Global Action. Local Change.

KDIGO Controversies Conference on Genetics in Chronic Kidney Disease
- Scope of Work -

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 set priorities for improving patient care and outcomes. In addition to highlighting areas for which additional research is needed, sometimes the conferences lead to KDIGO guideline development efforts.

GENETICS IN CKD: BACKGROUND AND RELEVANCE

Worldwide, chronic kidney disease (CKD) has been increasing in prevalence for the past 3 decades and represents a substantial burden on public health.[1] Approximately 10% of the global adult population has CKD,[1] which can progress to kidney failure with need for kidney replacement therapy. Not only is CKD itself a leading cause of death worldwide,[2] it also increases morbidity and mortality in the setting of other leading causes of death, including cardiovascular disease, hypertension, diabetes, HIV infection, and malaria.[3] Because multiple genetic and environmental risk factors contribute to kidney diseases, the underlying pathophysiologic mechanisms can be difficult to identify.

However, the use of large, integrated datasets of genomic and health information in genome-wide and phenome-wide association studies has led to valuable insights into genetic determinants of kidney function and CKD.[4] To date, more than 600 genes have been implicated in monogenic kidney diseases,[5] and known single-gene disorders account for up to 30% of specific forms of CKD in pediatric cohorts and 5%–30% in adult cohorts.[6] Yet in many kidney diseases, multiple factors contribute to the pathology, and the one gene-one disease model does not apply. Studies examining the influence of

genome-wide, common genetic variants on kidney function indicate that they currently explain approximately 20% of the estimated genetic heritability of kidney function measures.[7]

Genetic findings are increasingly used to inform clinical management of many nephropathies, enabling targeted disease surveillance, more precise diagnostics, and better-informed choices of therapy and family counselling.[8] Although the pace of discovery and the potential clinical implications continue to be promising, there is concern that rapid generation of genomic data can outpace accurate interpretation of the data, which is crucial for patient care.[9] For example, clinical interpretation of genome-wide sequencing is a semi-automated and labor intensive process,[10] and identifying causal variants in the vast amount of data generated and interpreting secondary findings can be challenging.

CONFERENCE OVERVIEW

To realize the promises of genomic medicine for kidney disease, many technical, logistical, and ethical questions related to genetic testing in nephrology must be addressed.[8] To fill knowledge gaps and translate genetic data into personalized care, physicians and geneticists must incorporate diagnostic sequencing information with clinical history, kidney biopsy results, and other sources of -omic data, including genetic association studies.[8]

The KDIGO Controversies Conference on Genetics in CKD will examine several issues related to monogenic kidney diseases, complex kidney diseases, applications of genetic findings in clinical medicine, and utilization of genomics for defining and stratifying CKD.

Drs. Anna Köttgen (University of Freiburg, Germany) and Ali Gharavi (Columbia University, United States) 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. This highly interactive conference will invite key thought leaders and relevant stakeholders, including patients, in nephrology and other related disciplines who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include

publication of a position statement that will help guide KDIGO and others on state of the art and future research in this topic area.

APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Monogenic Kidney Diseases

1. What is the specific definition of "monogenic" in contrast to "complex" kidney disease? How are those diseases characterized? What is the proportion of so-called monogenic kidney disease (including monogenic kidney cancer syndromes) among patients with CKD and/or kidney failure (separate for childhood-onset and adult-onset cohorts)? What are the most frequent inherited kidney diseases? What are the different inherited kidney diseases and how should they be classified?
2. What standards should be met for a variant to be classified as pathogenic? How do general variant classification systems such as ACMG comply with the needs of assessing variant pathogenicity in monogenic kidney diseases? For which conditions should we integrate or build upon disease-specific variant-databases (e.g., PKD-database)? How can nephrologists ensure that the existing standards for clinical genomic testing and interpretation are sensitive and specific enough for variants in genes associated with kidney disease?
3. Can we define actionable genes for kidney diseases? What criteria can be used to define different categories of actionable genes?
4. When is genetic testing highly indicated (e.g., familial kidney disease, related living donor kidney transplantation)? When should genetic testing be obtained in adults, children, and adolescents with kidney failure of unknown etiology? When should genetic testing be avoided or not be routinely offered?
5. What are the most urgent research topics and resources needed for studies of monogenic kidney diseases? For example, for which conditions may experimental high-throughput variant pathogenicity assessment be most beneficial? What could a unified gene and allele database for monogenic kidney diseases look like (ClinGen and others)? Can we agree on a **unified disease terminology** that includes the gene name in addition to the clinical name for monogenic kidney diseases (such as for *ADTKD-MUC1* etc)?

