Global Science. Local Change.

KDIGO Controversies Conference on *APOL1* Kidney Disease

Breakout Questions

Breakout Group 1: *APOL1* Kidney Disease: Pathogenesis/Pathophysiology and the Role of Modifiers

1. What is the appropriate terminology for *APOL1* kidney disease?
2. Which cell types (inside and outside of the kidney) express *APOL1* mRNA or protein under physiologic or pathologic conditions? What physiologic/pathologic conditions or environmental factors induce *APOL1* expression?
3. To what extent do available evidence support the paradigm that variants of *APOL1* cause kidney disease? Is there evidence indicating G0 *APOL1* is toxic?
4. What is the nature of kidney injury that results from variants of *APOL1*? How do we explain the spectrum of kidney diseases associated with the *APOL1* high-risk genotype?
5. What is the current state of knowledge about the pathomechanisms underlying *APOL1*-mediated cellular injury?
6. What are current gaps in experimental modeling of *APOL1* kidney disease? Which attributes of *APOL1* kidney disease do existing experimental models (animal and cell-based models) capture well, and which attributes are poorly captured by these models? What are promising strategies for modeling *APOL1*-associated, low-proteinuric kidney diseases such as hypertension-attributed CKD in experimental animals?

7. What is the current state of knowledge about genetic factors (modifiers and variants such as p.N264K) as well as environmental factors that contribute to *APOL1* kidney disease?

Breakout Group 2: Epidemiology of *APOL1* Kidney Disease: Characterization of Risk Phenotypes, Risk Factors, and Adverse Outcomes

1. What is the appropriate terminology for *APOL1* kidney disease?
2. What is the prevalence of the *APOL1* risk variants globally, and how does the prevalence vary across populations, especially in sub-Saharan Africa? Why does the *APOL1* high-risk variant frequency vary so much in different regions of Africa? What is the prevalence in Hispanic and LatinX populations within and outside Latin America??
3. What is the difference in kidney failure and CKD progression in *APOL1* high-risk versus low-risk genotypes? Does the risk differ in adult populations compared with pediatric populations? What is the risk of CKD progression in individuals with sickle cell trait and sickle cell disease?
4. Are there phenotypic differences between G1 and G2 alleles? Are there differences in microalbuminuria and macroalbuminuria for individuals with G1 versus G2 alleles?
5. Does the risk of incident CKD or CKD progression or the rate of estimated glomerular filtration rate (eGFR) decline vary between individuals with the G1 versus G2 alleles?
6. Do high- and low-risk genotypes confer higher CVD risk in those with CKD?

7. Does the *APOL1* high-risk genotype confer a higher risk heart failure, atherosclerosis, mortality, acute coronary syndrome, or stroke compared with low-risk genotypes in those with CKD?
8. Are there roles for *APOL1* p.N264K or M1 on *APOL1* genotype 2 as genetic modifiers for *APOL1*-mediated kidney disease?
9. Do high- and low-risk genotypes confer higher complication risks (e.g., preeclampsia) among pregnant women and increased risk of intrauterine fetal growth restriction?
10. What is the significance of fetal or maternal discordance in genotype on the risk of preeclampsia?
11. Are babies with high-risk *APOL1* variants at increased risk of subsequent development of hypertension and CKD?
12. Is there evidence dietary and lifestyle modifications reduce risk factors in *APOL1* kidney disease? Is there evidence that salt restriction offers larger benefits? Is a higher potassium diet beneficial for lowering blood pressure or CKD progression? Does BMI confer a higher risk of CKD or CKD progression compared to the general population?

Breakout Group 3: Prognosis, Current Management, and Novel Therapeutic Approaches

1. What is the appropriate terminology for *APOL1* kidney disease?
2. Which biomarkers predict development and progression of *APOL1* kidney disease (e.g., soluble urokinase plasminogen activator receptor [suPAR], kidney injury molecule 1 [KIM-1], tumor necrosis factor receptor 1 [TNFR1], TNFR2, proteinuria)?

3. Which tools can be used for prognostication (e.g., risk equations such as those from the CKD Prognosis Consortium)?
4. Describe therapeutic targets in *APOL1* kidney disease: inhibition of channel function or APOL1 production (antisense, antibody-mediated), downstream inflammatory pathways, or agents targeting environmental and or genetic modifiers.
5. What is the approach to management (and how would it change) if multiple drivers of CKD coexist (e.g., *APOL1* kidney disease and either lupus, HIV or COVID, sickle cell disease, or collapsing glomerulopathy)?
6. What is the role of treatment targeting APOL1 in slowing the progression of kidney diseases that are not necessarily associated with *APOL1* kidney disease (e.g., non-*APOL1* associated FSGS, minimal change disease, membranous glomerulonephritis, IgA nephropathy, diabetic nephropathy)?
7. What is the role of treatment targeting APOL1 in patients who received a kidney transplant from donors with high-risk *APOL1* genotypes, or living related donors with high-risk *APOL1* genotypes?
8. How do potential treatments affect those in endemic areas of trypanosomiasis and other infectious diseases?
9. What barriers and opportunities exist for advancing the diagnosis and treatment of *APOL1* kidney disease?

Breakout Group 4: Practical Issues Related to *APOL1* Screening and Diagnosis, and Ethical Issues Related to *APOL1* Genetic Testing

1. What is the appropriate terminology for *APOL1* kidney disease?

2. When is it most appropriate to perform *APOL1* genetic testing? Who has access to those data? Where do those data reside in the clinical system?
    a. Who should be tested for *APOL1* (self-identified African ancestry, admixture population, uncertain cause of CKD, individuals without CKD but with, for example, lupus)?
    b. What is the extent of testing for family members, and how should family members be approached and by whom?
    c. How should worldwide inequities in access to testing and potential treatment be addressed longitudinally?
3. What is the best way to operationalize *APOL1* genetic testing, and how are the results communicated to the patient and clinical team?
    a. What are the benefits and pitfalls of *APOL1* testing?
    b. How do you give informed consent for *APOL1* testing?
    c. What is the best way to educate about *APOL1*?
    d. What about pediatric populations and screening for *APOL1*? Should there be newborn screening?
4. What are the social implications and or consequences of *APOL1* testing?
    a. What are the psychological complications of knowing one is *APOL1* positive?
    b. What are the psychological benefits and/or complications of knowing one is *APOL1* positive?
    c. What are potential implications for patients—stigmatization, family planning, life insurance, discrimination?
5. What are the implications in the transplant setting when potential kidney donors (living or deceased) have *APOL1* risk alleles or phenotype?
    a. What are the implications of *APOL1* testing for potential living kidney transplant donors in respect to long-term prognosis and kidney disease risk?

   b. Is there a way to stratify risk of kidney disease development in living kidney donors who are *APOL1* positive?
   c. To what extent should *APOL1* phenotype, especially high-risk phenotypes, influence decision-making about acceptance of prospective living kidney donors?

6. What are the implications of *APOL1* in the transplant setting (with living or deceased donors) for potential kidney recipients?
   a. What is the effect of donor *APOL1* status on graft survival?
   b. What are the tradeoffs between accepting a kidney with *APOL1* risk allele(s) versus waitlisting?