Global Action. Local Change.

KDIGO Controversies Conference on Common Elements in Uncommon Kidney Diseases

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Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants what needs to be done in that specific area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and at other times they highlight areas for which additional research is needed to produce adequate evidence that might lead to guidelines in the future.

BACKGROUND

Rare kidney diseases represent at least 150 different disorders with an overall prevalence of ~60-80 cases per 100,000 total population in Europe and the US. At least 10% of adults and the majority of children progressing to renal replacement therapy (RRT) suffer from inherited kidney diseases, which represent the fifth most common cause of end-stage renal disease (ESRD) at all ages – after diabetes, hypertension, glomerulonephritis, and pyelonephritis.[1] Thanks to access and advances in RRT, patients with inherited kidney disorders rarely die when their disease progresses and may remain alive for many years. However, this apparent advantage is counterbalanced by compromised health with poor quality of life for many. Children born with severe congenital nephropathies face many decades of life with ESRD and high likelihood of

altered physical, cognitive and psychosocial development. Inherited kidney disorders often have multisystem complications which add another layer of complexity to the diagnosis, management, and treatment of these disorders. Due to this complexity, these patients often experience a diagnostic odyssey with years of struggle and contact with many physicians before identification of the correct disease entity. Furthermore, various aspects of renal function may be affected in rare, extrarenal disorders or polymalformative syndromes, including mitochondrial cytopathies.[2, 3]

The study of rare kidney diseases has been complicated by a number of common issues: 1) genetic causes for a majority of inherited nephropathies have yet to be identified; 2) limited availability of biomarkers for monitoring disease progression; 3) high degree of clinical (phenotypic) heterogeneity, which is likely a reflection of the large mutational diversity and the presence of modifier genes or other epigenetic factors; 4) outdated diagnostic classifications that do not integrate the latest molecular insights. An increasing number of rare kidney diseases (e.g., medullary cystic kidney disease), which previously have been considered as single entities, also were found to be etiologically heterogeneous.[1, 4]

Despite these challenges, there has been increased knowledge gained on the clinical, genetic and mechanistic aspects of inherited kidney disorders, accompanied by rapid technological advances and mobilization of interests from health care authorities, professional societies, and patients. One case in point has been the advent of next generation sequencing (NGS) techniques, which have greatly improve the diagnostic efficiency of genetic renal diseases by simultaneous investigation of all relevant genes for a given phenotype, at much reduced cost and turnaround times.[5] Successful application of NGS in diagnostic mutation screening, using multi-gene panels, has been demonstrated for Alport syndrome, steroid-resistant nephrotic syndrome, nephronophthisis and tubulointerstitial kidney diseases. Beyond disease-specific NGS panels, exome sequencing and potentially even whole genome sequencing will soon become part of routine molecular diagnostics, further improving the diagnostic yield.

The growing use of NGS is expected to increase diagnostic efficiency in rare kidney diseases. Accurate genetic counseling and possibilities for carrier testing will become available for increasing number of families, with potential for early prenatal or preimplantation diagnostic testing in severe cases. A definite genetic diagnosis may have important prognostic value in some diseases. Accordingly, policies to promote clinically relevant genetic testing and the adequate delivery and integration of genetic information need to be implemented.[6]

The abundance of genetic and molecular information generated by NGS poses new challenges, as bioinformatic capacities and analysis tools will need to be developed and novel ethical, legal and social issues will have to be considered.[7] Even for well-defined disorders, barriers to general clinical use of genetic testing may persist due to high cost and long turnaround times, insufficient genetic literacy, assumption that establishing a genetic diagnosis will not impact clinical management, and differences in accessibility and insurance coverage.[8] Some of these factors may particularly hold true in settings with limited resources.

