APOL1- kidney disease in African-American diaspora populations

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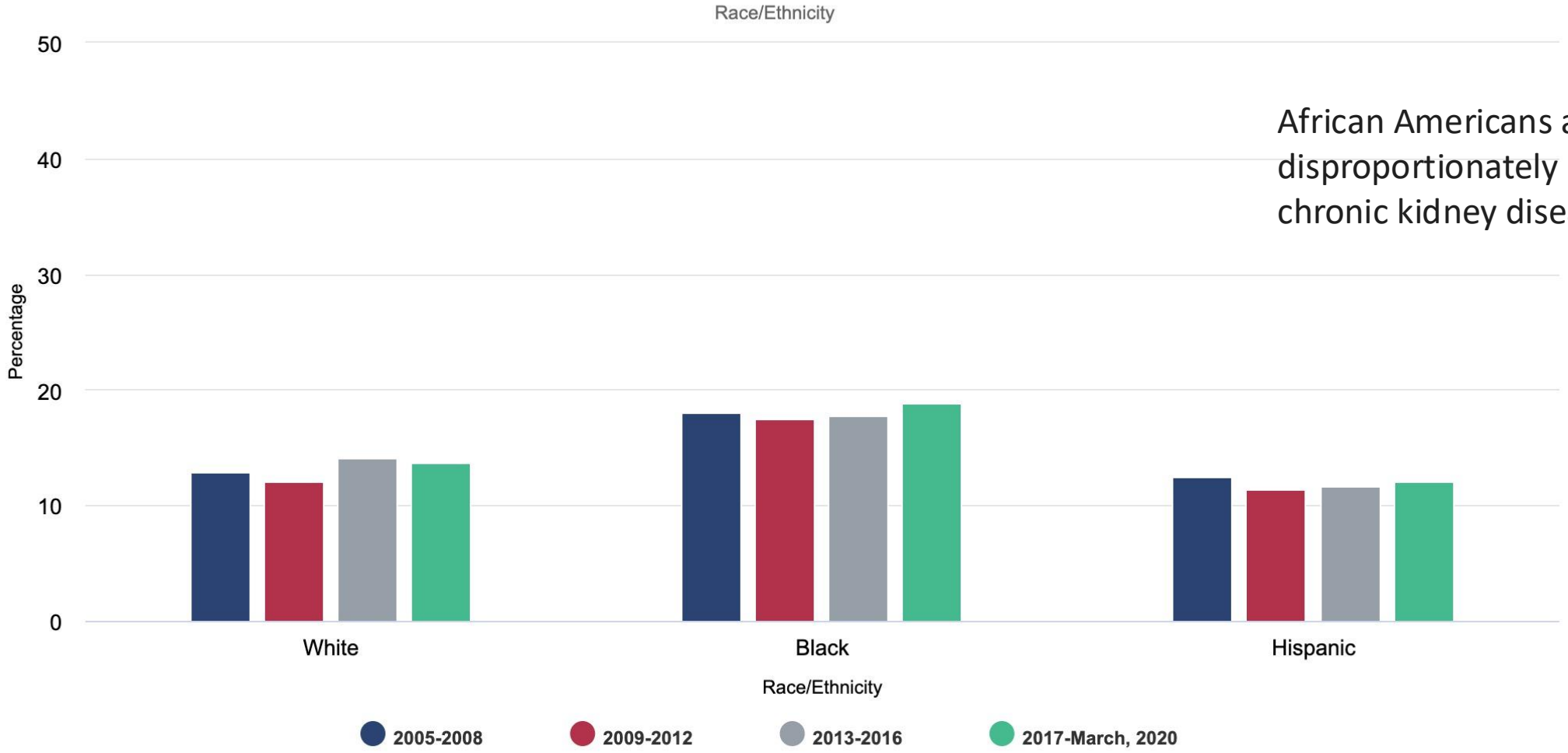
Outline

- APOL1 risk variants are common in people with recent African ancestry
- They drive a large fraction of kidney failure risk
- Precision therapies are now targeting *APOL1* biology (especially its pore/channel activity).
- Transplant decisions, access, and trust are directly affected by how we use APOL1 information.
- Equity: genetic advances can either reduce or widen disparities

