

KDIGO Controversies Conference on Genetics in Chronic Kidney Disease - Breakout Group Questions -

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. When is genetic testing highly indicated (e.g., familial kidney disease, related living donor kidney transplantation)? Which genetic testing approach is to be preferred (single genes vs panel vs WES/WGS)? 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?
3. 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? How can we ensure that the existing standards for clinical genomic testing and interpretation are sensitive and specific enough for variants in genes associated with kidney disease? What are the existing unified gene and allele database for monogenic kidney diseases (ClinGen/Clinvar, LOVD and others)? For which conditions should we integrate or build upon disease-specific variant-databases (e.g., PKD-database)? What are the reasons to submit identified variants to public databases?
4. What should be reported? Can we define actionable genes / amenable variants for kidney diseases? What criteria can be used to define different categories of actionable genes (e.g. treatment available or not, consequences on family



- planning, on specific screening or follow-up)? In which cases should variants of unknown significance be reported?
5. 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)?
 6. 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? Example #2, how can we ensure that genetic results are regularly reinterpreted as new genes are steadily being identified, Do we want to recommend re-analysis of exome/genome data after a specific time (1-2 years)?

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., heritability of 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*, risk variants for membranous nephropathy, other)? What are the key barriers for clinical implementation?

4. 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?
5. What are current gaps in the genetic studies of complex kidney diseases? How to prioritize future genetic studies of complex kidney disease? 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?

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?
6. Should all patients with CKD of unknown origin or CKD without diagnostic workup be referred to genetic testing?

7. What role do centers of excellence have in the implementation of genetic testing in nephrology?

Research on implementation

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

Cost

9. 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? Should tele-medicine play a role in broadening the access to genetic testing?

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?