While consensus reports for diagnosis and treatment of rare inherited kidney disorders are being established,[4, 9, 10] a major objective in the field of inherited kidney disorders is to ensure the expert knowledge from these guidance documents and the approaches developed at highly specialized and resourced tertiary care centers can be utilized in less resource-intensive local care settings.[1, 11] Practical ways to promote the adoption and implementation of clinically relevant genetic testing and provision of management and follow-up care of these patients should be devised. To this end, integrated centers of expertise are being established to improve health care access and to facilitate the transition of patients from pediatric to adult care.[11, 12] Timely referral to these specialized centers may require changes in the existing medical care models for many countries. This may be facilitated by strong advocacy from patient organizations, increased patient empowerment, and creation of online communities. Equally important are measures to ensure delivery of accurate disease information to physicians, patients and society in general, and to outline available resources (e.g., patient assistance or peer support programs). These efforts are supported by numerous

networks and initiatives, as well as organizations such as the NIH through its Genetic and Rare Diseases (GARD) Information Center and NORD (National Organizations of Rare Disorders) in the US, and Orphanet in Europe.

Measures to translate research insights into clinical benefits include creation of disease-specific patient registries and biorepositories, and centers of expertise that can offer adequate diagnostic and therapeutic capabilities, genetic counselling, and early detection or targeted screening programs.[11] Also, insights from rare disease research may be used to improve disease prognosis, modify established public health measures by identifying subsets of patients at particular risk, and facilitate approval of novel orphan drugs. Many of the same clinical trial obstacles encountered in CKD research are also observed in rare kidney disease research (e.g., inadequate sample size, long duration of follow-up, limited number of outcome events, etc.) and alternatives to traditional trial designs have recently been proposed to address these difficulties.[13] Also critical is the development of novel biomarkers and validated surrogate endpoints to encourage and accelerate research in this area. In this vein, alternative measures such as smaller decline of estimated glomerular filtration (eGFR) or use of total kidney volume (TKV) in the study of autosomal dominant polycystic kidney disease (ADPKD) and others merit further investigation.[14]

The role of patient organizations in closing the gap between understanding of disease pathophysiology and development of innovative therapeutics for rare diseases should be emphasized.[15, 16] Historically patient organizations have played instrumental roles in health policies, including the passage of the US Orphan Drug Act in 1983 and the EU Orphan Drug regulation in 1999. Many countries around the world now recognize rare diseases as a challenge which should be specifically addressed to ensure that patients receive the attention and services they deserve. In the US, the Rare Diseases Clinical Research Network (RDCRN) has been established to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing. In Europe, recently adopted national plans or strategies include the establishment of European Reference Networks (ERNs), aimed at providing optimal care to patients through trans-border collaboration between various centers of

expertise.[17] These efforts are now paralleled by initiatives launched by professional and scientific societies,[18] including the controversies conferences and consensus reports generated by KDIGO.[4, 9]

CONFERENCE OVERVIEW

The objective of this KDIGO conference is to gather a global panel of multi-disciplinary clinical and scientific expertise to address common clinical and patient issues across the field of rare kidney diseases. General themes for discussion will include but are not limited to: technological advances in diagnosis; role of genetic counselling and other ethical concerns as a result of improved diagnosis or screening; management of renal function and extrarenal manifestations; optimal pediatric transition care; approaches to overcome challenges in trial design and conduct; development of novel biomarkers or surrogates for improved disease prognosis; integration of advanced technologies and disease knowledge translation into innovative clinical research programs; critical quality-of-life issues that confront patients and their caregivers; comparison of policy initiatives from various parts of world in terms of rare kidney disease management, with insights from economists, ethicists, and representatives from regulatory agencies.

As such this conference seeks to provide guidance in clinical management, summarize outstanding knowledge gaps, and propose a research agenda to resolve outstanding controversial issues and address the paucity of data. It is hoped that the deliberations from this conference will help pave the way for more informed research in rare kidney diseases.

Drs. Olivier Devuyst (University of Zurich, Switzerland) and Lisa M. Guay-Woodford (Children's National Health System, George Washington University, Washington DC, USA) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers include worldwide leading experts, healthcare authorities, and patient representatives who will address key clinical questions detailed in the **Appendix: Scope of Coverage** below. The conference output will include publication of a position statement to help guide KDIGO and others on the future research related to general clinical and patient challenges encountered in rare kidney diseases.

