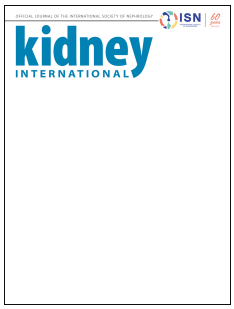

APOL1 Kidney Disease: Conclusions From a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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APOL1 Kidney Disease: Conclusions From a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Akinlolu O. Ojo,[1] Dwomoa Adu,[2] Kate Bramham,[3] Barry I. Freedman,[4] Rasheed A. Gbadegesin,[5] Titilayo O. Ilori,[6] Nichole Jefferson,[7] Opeyemi A. Olabisi,[8,9] Katalin Susztak,[10,11] Bessie A. Young,[12] Michael Cheung,[13] Jennifer M. King,[13] Morgan E. Grams,[14] Michel Jadoul,[15] and Ifeoma I. Ulasi,[16] for Conference Participants[*]

[1]University of Kansas School of Medicine, Kansas City, Kansas, USA;
[2]Department of Medicine and Therapeutics, School of Medicine, College of Health Sciences, University of Ghana, Accra, Ghana;
[3]Department of Renal Medicine, King's College London, London, United Kingdom;
[4]Department of Internal Medicine, Section on Nephrology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA;
[5]Department of Pediatrics, Duke University School of Medicine and Duke University Medical Center, Durham, North Carolina, USA;
[6]Division of Nephrology, Chobanian and Avedisian School of Medicine, Boston Medical Center, Boston University, Boston, Massachusetts, USA;
[7]Community Advisory Council APOL1 Long-Term Kidney Transplantation Outcomes Network, Dallas, Texas, USA;
[8]Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA;
[9]Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, North Carolina, USA;
[10]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA;
[11]Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA;
[12]Office of Healthcare Equity, Department of Medicine, Division of Nephrology, University of Washington, Seattle, Washington;
[13]KDIGO, Brussels, Belgium;
[14]Department of Medicine, New York University Langone School of Medicine, New York, New York, USA;
[15]Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium;
[16]Renal Unit, Department of Medicine, College of Medicine, University of Nigeria, Ituku-Ozalla, Enugu, Nigeria

[*]**Other conference participants:** Angela Opokua Afonope, Ghana; Godfred Akyea-Darkwah, Ghana; Jaime Albright, USA; Joshua Albright, USA; Sampson Antwi, Ghana; Gloria Ashuntantang, Cameroon; Vincent Boima, Ghana; Kirk N. Campbell, USA; Ewurabena Aniniwa Darkwah, Ghana; Victor Ezeibe, Nigeria; June Fabian, South Africa; Lori-Ann Fisher, Jamaica; David J. Friedman, USA; Keisha L. Gibson, USA; Raquel C. Greer, USA; Sumi Hidaka, Japan;

Taler B.K. Jefferson, USA; Krista L. Lentine, USA; Sophie Limou, France; Dominique E. Martin, Australia; Kevin Mott, USA; Marva M. Moxey-Mims, USA; Saraladevi Naicker, South Africa; Precil Diego Miranda de Menezes Neves, Brazil; Abdou Niang, Senegal; Irene L. Noronha, Brazil; Rulan S. Parekh, Canada; Afshin Parsa, USA; Brian L. Rayner, South Africa; Simone Sanna-Cherchi, USA; John R. Sedor, USA; Aude Servais, France; Barry Shingwenyana, South Africa; Bernard Sintim, Ghana; Junelle P. Speller, USA; Ernest Sumaili Kiswaya, Democratic Republic of the Congo; Fernanda Sales Luiz Vianna, Brazil

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Correspondence:
Akinlolu O. Ojo
University of Kansas School of Medicine
3901 Rainbow Boulevard, Mail Stop 1049
Kansas City, KS 66160
Phone: (913) 588-7201
Email: aojo@kumc.edu

Coauthor email addresses

Akinlolu O. Ojo, aojo@kumc.edu; Dwomoa Adu, dwoms15@gmail.com; Kate Bramham, kate.bramham@kcl.ac.uk; Barry I. Freedman, bfreedma@wakehealth.edu; Rasheed A. Gbadegesin, rasheed.gbadegesin@duke.edu; Titilayo O. Ilori, tilori1@bu.edu; Nichole Jefferson, nicholejeff@gmail.com; Opeyemi A. Olabisi, opeyemi.olabisi@duke.edu; Katalin Susztak, ksusztak@pennmedicine.upenn.edu; Bessie A. Young, youngb@uw.edu; Michael Cheung, michael.cheung@kdigo.org; Jennifer M. King, jennifer.king@kdigo.org; Morgan E. Grams, morgan.grams@nyulangone.org; Michel Jadoul, michel.jadoul@uclouvain.be; Ifeoma I. Ulasi, ifeoma.ulasi@unn.edu.ng

ABSTRACT

In people of African ancestry, *apolipoprotein L1* gene (*APOL1*) variants have been identified as causing increased risk of progressive chronic kidney disease (CKD). In April of 2024, KDIGO (Kidney Disease: Improving Global Outcomes) convened a Controversies Conference on *APOL1* Kidney Disease in Accra, Ghana. The goals of the conference were to review and discuss current evidence and controversies on *APOL1* kidney disease, including naming, epidemiology, pathophysiology, *APOL1* testing, treatment, and future research needs. Participants considered various terminologies for diseases related to *APOL1* risk variants (such as *APOL1*-mediated or -induced kidney disease) and had highest support for using *APOL1 kidney disease* to describe kidney pathologies associated with the *APOL1* G1 and G2 risk variants. Clinically, the term *APOL1* kidney disease can be used on its own or as an overall category of kidney disease, with further specification added as needed (for example, *APOL1* kidney disease, focal segmental glomerulosclerosis [FSGS]). Given that there currently are no established treatments for *APOL1* kidney disease, and *APOL1* genotype results are not by themselves actionable, there is insufficient evidence to guide recommendations for *APOL1* population screening or routine testing. However, genotyping can be an important clinical consideration for individuals to inform risk stratification, frequency of follow-up, living kidney donation, as well as clinical trial eligibility. Key areas of need and strategies for future research were delineated and are reported here.

INTRODUCTION

In people of African ancestry, two *apolipoprotein L1* gene (*APOL1*) variants have been identified as causing increased risk of progressive chronic kidney disease (CKD) compared with non–high-risk *APOL1* variants.[1-3] The risk variants, labelled G1 (two amino acid substitutions) and G2 (two deletions), confer resistance to infection from certain subspecies of the trypanosome parasite. Combinations of two risk variants (G1/G1, G2/G2, or G1/G2) are referred to as high-risk genotypes for the development or progression of CKD, and they are associated with a spectrum of kidney diseases of both continuous and categorical disease phenotypes (**Figure 1**).[4-7] There is emerging evidence that a single risk allele (G1/G0 or G2/G0) may also confer risk. For example, in Africa, the presence of one risk variant (G1/G0 or G2/G0) has been shown to elevate risk of CKD and focal segmental glomerulosclerosis (FSGS), but to a lesser degree than the high-risk genotype.[8]

Globally, the highest prevalence rates of the *APOL1* G1 and G2 variants are found in regions of West Africa (**Figures 2 and 3**).[8-10] Studies in African American individuals indicate that approximately 15%–20% of individuals with two *APOL1* risk alleles develop CKD, and 40%–60% of those with primary FSGS have two *APOL1* risk alleles.[11-13] Given that more than 100 million people in Sub-Saharan Africa may have two *APOL1* high-risk alleles, the potential burden of *APOL1* kidney disease in this region is catastrophically high.