Racial/ethnic disparities in CKD in the United States

Figure 1.1 Prevalence of CKD in U.S. adults



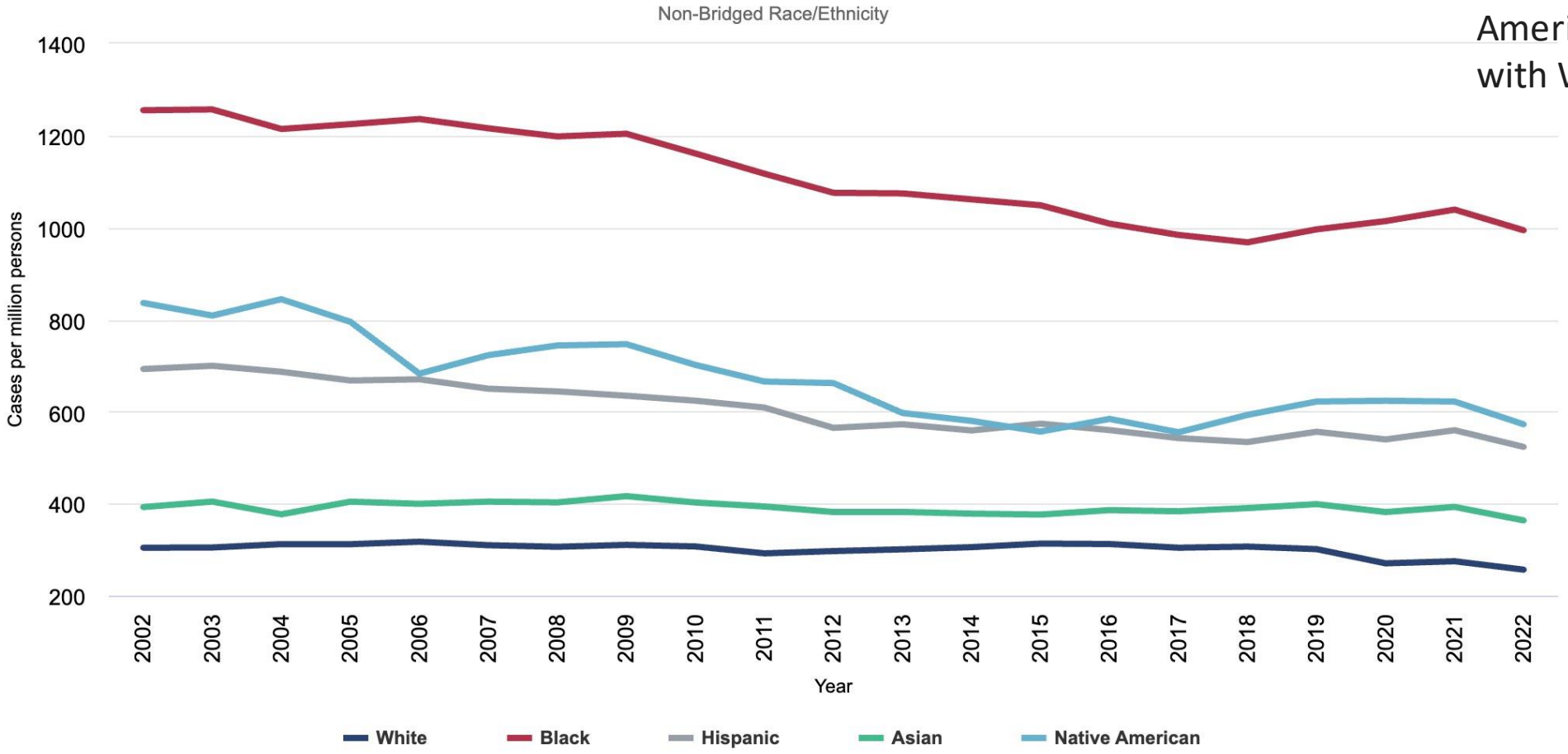
African Americans are slightly disproportionately diagnosed with chronic kidney disease (CKD)