APPENDIX: SCOPE OF COVERAGE

1. Diagnostic challenges

Q1. What is the potential importance of genetic testing for differential diagnosis, management, and research of rare genetic renal disorders? What is the value of genetic testing - often perceived not necessary- if there is no or weak treatment? Utility of testing should include both health care provider and patient perspectives. What about the right of not wanting to know the diagnosis vs. family responsibility?

Q2. What is the preferred method of genetic testing and what are the determining factors? (e.g., Sanger sequencing vs. NGS-disease related gene panels vs. Whole Exome Sequencing (WES)/Whole Genome Sequencing (WGS) combined with targeted sequence analyses of WES/WGS data). This discussion should include cost-effectiveness considerations, optimal allocation of resources, and the role of bioinformatics and genetic vendors.

Q3. Should a diagnosis be made on clinical (including biochemical/pathological) grounds, on genetic evidence or a combination thereof? Discussions should include value of renal biopsy and pathology findings; importance of family history and extra-renal manifestations.

Q4. What comprises pre-symptomatic screening (*in utero* (prenatal), newborn: biochemical, imaging, etc.)? What are the implications of pre-implantation genetic diagnosis (e.g., social, ethical, legal)?

Q5. How can we better leverage the use of biorepositories to advance the development of biomarkers for screening; assessment for renal function, ESRD risk, or treatment response via metabolomic/proteomic/ or other approaches?

Q6. How can we implement diagnosis-genetic networks in low-income countries?

To be addressed as part of the discussion for future research agenda

Q7. Which criteria should be used to define variants as pathogenic/likely pathogenic vs variant of unknown significance (e.g., minor allele frequency (MAF) in general population, *in silico* prediction, functional insights, others)? How can we facilitate reporting of genetic tests?

2. Management of renal function decline and CKD progression

Q1. Is the generally accepted wisdom in nephrology (such as use of ACE-inhibitors, avoidance of NSAID, etc.) applicable to specific rare diseases and at all levels of kidney function? Are most treatment targets (blood pressure, sodium, dietary protein, etc.) still applicable for this population? Are so-called "renoprotective drugs" dangerous in some rare kidney diseases, such as salt-wasting tubulopathies?

Q2. How can we optimize a cooperative approach of tertiary expert centers with local care centers, particularly in a patient transitioning from pediatric to adult care? Discuss specific problems in young adults (age 18-28 years).

Q3. How can growth-related issues and treatment be optimally managed?

Q4. How should one monitor for potential renal and extrarenal complications and if so, how frequently? How can we ensure multidisciplinarity and define expertise for a given center?

Q5. How can we improve standardization of care - specific examples?

Q6. How can we ensure equity of access to optimal care, including expensive drugs? Differentiate guidance for developed countries and developing countries.

Q7. How can we help the patient and family to accept the chronic disease, live with it and manage it responsibly? Any specific issues related to compliance, monitoring, and follow-up?

3. Challenges in clinical study design

Q1. What are the sample size and study design considerations in a rare disease study? How do they differ or are they similar to considerations in diseases that are not rare? Is it justifiable to combine etiologically heterogeneous diseases with similar clinical, biochemical and histopathological features in the same study? Can or should adults and children with the same disease be combined in the same study? Do we need genetic diagnosis for stratification?

Q2. Is it justifiable to extrapolate clinical trial results obtained in a defined rare kidney disease entity to other, etiologically and/or phenotypically related rare renal conditions in order to obtain broader drug approval? If so, what are the criteria for extrapolation? Discussion should include considerations of genetic and histopathological information.

Q3. What is the value of observational data, such as from registries and longitudinal natural history studies, as supporting information to small clinical trials from rare disease submitted by industry sponsors as part of new drug applications?

Q4. What outcomes should be targeted in clinical studies (e.g., mGFR or eGFR, proteinuria, etc.)? Outcomes such as requiring RRT have a large variability across sites. What are the options to standardize RRT definitions? What is the utility of alternative surrogates or outcome measures (e.g., TKV, composite outcomes, etc.)? Implications/acceptance by drug regulatory authorities?