The typical traits of *APOL1* kidney disease include recent (<10,000 years) African ancestry, variable proteinuria, interstitial fibrosis, and reduced kidney function. Even among individuals with a high-risk genotype, having two *APOL1* risk alleles does not necessarily lead to development of CKD. Approximately 15% of individuals with an *APOL1* high-risk genotype

will develop kidney failure, and a smaller fraction will develop FSGS.[5] The prevailing hypothesis is that individuals with high-risk genotypes require additional stressors or "second hits" to develop CKD. Despite the strong association between having a high-risk genotype and increased risk of kidney disease, it is not possible to predict which individuals with a high-risk genotype will develop CKD, idiopathic FSGS, hypertension-attributed kidney disease, HIV-1–associated nephropathy (HIVAN), or earlier failure of a kidney transplant from a donor with an *APOL1* high-risk genotype.

Since the original association between *APOL1* variants and kidney disease was reported in 2010,[1, 2] the field has advanced dramatically. However, significant gaps in knowledge remain regarding the genetics and clinical epidemiology of CKD caused by or attributable to *APOL1* risk variants, how the G1 and G2 variants mediate pathology, or what constitutes a second hit. In April of 2024, KDIGO (Kidney Disease: Improving Global Outcomes) convened a Controversies Conference on *APOL1* Kidney Disease in Accra, Ghana. Goals were to review the evidence base related to pathogenesis, epidemiology, and management of *APOL1* kidney disease as well as consider pragmatic and ethical issues surrounding *APOL1* genetic testing, especially as pertains to kidney transplantation. Priority research questions and strategies were outlined (**Table 1**). The meeting included 43 professionals in relevant disciplines globally as well as 11 participants from West Africa or the United States who represented either patients with kidney disease, their relatives, or caregivers.

TERMINOLOGY

Within existing literature, multiple terms have been used to describe diseases related to *APOL1* risk variants, such as *APOL1*-mediated,[14] *APOL1*-induced,[15] or *APOL1*-associated kidney

disease.[6] As discussed above, high-risk *APOL1* genotypes have been associated with a spectrum of kidney disease phenotypes: vascular disease (hypertension-attributed kidney failure), diseases of the podocyte, and infectious etiologies such as HIV- and COVID-associated nephropathy. In some of these, the causal relationship between high-risk *APOL1* variants and disease has been established. However, given the spectrum of disease phenotypes, it is possible there is a distinction between primary *APOL1* kidney diseases versus those where *APOL1* risk variants have a secondary or contributing role in nephropathy and its progression.

In debating the most precise terminology for conditions associated with *APOL1* risk variants, conference participants considered several terms based on the following factors: utility for all stakeholders, ease of use for patients and the community, flexibility to accommodate future knowledge, and capacity to encompass the spectrum of relevant kidney diseases. Hill's Criteria for Causation[16] were also used in considering relevant evidence (**Table 2**). The terms *APOL1*-mediated or -associated kidney disease lacked universal support largely because *APOL1* high-risk genotypes are probabilistic—not deterministic—risk factors for developing kidney disease, and most people with high-risk *APOL1* genotypes do not develop clinically apparent kidney disease.[5]

APOL1 kidney disease received the highest support for describing kidney pathologies associated with the G1 and G2 variants. Clinically, this term can be used on its own to prompt use of targeted therapies or as an overall category of disease, with further specification added as needed (for example, *APOL1* kidney disease, FSGS). The designation of *APOL1* kidney disease also represents the current state of knowledge of the pathogenesis while allowing for further

qualification, classification, description of secondary hits, or other factors as the field evolves. Use of the term *APOL1* kidney disease underscores a role for genetic testing but should not preclude diagnostic work-up (including a kidney biopsy, if indicated).

EPIDEMIOLOGY

Frequencies of *APOL1* high-risk genotypes are highest in West Africa, with up to 50% in Southeastern Nigeria, 37% in Central Ghana, and 25% in Southwestern Nigeria (**Figure 3**).[8] The available data regarding other Sub-Saharan African countries is sparse, although the few available studies show a quite significant prevalence of G1/G2 variants across Sub-Saharan Africa.[9, 29] Based on cohort and cross-sectional studies in the United States, the estimated allelic frequency among African Americans is 20% to 22% for G1 and 13% to 15% for G2, with approximately 10% to 15% having an *APOL1* high-risk genotype.[9] The global prevalences of the G1 and G2 alleles and the high-risk genotype are difficult to discern, as these vary widely between regions, many populations are either not tested or have small sampling, and it can be difficult to identify ancestry or ethnicity given gene flow and admixture.

Existing studies have focused on specific sub-populations, limiting understanding of the impact of *APOL1* variants in diverse populations of African descent that exist globally. Key areas of need include prevalence data for Black populations in the Caribbean, Brazil, the United Kingdom, Belgium, France, Sub-Saharan Africa, and any populations originating after dislocation by the diaspora (**Table 1**).

CKD Progression

The G1 and G2 *APOL1* alleles seem to associate with a similar phenotype, although analyses separating the two have shown heterogeneity in adverse outcomes between analyses and populations, possibly due to differences in sampling or environmental or socioeconomic factors (**Table 3**).[8, 19, 30-32] In most studies, the roles of G1 and G2 were analyzed together because associations can be attenuated when they are considered separately,[30, 33] possibly due to small sample size and owing to the difference of distribution and frequency of G1 and G2 among populations. Some studies have suggested a possible greater risk of having proteinuria or estimated glomerular filtration rate (eGFR) decline with genotypes containing the G1 allele.[9,20,30,33-35] Recent data from West Africa indicate these risks are greater with G2 alleles,[8] and that compared with G0/G0, the G2/G2 genotype is associated with the highest odds of FSGS,[8] with the adjusted odds ratio almost twice that of the G1/G1 genotype. In African American individuals, a graded risk of kidney failure in those with CKD and *APOL1* high-risk genotypes has been described; G1/G1 genotypes were associated with the highest risk, as well as earlier onset of kidney failure.[33] In patients with HIV, G1/G0 was associated with a higher risk of HIVAN than G2/G0 in one study.[20] In a separate study of patients with HIV, individuals with G2/G2 genotypes exhibited a tendency toward lower rates of kidney impairment, kidney failure, and HIVAN/FSGS, but the differences were not statistically significant.[35] More studies are needed to better ascertain the association of *APOL1* haplotypes with risks of adverse outcomes, especially in individuals with different types of CKD or without CKD.

The significance of possessing a single risk allele warrants further investigation given the cross-sectional data from West Africa indicating that individuals with a single risk allele, G1 or G2, have a higher risk of CKD compared with those with the G0/G0 genotype.[8] Additional studies

are also needed in minimally proteinuric CKD, because even without proteinuria there is a greater risk of kidney failure in individuals with high-risk genotypes.[36, 37] Based on data from the United States, hypertension accelerates all forms of CKD progression,[38] but it is not clear whether hypertension alone causes *APOL1* kidney disease. Although existing data demonstrate an association between *APOL1* risk variants and FSGS in children,[13, 39] the evidence regarding treatment-responsive FSGS remains inconclusive or non-definitive. And the relevance of G1/G2 *APOL1* in children or young adults with specific forms of CKD (*e.g.*, steroid-sensitive nephrotic syndrome, other glomerular diseases) is unclear.

Cardiovascular Disease

A metanalysis showed no overall association between the presence of *APOL1* risk variants and cardiovascular disease, suggesting that high-risk variants may not have a direct effect on cardiovascular disease independent from effects on kidney disease.[40] More studies are needed with sufficient power to investigate the association of *APOL1* genotypes with cardiovascular phenotypes in individuals with different etiologies of CKD and in individuals who do not have CKD.

Maternal and Fetal *APOL1* Genotype

Fetal *APOL1* genotype has been associated with maternal preeclampsia in preterm infants and with altered fetal growth in term infants.[41] There is a clear health disparity in the prevalence and severity of preeclampsia in Black women compared with Hispanic or white women, apparently due at least in part to having an *APOL1* high-risk genotype.[41-45] Whether the elevated risk of preeclampsia is due to maternal genotype, fetal genotype, or discordance between the two needs

to be determined for informed risk assessment and early intervention to improve pregnancy, maternal, and child outcomes in the short and long terms.