Breakout Group 2: Complex Kidney Diseases

1. What defines kidney diseases as "genetically complex"? What are the pros & cons of disease definitions based on kidney function vs. histology vs. molecular injury markers for genetic studies, clinical care, and precision medicine?

2. What is the current state of knowledge about the extent of genetic contributions to kidney function traits (e.g., eGFR, proteinuria), primary glomerulopathies (e.g., IgA nephropathy, membranous nephropathy, SSNS), secondary glomerulopathies (e.g., diabetic nephropathy, lupus nephritis), nephrolithiasis, and kidney cancers? What are the relative contributions of common versus rare germline genetic variants to these traits? What are the contributions of somatic (non-germline) mutations? To what extent do genetic risk variants influence complex kidney disease susceptibility through intra-renal versus extra-renal effects?

3. Which risk variants should be considered for genetic testing and return of results (e.g. *APOL1* or risk variants for membranous nephropathy)?

4. What are current gaps in the genetic studies of complex kidney diseases? Is there a need for more GWAS? What are the best strategies to assess contributions of rare variants and somatic events? How to increase ancestral diversity in genetic studies for kidney disease? What resources are needed to define causal variants, causal genes, and causal tissues/cell types for each kidney disease GWAS locus? How to best inform new drug development based on GWAS?

5. What is the current state of knowledge about polygenic risk scores (PRS) and their utility in predicting kidney disease or risk stratification for clinical implementation? What performance standards should be met for a PRS to be applied in clinical practice? What degree of risk or PRS thresholds would be considered as clinically meaningful or actionable? What are the factors that should be considered in the interpretation and management of high PRS for kidney disease?

6. Are any of the existing genetic findings for complex kidney disease ready for clinical implementation? Are there specific situations in which genetic testing for

the known genetic risk variants would change clinical practice? What are the key barriers for clinical implementation?

Breakout Group 3: Achieving Implementation in Clinical Medicine

Clinical knowledge

1. What should be the core competencies for clinicians undertaking informed clinical genomic consent and returning genomic results, and how should they be evaluated?
2. What are the educational gaps for both clinicians and patients in regards to referral, undertaking genetic testing, and return of genetic results?
3. How can we disseminate knowledge on inherited kidney diseases and available genetics tools among nephrologists? What are the online resources and existing initiatives available to clinicians (e.g., genereviews/orphanet/erknet …)?
4. Do we consider specific subspecialty tracks for genomic nephrology, similar to transplantation, etc.?

Clinical practice

5. What criteria or guidelines should be developed to decide when patients with kidney disease should be referred to reproductive counseling?

Research on implementation

6. Which outcomes can be measured to best inform value-based healthcare implementation and quality assurance of clinical genomics in nephrology?

Cost

7. What are the current issues with genetic test cost and reimbursement? How can equitable access to clinically indicated and accredited clinical genomics be achieved nationally, regionally and globally?

Breakout Group 4: Implications of Genomics for Definitions and Stratification of Chronic Kidney Disease

1. Is there utility in:

    a. using non-genomic parameters/traits to define groups of patients with kidney disease? If so, is there any hierarchy with regards to the value of these traits for defining groups?

    b. using rare variant data and PRS with other -omics parameters to stratify groups of patients with kidney disease for research and epidemiological studies?

2. Can we articulate the value in clinical care and research for genomics-based subgroup identification? What about specifically in the transplant population?

3. How should we be considering a patient's genetic background (e.g., ancestry, risk alleles not related to their primary condition) when using genomics to define and stratify patients with CKD?

    For example, does having an *APOL1* risk allele mean something different in someone of different degrees of African vs European vs Asian admixture? Or does a person's burden of CKD- or CVD-related risk alleles impact their experience of having a genomic form of their primary kidney disease?

4. What steps do we need to take to maximize our ability to effectively use country- or health system-based cohorts for genomic discovery for CKD?

    a. Are existing tools for computable phenotyping useful for identifying kidney disease subgroups? If not, can we adapt them to suit our needs or do we need to develop new ones?

    b. How do we validate computable phenotypes?

    c. Is there a "best in class" suite of analytic tools and/or accessible clinical and -omics databases that can be used to prioritize genes based on common

variants (e.g., Mendelian randomization, transcriptome wide association studies, eQTL, pQTL, mQTL, etc..)?

5. How do we assess the validity/accuracy of results emerging from drug trials or observational cohort studies if the patients' genomic profile is not known?
    a. Should all future cohort studies and/or drug trials include genotyping?
    b. Which specific pharmacogenomic variants are especially relevant for nephrology?
6. What specific partnerships and collaborations are accelerating progress in using genomics to define and stratify CKD?
    a. Are there additional opportunities for impactful partnerships and collaborations that we have not yet seized? With other academic entities? Private partners?

References

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