can be complex; relevance of questions answered by the analyses needs very careful discussion and agreement
<b>Bayesian design</b>	A formal (mathematical) way of combining data from previous trials and other experience with data from a current trial	Sometimes easier interpretation of results; there may be some benefit in not treating results from a study in complete isolation	Still controversial, so may be harder to gain acceptance of study conclusions; difficulty on agreeing how relevant past data and experience are to the current trial

<sup>a</sup>Many features of study design can be used in a variety of combinations (e.g., interim analyses with factorial designs, cluster randomization with crossover or parallel groups designs, repeated measures designs, and Bayesian designs).

For additional information, see International Rare Diseases Research Consortium.<sup>40</sup>

accompanied by additional, clinically relevant endpoints such as polyuria, physical functions (e.g., muscle strength, frequency of muscle cramps, headaches), and longitudinal growth in children (Supplementary Table S1).

Many rare kidney diseases are associated with primary or secondary neuropsychiatric consequences. Measurements of cognitive, psychosocial, and developmental changes can be used in the assessment of clinical trial outcomes in children and adults. Patient-reported outcome measures (PROMs) should be incorporated into clinical trials and registries of rare kidney diseases, at least as adjuncts to clinical endpoints. A limited set of kidney disease-specific PROMs have been defined (KD quality-of-life),<sup>49,50</sup> and further specific PROMs for adult and pediatric kidney diseases, such as polyuria and physical functions, will become validated in the future, taking PROMs beyond quality-of-life measures.

#### Shared interests in pharmacologic research

Collaboration and partnership between academia and industry in designing, conducting, analyzing, and publishing results of clinical trials as well as sharing data from clinical trials should be encouraged. Regulatory authorities should promote the use of both independent studies and industry-sponsored studies in applications for drug approval. In rare diseases, competing trials that are performed on small cohorts

can slow the progress of research. Therefore, collaboration should be encouraged between trialists and trial groups to accelerate and maximize the information obtained.

#### TRANSLATION OF RESEARCH TO CLINICAL CARE

Translation from research to care depends on policies, institutional contributions, widespread use of instruments and standards, and training of providers and patients.<sup>51,52</sup>

#### Specialized Centers, registries, and biobanks

Specialized Centers play key roles in translational medicine. In Europe, the scope, mission, and designation procedures for such centers have been defined and can serve as a model for other areas.<sup>53</sup> Connecting these centers with research groups and patient advocacy groups, nationally or internationally, through shared registries or biobanks, research collaboration, meetings, training, and exchanges is vital for distributing expertise and advancing knowledge.<sup>54</sup> Registries and biobanks are key instruments for research and development.<sup>55</sup> Quality data repositories accelerate clinical research, facilitate collaboration with industry, and provide data to regulatory or reimbursement bodies while avoiding duplication of efforts and wasting of resources. Because data accessibility depends on how data are stored, managed, and shared, toolboxes and platforms must be developed for establishing and managing



registries. As an example, the Clinical Data Interchange Standards Consortium has generated therapeutic area standards, including those for autosomal dominant polycystic kidney disease, that can be emulated.<sup>56,57</sup> Additional organizations working in this area are listed in [Supplementary Table S2](#). Strategies for the development of non-industry-driven registries have also been outlined recently.<sup>1</sup> Improved collaborative efforts by scientific societies and patient organizations to integrate such initiatives, rather than creating competing ones, should be encouraged.

Practical guidance for establishing rare disease registries is also outlined in [Table 4](#).<sup>58,59</sup> In regions where there may be more patients with rare, recessive diseases, there are opportunities for increasing participation in translational research ([Supplementary Table S3](#)). Similarly, the establishment of biobanks can provide widespread access to various samples types, which in turn enable the development of adapted cell and animal models to better understand disease pathophysiology, screen for new drugs, and generate relevant *in silico* models to identify new therapeutic targets.

#### Instruments and standards

**Informed consent.** Lengthy, dense informed consent forms can be a barrier to patient participation in clinical trials or registries. Consent forms should be designed to be quickly and easily understood while allowing maximal use of data and samples. Sharing approved consent forms may accelerate regulatory approval. Current efforts by the International Rare Diseases Research Consortium (IRDIRC) to create an electronic universal consent form for research in rare diseases should be supported by all stakeholders.<sup>60</sup>

**Standards of care.** Standards of care are lacking for individual rare kidney diseases. Standards should address all aspects of each disease, be developed with input from patients and relevant providers, and be applicable in low-income countries. These standards of care must be published and available online. Patient organizations and clinicians should

develop lay versions of the standards with iterative updating as appropriate.