Children

In the United States, children having a high-risk *APOL1* genotype are reportedly at increased risk for early onset CKD.[13, 46] Findings suggest a common natural history for children with *APOL1*-associated glomerular disease, where children with high-risk genotypes have a more aggressive form of glomerular disease, which may relate to high rates of FSGS and prematurity. Among children in Sub-Saharan Africa, *APOL1* risk genotypes are also associated with early kidney damage.[47] In young adults, cross sectional data indicate that one copy of an *APOL1* risk allele is associated with higher blood pressure.[48] In children and youth with perinatal HIV, *APOL1* high-risk genotypes have been associated with CKD.[46] Further research is needed to investigate the impact of *APOL1* genotypes on blood pressure, particularly in the early stages of the disease before the onset of overt proteinuria or a decline in eGFR.

APOL1 PATHOGENESIS AND PATHOPHYSIOLOGY

APOL1 Expression and Effects of Risk Variants

APOL1 protein can act as an ion channel (pore) in trypanosome and eukaryotic cells.[26, 49-51] The G1 and G2 variants of *APOL1* alter the normal pore-forming function of the APOL1 protein, leading to increased pore activity.[26] While this enhances defense against certain pathogens, it can also contribute to kidney cell damage, as impaired glomerular permeability is associated with disease progression. Risk genotypes overexpressed in podocytes play a crucial role in podocyte injury and correlate with disease severity.[3, 25] Although podocyte expression of G1/G2 *APOL1*

and engagement of downstream signaling mechanisms is necessary for glomerulosclerosis, there is a growing body of data for extra-podocyte roles of *APOL1* risk variants.[52]

Based on single cell gene expression and open chromatin (RNA and ATAC) data as well as immunohistochemistry studies in kidneys of patients with COVID-19–associated nephropathy, *APOL1* mRNA is expressed in peritubular endothelial cells, glomerular endothelial cells, and podocytes.[53, 54] Expression of *APOL1* is regulated by cytokines (mostly by interferon), inflammation, hypoxia/ischemia, viruses, and nucleic acids.[22, 55-58] Although RNA data suggest broad *APOL1* expression across several tissue types, it is unknown whether these extrarenal tissues express splice isoforms of *APOL1* or have measurable *APOL1* protein. Hepatocytes constitutively express and secrete APOL1 protein into the circulation.[59] Expression (RNA and protein) and function of APOL1 in distal tubular epithelial cells, immune cells, and vascular smooth muscle cells needs further confirmation.

In vitro, high-risk *APOL1* variants have somewhat different effects in podocytes, human embryonic kidney cells, and pulmonary endothelial cells. Cytotoxicity has been observed with the high-risk genotypes. In cell-based models, G0 is generally non-toxic whereas G1 and G2 express toxic, gain-of-function variants.[6] Cell death is the standard readout of *APOL1* risk variant activity, though it is not fully clear whether cell death is important *in vivo*. Other relevant cell phenotype effects on clinical outcomes remain unclear.

Transgenic expression of human *APOL1* in mice recapitulates key features of the pathology in humans.[3] Expression of G0 *APOL1* (except in transgenic mice with a pre-eclampsia–type

syndrome) was not associated with phenotypic changes, whereas G1 and G2 *APOL1* expression in podocytes induced proteinuria and glomerular histologic lesions similar to FSGS, demonstrating ability of the variants to cause disease. Although existing mouse models (cell-type: podocyte, endothelial; Bacterial Artificial Chromosome transgenic) recapitulate rapidly progressive, proteinuric glomerular disease and glomerulosclerosis, this phenotype accounts for a minority of human *APOL1* kidney disease. Currently, there are no models of the slowly progressive, low proteinuria, chronic disease that accounts for the vast majority of human *APOL1* kidney disease. Functions associated with G1 or G2 APOL1 overexpression in cells or mice include ion channel,[26] actin cytoskeleton,[51, 60, 61] or mitochondrial dysfunction;[62] endoplasmic reticulum stress;[3] reduction of global protein synthesis;[63, 64] suPAR (soluble urokinase plasminogen activator receptor)-dependent activation of integrin;[65] activation of nucleotide sensors; and inflammation.[57]

Factors Influencing Penetrance

An exciting recent discovery is the identification of genetic variants that modify the penetrance of disease. The *APOL1* p.N264K variant was recently found to genetically and almost completely negate the effect of G2 risk alleles to levels comparable to G0, and this observation has been replicated in subsequent studies, making *APOL1* p.N264K the most robust genetic modifier of *APOL1* G2 to date.[21, 66, 67] However, it should also be noted that the *APOL1* p.N264K variant is present only in *APOL1* G2. The fact that this variant is uncommon, found in less than 1% of individuals of African ancestry,[21] suggests that it does not explain most of the incomplete penetrance of kidney disease risk of *APOL1* risk variants.

Several non-genetic modifiers that are key to the penetrance of *APOL1* recessive genotypes have been identified, validated, and replicated. Non genetic second hits resulting in glomerular disease include high interferon states, viral infections (HIV and COVID-19), exposure to alpha, beta, or gamma interferon, and *APOL1* overexpression,[3, 6, 20, 22, 68] with high interferon states having the strongest evidence. Genes that may contribute to disease progression include *ubiquitin D,*[15] *AT-hook DNA-binding motif-containing protein 1, glutathione S-transferase mu 1,*[69] and *SPACR related modular calcium binding 2.*[70-73] A truncating variant of *APOL3,* rs1108978, was significantly associated with increased CKD risk in patients monoallelic for *APOL1* G1/G2, suggesting an epistatic interaction and a potential protective effect of wild-type *APOL3* against *APOL1* kidney disease.[74]

Identifying modifiers is difficult for several reasons. There is a wide spectrum of clinical manifestations of *APOL1* kidney disease, and different mechanisms of APOL1 toxicity may have different modifiers. Common pathologies are most likely confounded by an initiating event (*e.g.*, diabetes mellitus, systemic lupus erythematosus). The diseases in which *APOL1* kidney disease is linked to incident disease (*e.g.*, FSGS) are less common, limiting sample sizes for analyses.

MANAGEMENT

Evaluating Risk of Progression

Genetic testing is definitive for the presence of *APOL1* risk alleles, although the presence of risk alleles is not prognostic or diagnostic of any specific kidney diseases. Measurement of specific biomarkers has potential for prognosis, indicating likelihood of disease progression, which is critical for clinical care. Plasma concentrations of tumor necrosis factor receptor (TNFR) 1 and

TNFR 2 and kidney injury molecule-1 (KIM1) have been independently associated with kidney outcome (kidney failure or 40% sustained decline in eGFR), and elevation of all three further increases risk.[75]

Development of clinical biomarkers and panels would serve an important need for evaluating progression of *APOL1*-induced kidney injury. Genetic or environmental modifiers of *APOL1* expression or activity could be used as components of biomarker panels. Polygenic risk scores could be used to represent markers for CKD progression. For example, to improve prediction of development or progression of *APOL1* kidney disease, a possible strategy is coupling Kidney Failure Risk Equations (KFREs)[76] with biomarkers.

Of note, much of the data on CKD progression due to *APOL1* variants came before the widespread use of sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and dual angiotensin and endothelin receptor antagonists, and it is unclear whether such therapies influence disease development or progression.

Potential Treatments and Implications

Agents

For treating patients with *APOL1* high-risk genotypes, APOL1 small molecule inhibitors, *APOL1* antisense oligonucleotides, and agents involving the JAK/STAT pathway blockade are being evaluated in Phase 2 through 3 trials (**Table 4, Figure 4**).[14, 28, 77-79] Development of specific therapies for *APOL1* kidney disease are being evaluated in FSGS, HIVAN, COVAN, collapsing glomerulopathy, and solidified glomerulosclerosis. The effects of APOL1-specific treatments in patients with *APOL1* high-risk genotypes and diabetic kidney disease, membranous

glomerulonephritis, or other forms of CKD should also be explored. The combination of diabetic kidney disease with *APOL1* high-risk genotypes is important given the high frequency of diabetic kidney disease in populations with recent African ancestry.