Data Source: 2024 United States Renal Data System Annual Data Report

Racial/ethnic disparities in ESKD in the United States

in 2021, the prevalence of ESKD was >3.5x greater in African American individuals compared with White individuals

Figure 1.4a Adjusted incidence of ESRD by patient characteristics, 2002-2022



African Americans~ 2x ESKD risk compared to white patients, after accounting for differences in socioeconomic and clinical risk factors

Data Source: 2024 United States Renal Data System Annual Data Report

Disparities reflect multi-level causes

- Upstream: structural racism, socioeconomic factors, neighborhood/environmental exposures, food & medication access
- Health system: CKD detection, referral timing, quality of BP/DM care, access to nephrology & transplant
- Biology: *APOL1* (ancestry-linked), sickle cell trait and other variants, gene–environment interactions
- *APOL1*-Triggers ('second hits'): HIV, COVID-19, interferon signaling, sepsis, toxins/hemodynamic stress

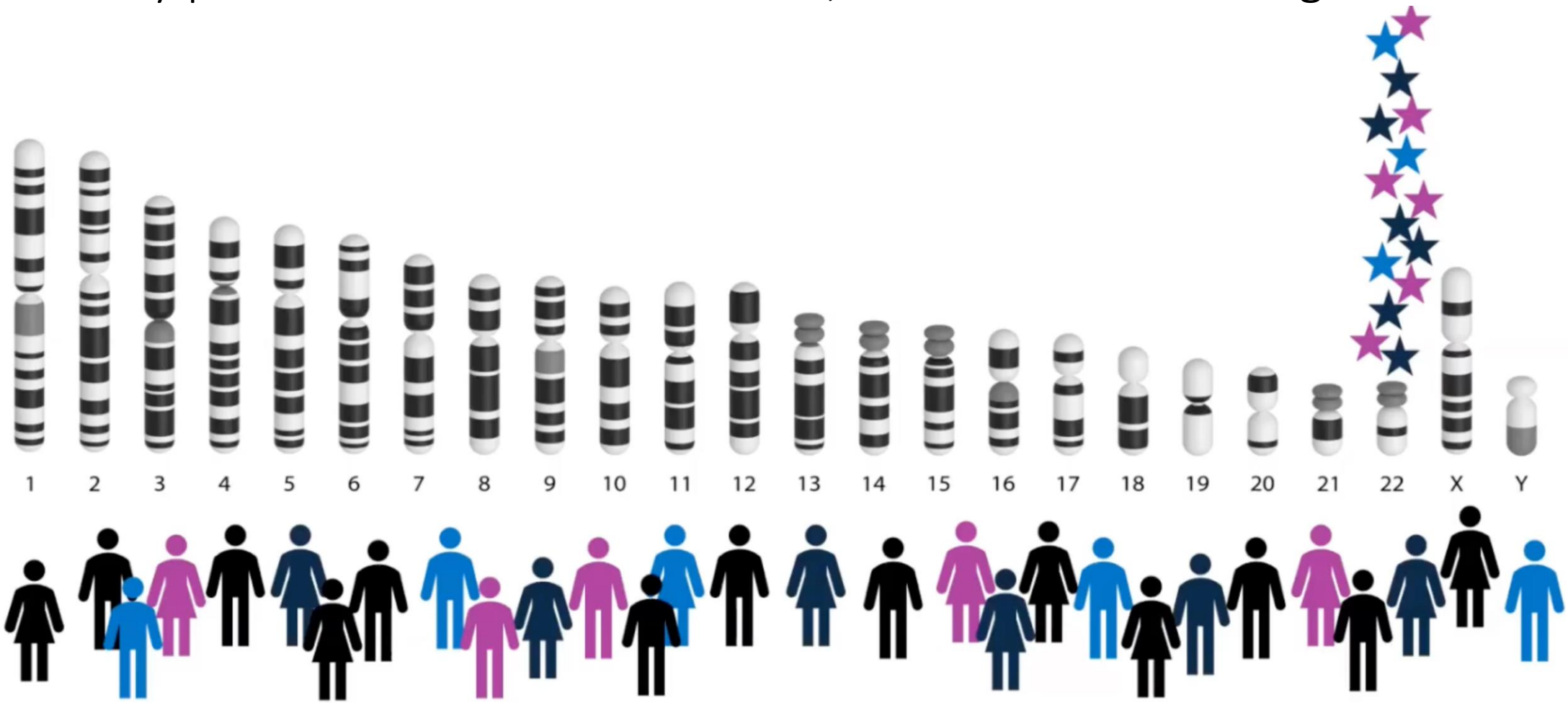
APOL1 discovery

- From diaspora genetics to a high-impact kidney gene