Q5. Patient-reported outcome measures (PROMs): What role should PROMs serve in the study design? Are they useful, given that improvement in QOL is not necessarily associated with better survival (e.g., EPO)? Should PROMs chosen for studies be generic, common to many diseases, with strong validity and reliability, or should the focus be on more renal disease-specific PROMs, due to their increased specificity, even if the validity and reliability are less well-established? What is the impact of subjectivity in patients' evaluation?

Q6. Role of patient advocacy groups: How can input from patients and advocacy groups be incorporated into clinical trial design? How can different priorities and perceptions of stakeholders be best negotiated into the design of clinical trials?

Q7. What are the major conceptual differences in clinical study design between academic and industry-driven clinical trials? How do these differences impact the translation of findings across studies and the progress in treating rare kidney diseases? Is there a risk that better-funded industry studies may decrease patient availability for academic research? If so, what can be done to overcome this risk?

Q8. Non-renal manifestations of renal disease: Should hypertension outcomes be considered primary or cardiac outcomes? What are the important cognitive, psychosocial, and developmental outcomes for adults and children?

Q9. What are some of the ethical challenges in designing clinical trials in rare diseases, especially in pediatrics and in pediatric to adult transition studies?

4. Accelerating translation from research to clinical care

Q1. What would be the optimal clinical research collaborative network or networks?

Q1.1: How might we overcome the barriers to the establishment of registries and biobanks, and the barriers to maintaining them?
Q1.2: What can we learn from existing collaborative efforts?
Q1.3: How can we ensure that the movement towards open data access in all fields is coordinated, given current different standards in various fields?
Q1.4: How can we ensure participation of lower-income countries?
Q1.5: How can we develop models of consent and assent in the ever-changing technology/research landscape?
Q1.6: How can we better engage or establish partnerships with patient- or family-initiated organizations for clinical and basic research studies?

Q2. What would be the positive practical outcomes for patients from improved translation from research to clinical care?

Q2.1: Have we produced sufficient best practice reports? How can we do better, in terms of format of the recommendations? For which diseases?
Q2.2: How can we ensure that best practice recommendations also apply to countries with lower income?

Q2.3: How can we include the patient perspective into every step of the research and development process and the subsequent translation into practice?

Q3. How do we develop successful trials for rare renal diseases?

Q3.1: What predictive biomarkers exist and how useful are they? How can we encourage the development of new biomarkers?
Q3.2: How can we develop patient-centered outcome measures?

Q4. How might we ensure optimal use of genetic services/genomics for patients?

Q4.1: What is the best timing for patient referral for genetic services?
Q4.2: What is the optimal approach for testing (e.g., targeted testing, gene panels, exome sequencing, whole genome sequencing)?
Q4.3: How can we leverage our technical advances and knowledge of molecular insights (e.g., multilevel genomics technologies such as mutation analyses, *in silico* predictions, functional characterizations, etc.) to assess individual patient characteristics and better inform disease prognosis, treatment response, and other important decisions (e.g., should carriers be allowed to be living organ donors)?
Q4.4: Can we improve upon the translation of genetic information for clinical practice?
Q4.5: How can we enhance the training and awareness of the medical community? How can we educate local renal unit about rare disease? How can we better target trainees on rare kidney diseases (e.g., revise curriculum and teaching; roles of professional societies and local kidney foundations; regional committees of ISN; World Kidney Day?

Q5. What is the best organization of care to ensure that clinical research develops and leads to clinical practice recommendations that benefit all?

Q5.1: What can be learned from existing centers of expertise/ excellence/ reference?
Q5.2: How can we enhance the training and awareness of the medical community?