Beyond targeting APOL1, another approach is determining the effects of conventional therapies for FSGS and other glomerular diseases in those with *APOL1* high-risk genotypes. Investigational therapeutic targets could also include modifiers known to worsen CKD risk.

Transplant Recipients and Donors

If donor *APOL1* genotype is validated as a major cause of more rapid ~~earlier~~ graft failure after kidney transplantation and higher risk for reduced kidney function in live donors with recent African ancestry,[80] agents efficacious in native *APOL1* kidney disease should also be tested in the transplant setting. This is particularly important for recipients of *APOL1* high-risk donor kidneys and in *APOL1* high-risk genotype living kidney donors who have marked reductions in nephron mass following kidney donation. Agents must be shown to be safe in the transplant setting, including lack of interaction with immunosuppressive agents. Safety of kidney donation in live donor candidates with high-risk genotypes who are younger (as in child to parent or young sibling to sibling donation) is an important consideration.

Questions related to initiating potentially therapeutic agents in transplant medicine include whether they should be started immediately post-transplant or post-donation to prevent (or slow) nephropathy development, or once evidence of kidney disease is detected, and based on which criteria?

Areas Endemic for Trypanosomiasis and Other Infectious Diseases

Throughout Africa, marked regional differences exist in prevalence of *APOL1* variants and risk of CKD, as well as rates of sickle cell disease and HIV infection. Studies in admixed African American populations alone may not represent results in continental Africa. Therefore, a priority for therapeutic development is including African sites in randomized controlled trials. Post market, availability of treatments is of utmost importance.

It is not clear whether APOL1 blocking or lowering affects risk of trypanosomiasis. Although trypanosomiasis is at low rates in Sub-Saharan Africa (<1,000 cases/year),[81] performing a risk-benefit ratio for preventing kidney failure versus infection risk and monitoring for increasing trypanosomal and other infections during APOL1-targeting treatments will be important. Surveillance for trypanosomal infection and other infectious diseases should be part of clinical trial designs.

PRACTICAL AND ETHICAL ISSUES RELATED TO *APOL1* GENETIC TESTING

Screening or Testing

At population levels, there is insufficient evidence to guide recommendations for *APOL1* routine testing or screening. There are no established treatments or treatment recommendations for *APOL1* kidney disease, and *APOL1* genotype results are not by themselves actionable for changing management. *APOL1* testing has the potential to reinforce racialized medicine given the historical and ongoing conflation between race, ethnicity, and ancestry.

However, for individuals, genotyping is an important clinical consideration given that the high-risk *APOL1* genotypes are associated with significantly increased risk of CKD progression, and genotyping could inform risk stratification and frequency of follow-up. Patient and clinician knowledge of the presence of an *APOL1* high-risk genotype has been associated with a greater reduction in blood pressure, an increase in screening for kidney disease, as well as increased self-reported behavior changes relative to patients whose tests revealed low-risk genotypes or control subjects waiting for testing.[82]

Box 1 outlines principles for guiding decision-making about *APOL1* testing inclusive of patients with a high potential of having an *APOL1* high-risk genotype. Established guidance on disclosure of genetic test results to family members (cascade testing) should be followed. This typically involves provision of support and resources to a patient for passing on information to the family (if they choose) who may then seek counseling and testing. Additional considerations for *APOL1* genotyping include risk of stigmatization related to test results, implications of test results for genetic relatives, and the possibility of unexpected paternity revelations. Practical guidance related to counseling, genotyping, and diagnosis for patients who may have *APOL1*-associated nephropathy was developed by a multidisciplinary, racially diverse group and is described in Freedman et al., 2021.[83]

At population levels, evaluation of costs and potential benefits is important prior to investing in *APOL1* testing. Consideration will be informed by the availability of testing or management for CKD. Consolidation of resources may be helpful in facilitating access to *APOL1* testing at regional or national levels, and successful scale-up approaches in other disease areas, such as

HIV, may be informative. For operationalizing genetic testing, the following are necessary: a validated test in a registered laboratory with appropriately trained staff; pre- and post-testing counseling; availability of co-designed educational material tailored to levels of health literacy; and a process for early surveillance and intervention, including in children. In high prevalence populations, community leaders, content experts, and faith leaders should be engaged to facilitate community education initiatives.

Community engagement is also key to facilitating widespread acceptance of early surveillance and potential intervention. Authentic community engagement is critical in designing and implementing *APOL1* prevalence and research studies, testing in clinical care, as well as communicating how findings inform recommendations. To avoid the racialization of *APOL1* genetic testing, consistent use of clear terminology is very important to prevent conflation between race, ethnicity, ancestry, and *APOL1* genotype.

Testing in infants/children. In children with FSGS and CKD, *APOL1* genotyping can inform prognosis, and early targeted testing for *APOL1* genotype in infants and children could make possible early surveillance and intervention. Yet unnecessary testing would be costly and potentially anxiety-provoking. Once efficacious treatments are available, guideline recommendations for screening and early testing of infants and children should be considered for development. Studies comparing children with slow versus fast progression to CKD will be important, as will determining eGFR slope and the role of modifiers at the inflection point where individuals begin to decline.

Implications for Kidney Transplant

In the United States, living donors with *APOL1* high-risk genotypes more often develop advanced CKD post-donation,[84] and receipt of deceased donor kidneys from *APOL1* high-risk genotype donors are associated with more rapid graft failure.[85-87] Results are mixed,[88-90] but recipients with high-risk *APOL1* genotypes may also have reduced graft survival. The ongoing APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO) is prospectively assessing kidney allograft survival from donors with recent African ancestry based on donor and recipient *APOL1* genotypes.[80] Existing prediction tools to support decision-making about graft outcomes,[91] including wait list times, do not include graft *APOL1* genotype data, although including *APOL1* genotyping in The Kidney Donor Risk Index has been shown to improve tool performance.[92] Considering *APOL1* genotype instead of race changes the perceived quality of kidneys from African American deceased donors and may impact their allocation.[92]

Currently there is global and center variation in *APOL1* genotyping for candidate donors. Among transplant centers in the United States, in one survey, half of centers offered *APOL1* testing.[93] The KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors[94] suggests that *APOL1* genotyping may be offered to donor candidates with Sub-Saharan African ancestry. The British Transplantation Society[95] recommends offering *APOL1* genotyping (which is publicly funded by the United Kingdom National Health Service) as part of the assessment and communication of donor risk early in the evaluation of all potential donors of African heritage under 60 years old. A Delphi consensus panel supported policy options involving discussion and shared decision-making among patients, donors, and family

stakeholders, with opposition to unilateral decision-making by transplant programs or to prohibiting donation.[96]

There are no data to assess the impact of *APOL1* genotyping on donor candidate experiences and outcomes, but based on the existing evidence best practice should include the following: a holistic, personalized evaluation of potential benefits and risks for prospective living donor and transplant candidates (KDIGO living donor equitable decision-making framework[94]); specific risk assessment for individuals (genotype alone may not confer substantive risk); availability of alternative options for intended recipient, *e.g.* living or deceased donor (and/or dialysis); pre- AND post-testing genetic counseling; consideration of resources; opportunity for follow-up; and potential access to future therapies such as APOL1-targeted treatments.

Increasing Participation in Clinical Trials

To raise awareness about CKD and *APOL1* kidney disease as well as encourage participation in clinical trials, community outreach is required to develop, strengthen, and sustain relationships with trusted community leaders and partners. Figure 5 highlights strategies for engaging patients, caregivers, and community partners impacted by *APOL1* kidney disease throughout the clinical research process.