Admixture mapping in African Americans linked non-diabetic ESKD/FSGS to the MYH9 region (chr22)

APOL1 G1/G2 coding variants identified as the major signal
(Genovese et al., Science; Freedman et al., JASN; Tzur et al., Hum Genet)

Genome-wide admixture analysis of people with CKD and African ancestry pointed to Chromosome 22[1,2], and then the *APOL1* gene[3,4]



1. Kopp JB, et al. Nat Genet. 2008;40:1175-1184; 2. Kao WH, et al. Nat Genet. 2008;40:1185-1192; 3. Genovese O, et al. Science. 2010;329:841-845; 4. Kopp JB, et al. J Am Soc Nephrol. 2011;22(11):2129-2137.

APOL1 "High Risk Variants/Haplotypes" Quick Review

- G0 = Reference/ wild-type, non-risk sequence
- Most common worldwide
- No increased kidney risk
- G1 = two single nucleotide substitutions (S342G and I384M)
- Made of two small protein changes
- Common in people with recent African ancestry
- Protects against parasites
- G2 = Contains a 6 base-pair deletion (N264del, Y265del).
- A small deletion in the gene
- Also protects against parasites

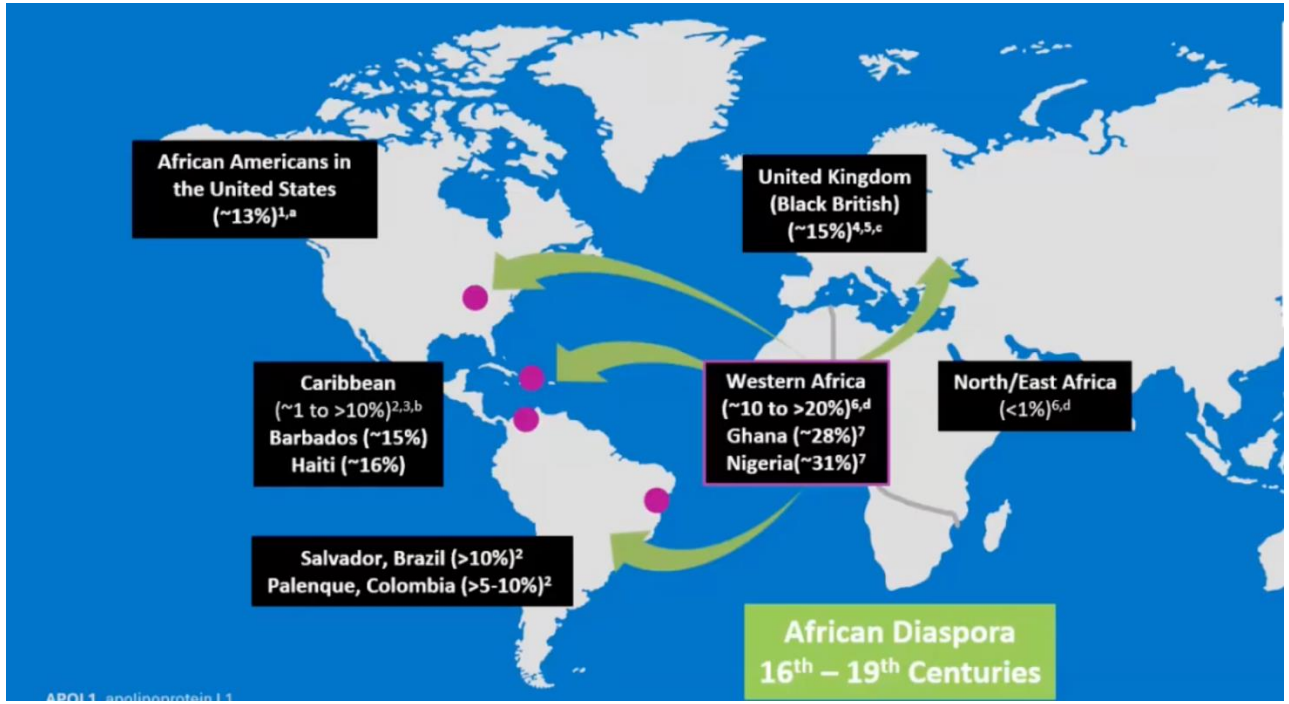
When we say "two high-risk APOL1 variants"…