**Patient-reported outcome measures.** PROMs help ensure that interventions have effectiveness in improving functional abilities that matter most to patients. The development of PROMs requires investment and collaboration from all stakeholders. Increasingly, regulatory bodies and payers are seeking evidence that any given intervention improves  $\geq 1$  PROMs. To this end, IRDiRC has published recommendations for accelerating and validating PROMs for rare diseases ([www.irdirc.org](http://www.irdirc.org)).<sup>61,62</sup> Likewise, the Patient-Centered Outcomes Research Institute and Core Outcome Measures in Effectiveness Trials initiatives have issued guidance for creating and standardizing novel PROMs.

#### Providers and patients

**Clinician training.** A curriculum on the common features of rare diseases should be disseminated in the form of tool kits and webinars. Recommendations for the global assessment and treatment of rare diseases should be summarized and customized to fit the needs of specific rare kidney diseases and local settings. Professional societies, including the International Society of Nephrology, as well as local foundations and regional committees should serve as training resources.

**Promoting awareness of the larger community.** To increase general awareness, World Kidney Day should focus on rare kidney diseases as 1 of its yearly themes. Communities should also be educated on issues important to patients, including the prohibitively high cost of certain drugs. Relevant stakeholders should create and take advantage of lobbying opportunities.

**Patient empowerment.** Patients are partners in their own care, but they need to be trained to fully deliver on their implicit potential. For example, Summer School, an annual training program sponsored by EURORDIS–Rare Diseases Europe ([www.eurordis.org](http://www.eurordis.org)), an alliance of more than 700 rare disease patient organizations, builds capabilities among researchers and patients in the area of medicine development.

**Table 4 | Recommendations for establishing rare disease registries**

- Establish as early as possible, even before potential drug development.
- Conceive and develop with input from academic teams and patient organizations.
- Apply a bottom-up approach when setting up and running registries.
- Do not request clinicians to register their data twice (they are too busy).
- Use existing computerized systems at clinical level or establish a clinical level system.
- Make systems interoperable—use common phenome descriptors (Human Phenome Ontology) and use common nomenclature of diseases (orpha codes).
- Provide open access to data.

Source: European Union Committee of Experts on Rare Diseases. EUCERD core recommendations on rare disease patient registration and data collection, 5 June 2013. Available at: [http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD\\_Recommendations\\_RDRegistryDataCollection\\_adopted.pdf](http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf). Accessed February 3, 2017<sup>58</sup> and Gliklich RE, Dreyer NA, Leavy MB, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. 3rd ed. Report no. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality (USA); April 2014.<sup>59</sup>

#### PROVIDING PRACTICAL AND INTEGRATED PATIENT SUPPORT

Persons with long-term health conditions typically manage symptoms and treatments on their own or with their families and have very limited in-person contact with a health care professional. Therefore, patients should be supplied with written materials, websites, and checklists to serve as a continuous resource outside of their provider visits. Although there continues to be unmet needs regarding patient and caregiver support ([Supplementary Table S4](#)),<sup>31</sup> there are many potential avenues for providing support ([Table 5](#), [Figure 1](#)).<sup>63</sup>

#### Psychological support for patients and their families

The psychological impact of being diagnosed with an inherited kidney disease is different for every patient and can vary over time with disease progression.<sup>64</sup> Patients and their

**Table 5 | Approaches to helping patients in health care systems with differing resources**

Health care systems	
Well-resourced	Low-resourced
<p>Early access to financial support for eligible patients. Provide patients with help in navigating the system.</p> <p><b>Multidisciplinary care</b></p> <ul style="list-style-type: none"> <li>• Joined-up appointments</li> <li>• Multimodal resources</li> <li>• Face-to-face, groups, workshops</li> <li>• Research, trials, registries</li> <li>• Lots of liaison: teams, hospitals, education, employer</li> </ul> <p><b>Information</b></p> <ul style="list-style-type: none"> <li>• Websites</li> <li>• Webinars</li> <li>• Pamphlets</li> <li>• Podcasts</li> <li>• Films</li> <li>• Audio</li> <li>• Social media</li> </ul> <p><b>Patient associations</b></p> <ul style="list-style-type: none"> <li>• Involved at every level</li> <li>• Provide support</li> <li>• Research and development</li> <li>• Registries</li> <li>• Advice</li> <li>• Financial</li> <li>• Strategic as well as supportive</li> <li>• Seek representativeness</li> </ul>	<p>Knowledge of available networks and opportunities such as grants or voluntary exchange programs</p> <p><b>Maximum use of technology and links with Specialized Centers</b></p> <ul style="list-style-type: none"> <li>• Engage routine resources</li> <li>• Make as much information available as possible</li> <li>• Engage key groups/systems already available, such as church, community groups and leaders, or schools</li> </ul> <p><b>Information</b></p> <ul style="list-style-type: none"> <li>• Simple film, audio and print information targeting visual or auditory learners may be most effective</li> </ul> <p><b>Facilitate access globally to information and learning</b></p> <ul style="list-style-type: none"> <li>• Proactively seek connections with groups or individuals affiliated with Specialized Centers</li> </ul>