FUTURE DIRECTIONS

APOL1 kidney disease disproportionately affects communities with limited resources and infrastructure for healthcare research and delivery. As the understanding of and treatments for *APOL1* kidney disease are further developed, engagement and education of communities and

healthcare professionals, including those in primary care, will be key in improving patient health in all regions affected. To guide research on *APOL1* kidney disease, continued discussion among stakeholders is needed along with concerted efforts to ensure active and informed participation in clinical studies by members of the affected community.[97] Having study sites in underserved regions, such as West Africa, is important for gaining understanding of pathogenesis and treatment as well as engaging with local communities. When treatments become available, patient access to nephrologists with experience or knowledge of *APOL1* kidney disease will be paramount, as will affordability of any new therapies.

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Table 1. Key questions, knowledge gaps, and research recommendations for *APOL1* kidney disease

Clinical realm	Questions and knowledge gaps	Strategies for research
Epidemiology	• What are prevalence data for *APOL1* risk alleles in children, young adults, and pregnant women? • What are prevalence data for sickle cell trait and sickle cell trait combined with *APOL1* high-risk genotypes? • Where are the gaps in data among populations and ethnicities, some of whom may have variations influenced by transatlantic slave trade or migration? • What is the long-term progression of *APOL1*kidney disease in individuals with different genotypes, and how can longitudinal data address this? • What is the role of *APOL1* genotypes in pediatric and young adult populations with specific forms of CKD, such as steroid-sensitive nephrotic syndrome, treatment-responsive FSGS, and other glomerular diseases? • How do proteinuria levels and potential "second hits" modify the progression of *APOL1* kidney disease, and why do some high-risk individuals not progress? Does this vary by geographic location? • Is preeclampsia due the maternal and fetal *APOL1* genotype discordance? • What is the association of *APOL1* genotypes with fetal birth weight? • How do we separate the effect of cardiovascular disease and CKD in high-risk *APOL1* genotypes?	• Update prevalence data across various populations at risk globally. • Report prevalence and outcome data by haplotype. • Evaluate incidence and prevalence of cardiovascular disease in individuals with *APOL1* risk alleles without kidney disease or mild disease. • Determine incidence of incident hypertension in children based on *APOL1* genotype. • Evaluate longitudinal data stratified by proteinuria or second hits or modifiers, including individuals with *APOL1* high-risk genotypes who do not progress to kidney disease. • Study COVID-19–associated nephropathy and multisystem inflammatory syndrome in children and adults to understand the influence of *APOL1* genotype. • Perform studies including individuals with *APOL1* high-risk genotypes and no CKD, especially in areas of high prevalence.

	• How do *APOL1* high-risk genotypes influence the risk of kidney complications, including HIVAN, in HIV-infected individuals? Are the observed associations consistent across different populations and study designs?	
Pathogenesis and pathophysiology	• How can *APOL1* risk variants act as disease causing or disease accelerating in different patients? • What is the regulation of expression (RNA and protein) and function of APOL1 in distal tubular epithelial cells, immune cells, and vascular smooth muscle cells? • Do *APOL1* risk variants cause hypertension-attributed kidney disease, or are elevated blood pressures secondary to CKD? What are *APOL1* risk variant effects on progression of other forms of kidney disease (*e.g.*, membranous, lupus). • Is there an association between *APOL1* genotype and incident hypertension in children? • What are the effects of environmental triggers on phenotype development? • What are the effects of cell type expression on disease phenotypic manifestation? • In which cell types are APOL1 risk variant proteins damaging versus protective?	• Further characterize the mechanism of *APOL1*-related injury in multiple cell types. • Explore the relationship between *APOL1* genotype and ion channel function, APOL1 protein trafficking, inflammation, and cell death. • Develop cellular models of modifiers (genetic, environmental). • Study the regulation of *APOL1* expression and function in immune cells, vascular smooth muscle, and tubular epithelial cells. • Confirm APOL1 protein expression in healthy control and diseased tissue across candidate tissues and cell types. • Determine the molecular signature of *APOL1* kidney disease. • Characterize *APOL1* copy number variation in African, Brazilian, and North American populations and test association of copy number with kidney disease phenotypes. • Develop animal models for slowly progressive disease phenotypes and

	• What cell types (podocytes, endothelial, immune cells) does APOL1 injure in *APOL1* kidney disease? • Does circulating APOL1, either on HDL or in immune cells, influence *APOL1* kidney disease? • How do *APOL1* risk alleles contribute to kidney failure in non-proteinuria forms of kidney disease, and what mechanisms drive progression in these cases? • Are there differences in the mechanism by which G1 and G2 injure kidney cells? • Why do some cell types (e.g. hepatocytes) not develop *APOL1*-mediated injury? • Is p.N264K a protective haplotype or genetic modifier? • For multiple extra renal tissues, does the presence of RNA translates to measurable APOL1 protein? • Do different types of tissue express splice isoforms of APOL1?	determine their concordance with human *APOL1* kidney disease phenotypes. • Determine if APOL1 modulates kidney endothelial phenotypes. • Conduct a comprehensive omics analysis of cell injury following expression of *APOL1* high-risk alleles. • Perform comparative analysis of injury in different cell types following expression of *APOL1* high-risk alleles. • Develop cellular and animal models for cardiovascular disease and major adverse cardiovascular events. • Compare phenotype cell and model organism phenotypes to enable cellular studies. • Conduct more sequencing of *APOL1* as well as whole-genome sequencing in Africa with different tools (including long read) to capture the full spectrum of common and rare genetic variation (single nucleotide polymorphisms and structural variants). • Incorporate p.N264K and other modifier variants into refined genotypes to assess the contribution of heterozygous high-risk genotypes to CKD, kidney failure, or FSGS. • Increase utilization of p.N264K in inclusion criteria of clinical trials.

		• Apply knowledge about p.N264K to study existing cohorts to measure outcome. • Characterize the full range of *APOL1* variants in *in vitro* systems.

Management	• When APOL1-directed therapy is available, who should be treated and when?
	  ○ Should we treat when there is evidence of—
	  ▪ significant podocytopathy (heavy proteinuria)?
	  ▪ moderate CKD progression in younger individuals?
	  ▪ high risk for kidney failure using validated prediction equations and biomarker panels?
	• If we design medicines targeting p.N264K variant, might they work against the G1 variant?
	• What is the role of dual angiotensin receptor blockers, endothelin receptor antagonists, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists on diagnosis course?
	• Is gene editing (CRISPR) needed with new directed therapies?
	• What is the role of one *APOL1* risk variant in FSGS and solidified glomerulosclerosis?
	• What is the prognostic importance of having slightly reduced eGFR in *APOL1* high-risk
		• Identify biomarkers for *APOL1* kidney disease injury.
		• Identify biomarkers of *APOL1* kidney injury in donor kidneys to determine potential effects on recipient outcomes and safety of living kidney donation.
		• Determine the role of *APOL1* p.N264K variant, other genetic modifiers, and polygenic risk scores in improving performance of biomarker panels for disease progression.
		• Determine the effects of conventional therapies for FSGS and other glomerular diseases in those with *APOL1* high-risk genotypes.
		• Identify biomarkers of *APOL1* kidney disease in deceased donor kidneys, such as rapidly determined expression levels of APOL1 protein, *APOL1* mRNA, *etc.*
		• Evaluate novel therapies in African clinical study sites.

	living kidney donors who lack proteinuria or elevated blood pressure? • What is the role of *APOL1* high-risk genotype in the clinical course of pediatric nephrotic syndrome or minimal change disease (related to issues such as frequent relapse or steroid dependency)? • Is there a role for conventional treatment of FSGS and other glomerular diseases (calcineurin inhibitors, cytotoxic agents) in patients with *APOL1* high-risk genotypes? • What is the role of *APOL1* high-risk genotypes in progression of forms of CKD not in the *APOL1* disease spectrum: especially diabetic kidney disease (due to high frequency), as well as membranous glomerulonephritis, IgA nephropathy, minimal change disease, and polycystic kidney disease	
Issues related to testing	• What are the optimal ways to protect patients from issues related to potential for stigmatization and discrimination (*i.e.* policies and legislation for how genetic results will be used) • What are the long-term health impacts, including cardiovascular disease and pregnancy, for living kidney donors who have high-risk *APOL1* genotypes? • What are the impacts of different risk alleles (G1/G1, G1/G2, G2/G2) and protective variants on living donor outcomes, and what are the important triggers for developing CKD?	• Gather data on qualitative and quantitative patient and family member experiences of testing. • Increase population data necessary for understanding who would benefit from *APOL1* testing, including pediatric populations.