We are talking about an individual who has G1/G1, G2/G2 or G1/G2, i.e. two copies of the high-risk haplotype.

Traditionally we have assumed a **recessive** inheritance model for kidney disease:

APOL1 copies	Risk level
G0 / G0	Low risk
G0 / G1 or **G0 / G2**	Low risk
G1 / G1, **G2 / G2**, or **G1 / G2**	**High risk**

How common is is to have 2 copies of the high-risk variants in U.S. cohorts?

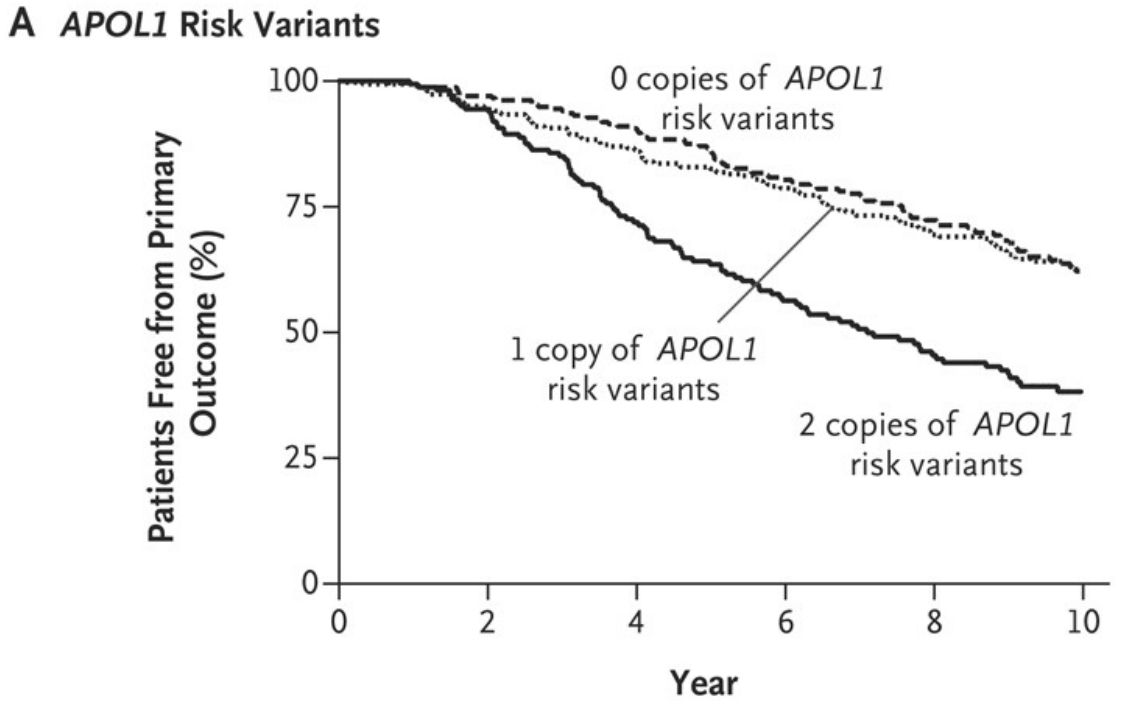


- Typical cohort-level estimates (varies by sampling & ancestry mix):
- ~10–15% of African Americans have 2 high risk variants
- ~35–45% have ≥1 high risk variant
- Rare in individuals without recent African ancestry