families can experience anger, fear, grief, anxiety, denial, and depression.<sup>65</sup> For children and adolescents, having CKD increases the risk of developing depression and anxiety.<sup>66</sup> The psychological impact of having a chronic disease depends on a complex interaction of risk and resilience factors that must be considered by care providers.

Children, adolescents, and young adults with a chronic illness are vulnerable to falling behind socially and educationally, with potential deleterious impact on future earning potential and a reduced quality of life. Typically, education systems are not equipped to handle students with chronic illnesses, thus disadvantaging these students.<sup>67</sup> Assisting patients with disease management and providing treatment plans that minimize the impact on daily living (e.g., home dialysis at night, grouping health care appointments, addressing medication side effects) help patients maintain a sense of normalcy. Treatment adherence is particularly at risk in college-aged students, warranting extra support.

Patients and their support systems may have different needs at various stages of disease, including diagnosis, managing symptoms or treatments, or managing transitions in care from pediatric to adult health care systems.<sup>32,33</sup> The challenge to sustain lifestyle adaptations that affect disease



**Figure 1 | Issues surrounding patient care.**

progression may require specific strategies to change an individual’s behavior and maintain these changes.

The health care community can take several steps to help patients and families manage the psychological impact of rare kidney diseases, including specific training on the impact of mental health on a patient and his/her support system, how to discuss mental health issues with patients and their families, and how to assess specific needs and integrate awareness of mental health into medical care planning. Health care providers should also be counseled on the importance of talking separately to patients and their family members to distinguish individual versus familial perspectives and needs.

Patients should be made aware of support groups, especially peer-to-peer groups that operate locally or more globally, including online support. Periodic psychological assessments should be considered to determine whether interventions are needed.

**Patient organizations**

Patient organizations can promote disease awareness and education to influence health policy locally, nationally, and internationally. Examples are lobbying for reimbursement coverage for treatments, improved health care provisions, and government assistance with life insurance for families with a genetic disease. Patient organizations can be helpful in encouraging patients to get more care, earlier. They can also interact with clinicians, academia, industry, and government and regulatory agencies to promote research,<sup>68</sup> develop new treatments, and implement risk-benefit assessments.

The financial impact of a chronic disease is considerable and long-lasting for patients and their caregivers. Although available financial support varies considerably throughout the globe, patient support organizations can be reliable sources of information. Some patient organizations also