	• Is there interaction between recipient and donor genotypes that could affect paired scheme donations? • What are the outcomes for high-risk *APOL1* living kidney donors in non-US countries with different resources? • What are the impacts on individuals, families, and communities of donating and not donating kidneys from individuals with high-risk *APOL1* genotypes (economic, psychological, societal), including consequences of continuing dialysis? • What are the impacts of *APOL1* testing on overall number of living kidney donations and perception of future kidney donation? • What are the effects of donor and recipient *APOL1* status (including differences in G1/G2 variants and protective factor) on graft survival in countries outside of the United States? • What are the impacts of recipient status on other health outcomes (infection, non-kidney)? • What is the role of rapid testing to inform decision-making about accepting a graft? • What is the best method of communicating *APOL1* graft status, and how does status impact patient experience (*e.g.*, increase or reduce anxiety)?	

APOL1, apolipoprotein L1; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CRISPR, clustered regularly interspaced short palindromic repeats; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; IgA, immunoglobulin A.

Table 2. Applying Hill's Criteria for Causation[16] to the association between APOL1 genotype and development of kidney disease

Criterion	Comments and clarifications	Evidence
Strength of the association	Is the effect size sufficient?	• *APOL1* kidney risk variants have been reproducibly associated with a spectrum of kidney diseases, including both continuous and categorical kidney disease phenotypes.[4-6] • Effect sizes are large for common variants. • *APOL1* kidney disease transcends standard histopathologic classification, encompassing both immune (e.g. HIVAN, COVAN) and non-immune CKDs (hypertension-CKD).
Consistency of the association	Has the association been repeatedly observed by different persons and in different places, circumstances, and times?	• Genetic associations have been replicated in multiple cohorts.[1, 17-21] • ***APOL1* high-risk genotypes do not lead to clinical disease in the majority of people with them.**

Specificity of the association	Evaluating specificity may not be appropriate for diseases that have more than one cause.	• **Diseases such as HIVAN, COVAN, FSGS can occur in the absence of the *APOL1* high risk genotype.**
Temporal relationship of the association	Is there evidence one event precedes the other?	• There is such evidence in therapeutic interferon-induced kidney disease;[22] COVAN-associated kidney disease;[23] and mouse models.[3, 24, 25]
Biological gradient (dose-response curve)	Quantitative measurement may be difficult.	• In HEK cells,[26, 27] risk variant *APOL1* causes dose-dependent cytotoxicity. • Podocyte-specific *APOL1* high-risk genotype mice develop dose-dependent disease.[3]
Plausibility	Is causation biologically plausible?	• Data from cell and mouse models support plausible causation.
Coherence	A causal interpretation should not conflict with the generally known facts of the natural history and biology of the disease.	• A causal interpretation does not conflict with clinical and epidemiological data.
Experiment	Is there experimental or semi-experimental evidence? Can specific	• Podocyte-specific *APOL1* high-risk genotype mice develop dose-dependent disease.[3]

	actions prevent or attenuate disease?	• Mice transgenic for *APOL1* G1, or G2 but not G0 BACs or fosmids with the endogenous human promoter develop albuminuria and azotemia after interferon-gamma treatment, replicating the human glomerular phenotype including albuminuria and global sclerosis.[24, 25] • Phase 2 clinical trial data showed reductions in proteinuria with targeted treatment.[28]
Analogy	May be applied in some circumstances. Is it fair to judge by analogy—meaning accepting slighter but similar evidence based on another drug or cause of disease?	No analogies have been identified.

APOL1, apolipoprotein L1; BAC, bacterial artificial chromosome; CKD, chronic kidney disease; COVAN, COVID-19–associated nephropathy; HEK, human embryonic kidney; HIVAN, HIV-associated nephropathy; IFN, interferon.

Table 3. Association of risk indicators of chronic kidney disease with *APOL1* genotypes

Genotype	N (total)	Odds ratio (95% CI)		
UK Biobank (Adamson et al, 2024[30])[a]				
		UACR > 3 mg/mmol or eGFR <60 ml/min per 1.73m^2		
G0/G0	2853	1.0 (ref)		
G0/G1	2273	1.0 (0.8–1.3)		
G0/G2	1219	1.1 (0.9–1.4)		
G1/G1	644	1.4 (1.1–1.9)		
G1/G2	320	1.6 (1.1–2.2)		
G2/G2	153	1.2 (0.7–2.0)		
H3Africa Kidney Disease Research Network (Gbadegesin et al, 2025[8])[b]				
		UACR > 3 mg/mmol or eGFR <60 ml/min per 1.73m^2		
G0/G0	2284	1.0 (ref)		
G0/G1	2566	1.2 (1.0-1.4)		
G0/G2	1028	1.2 (1.0-1.4)		
G1/G1	1387	1.4 (1.2-1.6)		
G1/G2	929	1.3 (1.1-1.6)		
G2/G2	160	2.1 (1.4-3.1)		
African American Study of Kidney Disease and Hypertension (AASK, Parsa et al 2013[19])				
No. *APOL 1* risk alleles		**Kidney failure**	**Kidney failure or doubling of serum creatinine**	**CKD progression**

0	234	1.00 (ref)	1.00 (ref)	Ref
1	299	1.04 (0.72-1.48)	1.15(0.86-1.53)	
2	160	2.21 (1.56-3.14)	2.03 (1.50-2.74)	1.88 (1.46-2.42)
African Americans in the Atherosclerosis Risk in Communities Study (Foster et al, 2013[31])				
No. *APOL1* risk alleles		**Incident kidney failure**	**Incident CKD**	**CKD progression**
0 or 1	2661	1.00 (ref)	1 .00 (ref)	1.00
2	404	1.92 91.19 -3.10)	1.51 (1.01 -2.24)	2.43 (1.00-5.95)
Jackson Heart Study (Young et al, 2021[32])				
		Incident kidney failure	**Incident CKD**	**Incident albuminuria**
G0/G0		1.00 (ref)	1.00 (ref)	1.00 (ref)
G0/G1		2.47 (0.49-12.42)	1.14 (0.83 -1.56)	1.50 (0.98 TO 2.30)
G0/G2		9.05 (1.79 to 45.85)	1.65 (1.06-2.57)	1.88 (1.04-3.40)

[a]Association of risk of hospitalization and death as a result of a (non-COVID-19) infectious disease with *APOL1* genotypes compared with G0/G0, adjusted for age, sex, Townsend deprivation index, and genetic principal components 1–4.

[b]N represents cases and controls.

CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; ref, reference.

Table 4. *APOL1* inhibitors in clinical development (as of March 2025)

Agent class	Name	Route of administration	ClinicalTrials.gov identifier	Patient population	Phase	Status
Antisense oligonucleotide inhibitor	AZD2373	Subcutaneous injection	NCT05351047	Healthy males of sub-Saharan West African ancestry	1	Completed
			NCT06824987	Adults with *APOL1*-mediated kidney disease	2	Enrolling
APOL1 inhibitor	Inaxaplin (VX-147)	Oral tablet	NCT05324410	Healthy participants	1	Completed[78]
			NCT04340362	Adults with *APOL1*-mediated FSGS	2A	Completed[28]
			NCT05312879	Adults and children with *APOL1*-mediated proteinuric kidney disease	2/3	Enrolling
	MZE829	Oral capsules	NCT06830629	Adults with *APOL1* proteinuric kidney disease	2	Enrolling
JAK-STAT inhibitor	Baricitinib	Oral pill	NCT05237388	Adults with FSGS or hypertension-attributed CKD	2	Enrolling[79]

APOL1, apolipoprotein L1; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; JAK-STAT, Janus kinase/signal transducer and activator of transcription; NCT, National Clinical Trial.