Observational study: 2 high-risk variants associated with faster CKD progression

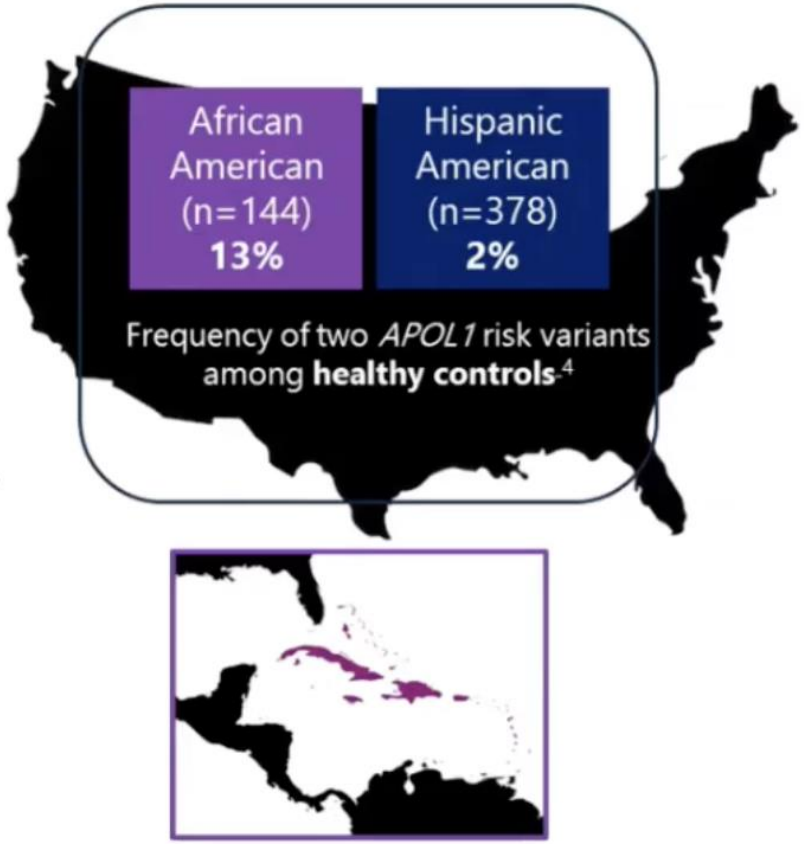
Across U.S. cohorts (i.e., AASK, CRIC):

- High-risk genotype associated with higher risk of CKD progression/ESKD
- Effect strongest for non-diabetic nephropathies and podocytopathies (FSGS)
- Reinforced APOL1 as one contributor to ESKD disparities in the diaspora



No. at Risk						
0 *APOL1* variants	234	225	208	177	146	80
1 *APOL1* variants	299	283	254	223	179	111
2 *APOL1* variants	160	151	114	85	61	30

Parsa A., et al. *NEJM* 2013



A 2017 study showed people in the Caribbean had 10x higher frequency of carrying two *APOL1* risk variants (1.0% versus 0.1% Mainland)[2]

Frequency of two *APOL1* risk variants among 995 individuals with ESKD on hemodialysis[1]

African Americans Non-diabetic n=358	**39%**
Diabetic n=408	**22%**
Hispanic Americans Non-diabetic n=98	**20%**
Diabetic n=131	**6%**

For nondiabetic patients, mean age of dialysis initiation was 9-12 years earlier with 2 *APOL1* risk variants vs 0 or 1[1]