Q5.3: How can we educate local renal units about rare diseases so that optimal timing for patient referral expert centers is better understood?
Q5.4: How can we better interest trainees in rare kidney diseases (e.g., revise curriculum and teaching)?
Q5.5: Can we leverage the roles of professional societies and local kidney foundations; regional committees of ISN; World Kidney Day?
Q5.6: What are the optimal infrastructure requirements for a center of expertise/ excellence/ reference? How can we integrate such centers into existing models of care, which can be disparate in various parts of the world?
Q5.7: How can we improve access to expert care, aiming for equal care everywhere?
Q5.8: Is there utility in establishing a guide for expert referral (i.e., diagnosis, management, etc.)?

Q6. What initiatives can boost drug development and inform usage?

Q6.1: How can academic-industry-patient groups come together to improve the process of drug development?

Q7. How can good practices for translational medicine as concluded from this conference be disseminated for wide adoption?

5. Practical and integrated patient support

Q1. What is the benefit to a patient for going to a "Center of Excellence"? In addition to optimizing diagnostic tools and treatments, what should these centers offer (e.g., disease education, access to clinical trials, social service support to address financial issues, access to patient support groups, others)? What are the challenges in cross-border care?

Q2. What ethical, moral, legal, financial, and religious perspectives should be considered in family planning decisions? Should pre-implantation genetic

diagnosis be available to patients with inherited kidney diseases and if so, which ones? When is pre-symptomatic screening appropriate?

Q3. What is the psychological impact of diagnosing an inherited renal disease for the individual and the family, and what can be done to reduce the impact? What is the financial impact of an inherited kidney disease diagnosis (e.g., career choice/progress, potential reduced income, life and health insurance, long-term care, etc.) and what can be done to reduce the impact? Are these barriers to diagnosis and early treatment? How can we address these in children? What are the long-term emotional implications (e.g., depression, suicide, life independence) of a chronic disease when symptoms appear and interventions are required in childhood?

Q4. How can patient organizations promote disease awareness and education to influence health policy locally, nationally and internationally? How can they interact with clinicians, academics, industry and government to foster research and develop new treatments? How can they interact with regulatory agents concerning risk-benefit assessment and reimbursement of a new medication? Should these patient organizations organize into an international network to enhance their political influence?

Q5. Why are lifestyle adaptations (e.g., diet, exercise, smoking cessation, etc.) so difficult to implement and sustain? What are the barriers to medication adherence? What can be done to raise and sustain adherence to a beneficial lifestyle? How are lifestyle adaptations and strategies different in children compared to adults? How can we improve diet adherence (role for web-based approaches, etc.)?

Q6. How should schooling be adapted to meet the specific needs of pediatric patients? How does kidney disease and ESRD impact children emotionally and socially? Can educational continuity and development be possible between school and healthcare facilities? For adults, how can we educate employers to adapt work demands to meet the specific needs of patients?

Q7. Are PROMs useful to guide clinical management? What is the role of technical advances in the adoption and integration of PROMs in clinical care?

Q8. Should best-practice guidance documents, care pathways and checklists be available for all inherited kidney diseases? How can we render this information in an easily understood manner to patients and caregivers? How can we reduce health care disparities and ensure that these practice guidelines, care pathways and checklists are implemented everywhere regardless of geographic location, race/ethnicity, socioeconomic status, gender, disability, and age? How can we use technology (e.g., internet, Smartphone apps, etc.) to disseminate information? How can patient groups avoid the duplication in developing patient information resources and reference materials?

Q9. What are the barriers to drug access (e.g., pre-approval access, regulatory challenges, high pricing, intellectual property restrictions for new drugs, lack of funding to conduct clinical trials for repurposed drugs, etc.)? How do these barriers vary from country to country?

Q10. How can we support pediatric patients early on in their care to promote the best outcome for teen and college years, compliance for healthcare monitoring, treatment and self-care? At what age is it best to start the transition from pediatric center to adult center?

Q11. What impact does caregiver/parent advocate fatigue have on the treatment and medical care, and therefore outcomes of patients? If negative impact is apparent, can we change or reduce it? How can we help parent caregivers transition their caregiving and advocacy to their children? What is the emotional impact/fallout on caregivers in the long term and how can we promote self-care and encourage as much independence in patients as possible?

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