Box 1. Principles to guide decision-making for *APOL1* testing of populations, families, or individuals

The individual (or their substitute decision-maker) provides informed consent.
AND
The individual is a member of a population with known or suspected high prevalence of *APOL1* risk variants (*e.g.*, self-identified recent African ancestry OR member of population with a high level of genetic admixture).
AND
The individual has kidney disease OR is a prospective living kidney donor OR has a relative with an *APOL1* high-risk genotype.
AND
CKD care and screening are available AND *APOL1* test results could change management (*e.g.*, an effective treatment for *APOL1* is available OR results could lead to increased surveillance for CKD OR results would inform risk/benefit evaluation in decision-making about living kidney donation).
AND
If *APOL1* genetic testing does not present an unacceptable risk of harm as determined by the individual.
AND
Appropriately qualified counseling is available to support voluntary and informed decision-making about testing.
AND/OR
APOL1 test results could assist in relieving significant anxiety or inform reproductive decision-making.

Figure Legends

Figure 1. *APOL1* high-risk genotypes increase the risk of many types of kidney disease in individuals of recent African ancestry. High-risk genotype refers to having an *APOL1* allelic combination of G1/G1, G1/G2, or G2/G2. CKD, chronic kidney disease; DKD, diabetic kidney disease; FSGS, focal segmental glomerulosclerosis; H-ESRD, hypertension-attributed end-stage kidney disease; HIVAN, HIV-associated nephropathy; HR, high risk; OR, odds ratio. Modified from Friedman and Pollak, 2021.[5]

Figure 2. Global frequency of *APOL1* high-risk genotypes. High-risk genotype refers to having an *APOL1* allelic combination of G1/G1, G1/G2, or G2/G2. ATG, Antigua and Barbuda; DR, Dominican Republic; TTO, Trinidad and Tobago; US, United States. Data from Choudhury et al, 2020[10] and Gbadegesin et al., 2025.[8]

Figure 3. *APOL1* risk haplotypes in African populations. Map shows prevalences of high-risk *APOL1* genotypes (G1/G1, G1/G2, or G2/G2). Data from Choudhury et al, 2020[10] and Gbadegesin et al., 2025.[8]

Figure 4. Investigational therapies for *APOL1* kidney disease. APOL1, apolipoprotein L1; COVAN, COVID-19–associated nephropathy; IFN, interferon; IL, interleukin; JAK, Janus kinase; NLRP, nod-like receptor family pyrin-domain containing; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; TYK2, tyrosine kinase 2.

Figure 5. Engaging the community in *APOL1* clinical studies. Strategies for engaging patients, caregivers, and community partners impacted by *APOL1* kidney disease.