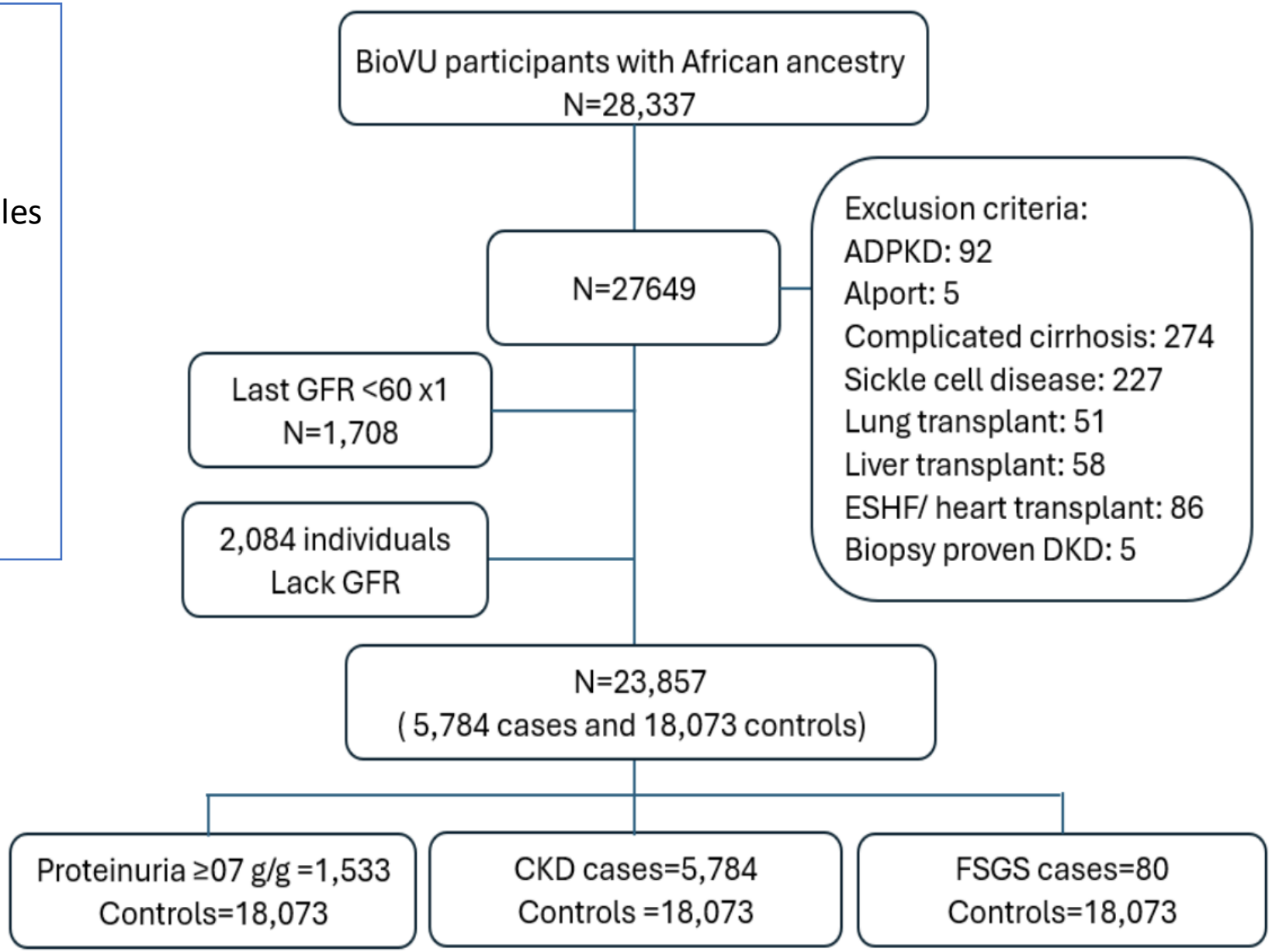
(t-test FDR corrected P=0.0003)

1. Tzur S, et al. Nephrol Dial Transplant. 2012 Apr;27(4):1498-505; 2.Kramer HJ, et al. J Am Soc Nephrol. 2017 Mar;28(3):915-922

Maybe APOL1 risk is not truly binary?