**Table 6 | Gaps in knowledge for future research**

- **How should genetic test results be reported?** It can be difficult to discern whether genetic variants are pathogenic, likely pathogenic, or of unknown clinical importance. To facilitate better reporting of genetic tests, data sharing in the form of disease-specific variant databases such as the Human Gene Mutation database ([www.hgmd.org](http://www.hgmd.org)), ClinVar ([www.ncbi.nlm.nih.gov/clinvar](http://www.ncbi.nlm.nih.gov/clinvar)), and the Leiden Open Access Variation database ([www.lovd.nl](http://www.lovd.nl)) may be key. Centers conducting genetic testing should also examine any available guidelines, such as those from the European Molecular Genetics Quality Network (<http://www.emqn.org/emqn/Home>) and the American College of Medical Genetics and Genomics (<https://www.acmg.net>). Can reports be presented to include a clear conclusion regarding whether a pathogenic variant was absent or present, as well as the need for referral to a clinical geneticist or genetic counselor?
- **How can we determine the preferred method of genetic testing?** Successful application of next-generation sequencing in diagnostic mutation screening, using multigene, disease-specific panels, has been demonstrated for Alport syndrome, steroid-resistant nephrotic syndrome, nephronophthisis, other renal ciliopathies, and tubulointerstitial kidney diseases. Beyond disease-specific next-generation sequencing panels, whole exome sequencing and potentially whole genome sequencing may soon become part of routine molecular diagnostics in some countries, further improving the diagnostic yield. For example, rapid whole genome sequencing (with whole exome sequencing and copy number variation analysis) might be clinically useful in diagnosing neonates with unexplained kidney failure. How can the nephrology community and health economists determine the cost-effectiveness of these various genetic testing approaches?
- **What studies can be conducted to better understand the health risks of and potential for kidney donation for heterozygous carriers of recessive mutations?**
- **Can we identify the best methods to estimate glomerular filtration rate during adolescence? What are other innovative ways to improve medication adherence in adolescents?**
- **How can adaptive designs be best used in small trials?** Although the value of adaptive designs in small trials seems clear, the amount of information available from a small trial may be insufficient to reliably assess what features might best be adapted. This ranges from relatively simple adaptations such as sample-size reestimation, to more complex adaptations such as changing doses, changing endpoints, changing comparator groups, and such.
- **How can fully Bayesian designs be made acceptable to all stakeholders?** A great value of Bayesian designs might be the ability to incorporate “informative” priors that can add more information to the data collected in a study. However, despite progress in how to elicit prior beliefs from experts, different priors might legitimately be held by experts, patients, sponsors, and regulators. Without agreement on an acceptable prior by all stakeholders, results of Bayesian analyses are likely to remain controversial.
- **How can we better utilize biorepositories to advance diagnosis and treatment of rare kidney diseases?** The use of biorepositories could advance development of biomarkers for screening and assessments for kidney function, end-stage kidney disease, or treatment response. Biobanking that includes samples from patients with rare kidney diseases should be encouraged on national and international scales. Biobanks should include pretreatment urine and plasma specimens as well as serial samples of RNA and DNA over time. It is also imperative that specimens are linked to rich phenotypic databases. With increased collaboration between different biorepository networks in the future, how can we resolve issues regarding ownership of biobank material or specific usages that were not covered in the initial consent?
- **What are some of the challenges for maintaining effective registries?** Poor data quality, especially with long-term data collection done on a voluntary basis with poorly defined objectives, is such a problem. Would it be practical for registries to provide a minimum set of data for all relevant patients and greater detail for a subset of patients? In addition, will jurisdiction laws from different countries hamper international collaboration?
- **What will the Specialized Center model look like in less developed countries?**
- **What studies can be conducted to better understand how the transition process from pediatric to adult be optimized for individual rare kidney diseases?**
- **How can psychosocial factors be better assessed in patients to predict successful transitional readiness from pediatric to adult care?**

provide financial assistance programs to patients or grants to researchers.

## CONCLUSION

A common theme that emerged from the meeting is the importance of collaboration in advancing care and research for rare kidney diseases (Tables 2, 5, and 6). Improvements in diagnosis and treatment depend on the collaborative interactions among clinicians, patients, industry representatives, regulatory agents, and government agencies to support innovative approaches for diagnosis and management of patients with rare kidney diseases.

## DISCLOSURE

SA declared having received consultancy fees from Biogen. DB declared having received consultancy fees from Raptor. SD declared having received consultancy fees from Baxalta, Pharmalink, and Shire. OD declared having received research support from Otsuka. LMG-W declared having received consultancy fees from Otsuka and research support from the National Institutes of Health (National Center for Advancing Translational Sciences and National Institute of Diabetes and Digestive and Kidney Diseases). JBK declared having received consultancy fees from Akebia. NVAMK declared having received speaker honoraria from Seinen Congress Event Management and Foundation Devenir. RDP declared having received consultancy fees from Genzyme, Mitsubishi Tanabe, Otsuka, Palladio, and Regulus; speaker honoraria from Otsuka Canada; and research support from Otsuka and the US Department of Defense. FS declared having

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#### SUPPLEMENTARY MATERIAL

**Figure S1.** Use of frequent estimated glomerular filtration rate measurements (here: twice monthly) and longitudinal data smoothing to improve accuracy of time-to-event assessment.

**Table S1.** Possible quantitative renal endpoints for clinical trials in rare kidney diseases.

**Table S2.** Organizations and initiatives for international standards.

**Table S3.** Potential solutions for low-income countries to participate in translational research.

**Table S4.** Unmet needs for patient and caregiver support.

Supplementary material is linked to the online version of the paper at [www.kidney-international.org](http://www.kidney-international.org).

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## APPENDIX

### Other Conference Participants

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