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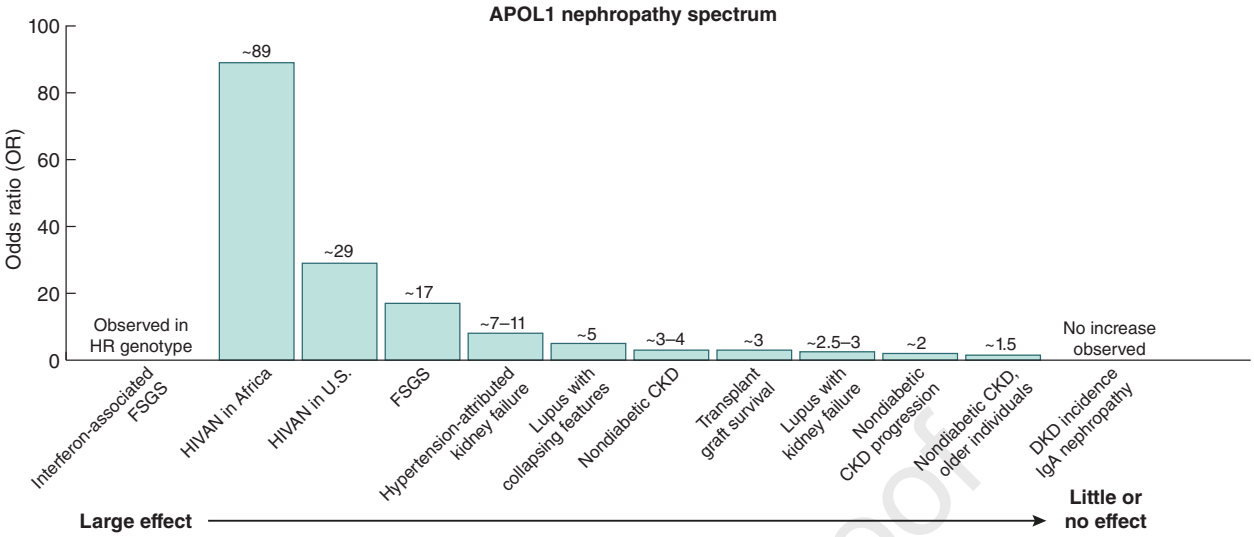
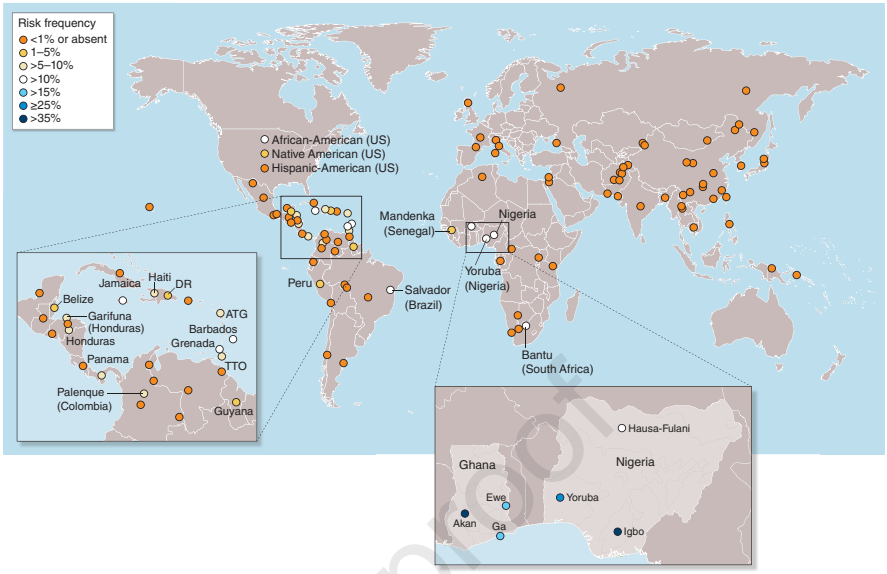
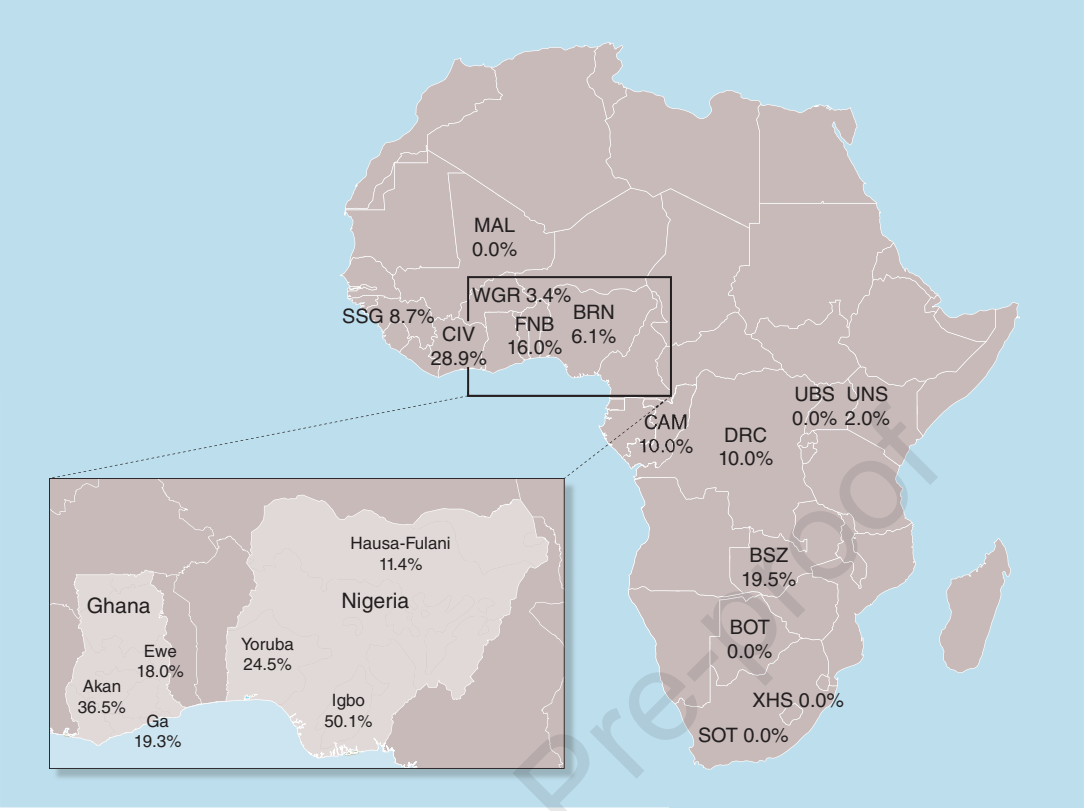
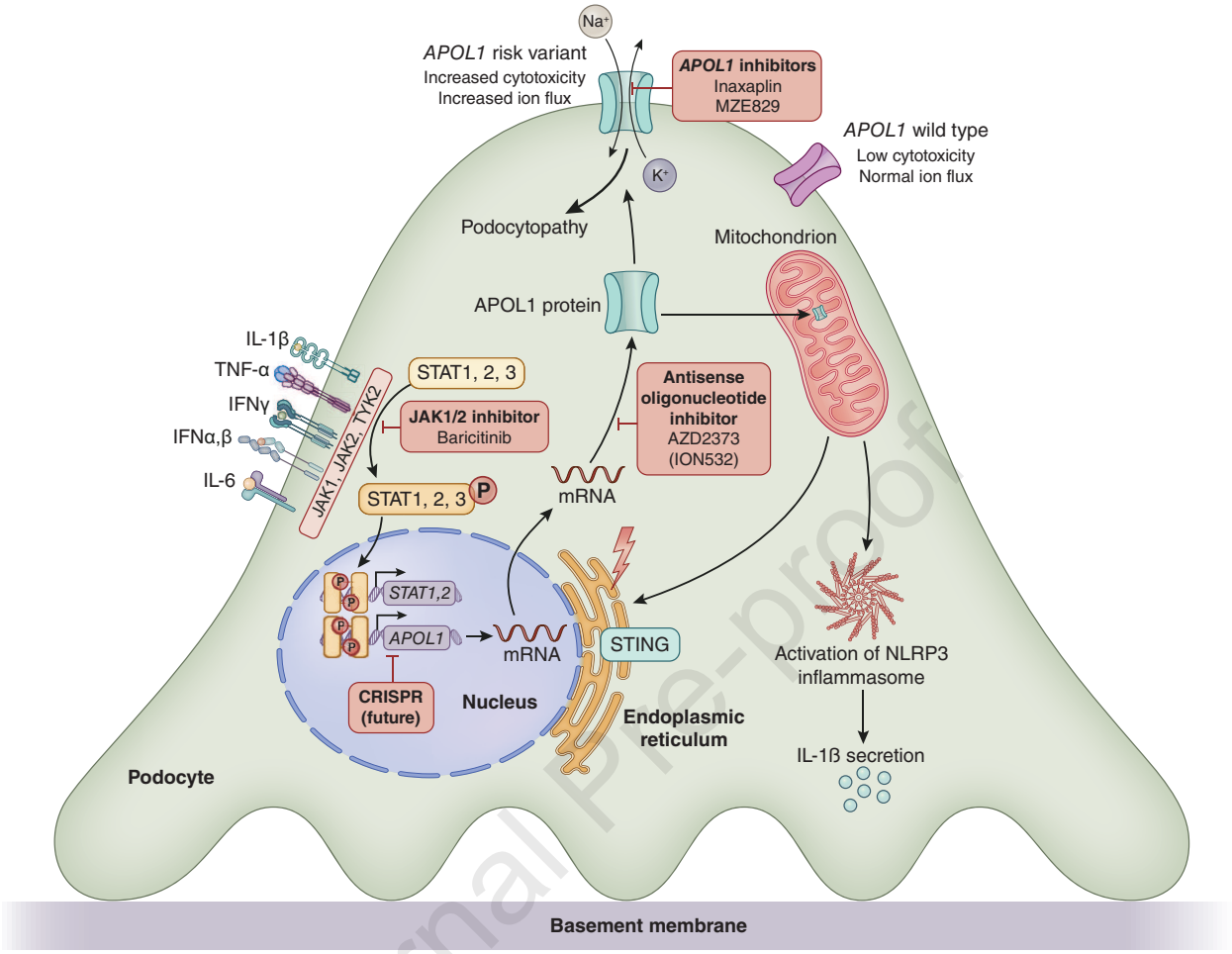






	APOL1 genotype frequencies (%)					
Population	**G1**	**G2**	**G1/G2**	**G1/G1**	**G2/G2**	**High-risk genotype**
Mali (MAL)	8.3	9.0	0.0	0.0	0.0	0.0
Guinea (SSG)	14.8	15.2	4.3	2.2	2.2	8.7
Congo (CAM)	16.0	13.0	2.0	4.0	4.0	10.0
Gur West Africa (WGR)	11.4	15.3	1.7	1.7	0.0	3.4
Côte d'Ivoire (CIV)	43.2	11.8	0.0	23.7	5.3	28.9
Fon from Benin (FNB)	34.1	9.0	4.0	12.0	0.0	16.0
Berom Nigeria (BRN)	13.3	8.2	0.0	6.1	0.0	6.1
Democratic Republic of Congo (DRC)	8.3	8.3	3.3	6.7	0.0	10.0
Uganda Bantu (UBS)	14.3	10.6	0.0	0.0	0.0	0.0
Uganda (UNS)	1.7	11.5	2.0	0.0	0.0	2.0
Bantu Zambia (BSZ)	5.2		7.3	0.0	12.2	19.5
Botswana (BOT)	5.2	10.4	0.0	0.0	0.0	0.0
South Africa, Sotho (SOT)	0.0	18.8	0.0	0.0	0.0	0.0
South Africa, Xhosa (XHS)	6.3	18.8	0.0	0.0	0.0	0.0
Akan	31.8	11.7	11.7	23.2	1.6	36.5
Ewe	26.3	14.7	7.2	9.0	1.8	18.0
Ga	32.6	15.2	7.6	9.5	2.3	19.3
Yoruba	35.9	11.0	8.9	14.4	1.2	24.5
Igbo	25.0	12.1	19.6	26.7	3.8	50.1
Hausa-Fulani	12.2	12.0	4.5	5.3	1.6	11.4



Engaging the community in *APOL1* clinical studies

Design studies with input from the community to address barriers to recruitment and retention (e.g., conduct clinical trial visits within community settings or aid transportation to study sites.)

Involve community members in design of trials with the aim of addressing potential barriers to recruitment and retention.

Co-create and develop culturally sensitive trial materials (e.g., informed consent forms, videos, infographics) that are appropriate to participant literacy level and linguistic background.

Reimburse community members for relevant time and effort.

Disseminate trial updates and research findings to the community.

Contribute to local community needs regarding health, wellbeing, infrastructure, resources, research translation, and capacity for ongoing co-designed research.

Assemble diverse research teams, staff, and peer mentors, including those with concordant language and culture.