APOL1 kidney risk traditionally modeled as **recessive** (2 risk alleles → highest risk)
Growing data suggest **intermediate risk with 1 allele**, especially for CKD and ESKD

Emerging work in this area



Clapp et al. *medRxiv* 2025

APOL1 Genotypes	***Odds Ratio (95% CI)**		
	Unadjusted	Minimally adjusted	Fully adjusted
Primary Outcome: Chronic Kidney Disease			
Sample size 5784/18,073			
2 APOL1HR vs. < 2 (recessive)	1.61 (1.49, 1. 74)	1.69 (1.54, 1.85)	1.72 (1.57, 1.89)
APOL1 HR additive model	1.28 (1.23, 1.34)	1.27 (1.21, 1.33)	1.28 (1.22, 1.34)
Individual APOL1 genotypes (variable sample size depending on the count for the genotype)			
G1/G1 vs. G0/G0	2.02 (1.79, 2.28)	2.08 (1.82, 2.39)	2.06 (1.79, 2.37)
G1/G2 vs. G0/G0	1.58 (1.40, 1.78)	1.56 (1.37, 1.79)	1.59 (1.38, 1.83)
G2/G2 vs. G0/G0	1.44(1.17, 1.78)	1.58 (1.25, 2.00)	1.64 (1.28, 2.10)
G0/G1 and G0/G2 vs. G0/G0	1.15 (1.08, 1.23)	1.08 (1.00, 1.16)	1.07 (0.99, 1.15) †
G0/G2 vs. G0G0	1.22 (1.12, 1.33)	1.12 (1.02, 1.23)	1.11 (1.01, 1.23)
G0/G1 vs. G0/G0	1.11 (1.03, 1.20)	1.05 (0.97, 1.14) †	1.04 (0.96, 1.13) †

Clapp et al. *medRxiv* 2025

Secondary Outcomes			
Proteinuria			
Sample size 1533/22,324			
2 APOL1HR vs. < 2 (recessive)	2.15 (1.90, 2.43)	2.02 (1.77, 2.33)	2.02 (1.77, 2.31)
APOL1 HR additive model	1.55 (1.45, 1.67)	1.48 (1.37, 1.60)	1.48 (1.37, 1.60)
Individual APOL1 genotypes (variable sample size depending on the count for the genotype)			
G1/G1 vs. G0/G0	2.80 (2.33, 3.37)	2.43 (2.00, 2.96)	2.37 (1.94, 2.91)
G1/G2 vs. G0/G0	2.49 (2.07, 2.99)	2.28 (1.88, 2.78)	2.32 (1.90, 2.84)
G2/G2 vs. G0/G0	1.62 (1.13, 2.32)	1.58 (1.09, 2.30)	1.63 (1.11, 2.40)
G0/G1 and G0/G2 vs. G0/G0	1.32 (1.17, 1.48)	1.23 (1.09, 1.39)	1.23 (1.09, 1.39)
G0/G2 vs. G0G0	1.47 (1.27, 1.71)	1.37 (1.17, 1.60)	1.34 (1.15, 1.59)
G0/G1 vs. G0/G0	1.22 (1.07, 1.40)	1.15 (1.00, 1.32) †	1.14 (0.99, 1.32) †
FSGS			
Sample size 80/18,073			
2 APOL1HR vs. < 2 (recessive)	17.67 (10.91, 28.61)	17.83 (10.76, 29.55)	17.48 (10.53, 29.02)
APOL1 HR additive model	7.91 (5.33, 11.73)	8.07 (5.36, 12.16)	7.93 (5.25, 11.98)
Individual APOL1 genotypes (variable sample size depending on the count for the genotype)			
G1/G1 vs. G0/G0	34.77 (15.51, 77.97)	41.68 (16.67, 104.24)	35.32 (14.21, 87.83)
G1/G2 vs. G0/G0	27.88 (12.40, 62.67)	28.43 (11.92, 67.83)	30.73 (12.65, 74.67)
G0/G1 vs. G0/G0	3.19 (1.33, 7.63)	2.99 (1.25, 7.18)	2.83 (1.18, 6.79)

Clapp et al. *medRxiv* 2025

APOL1 discovery

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Admixture mapping in African Americans linked non-diabetic ESKD/FSGS to the MYH9 region (chr22)

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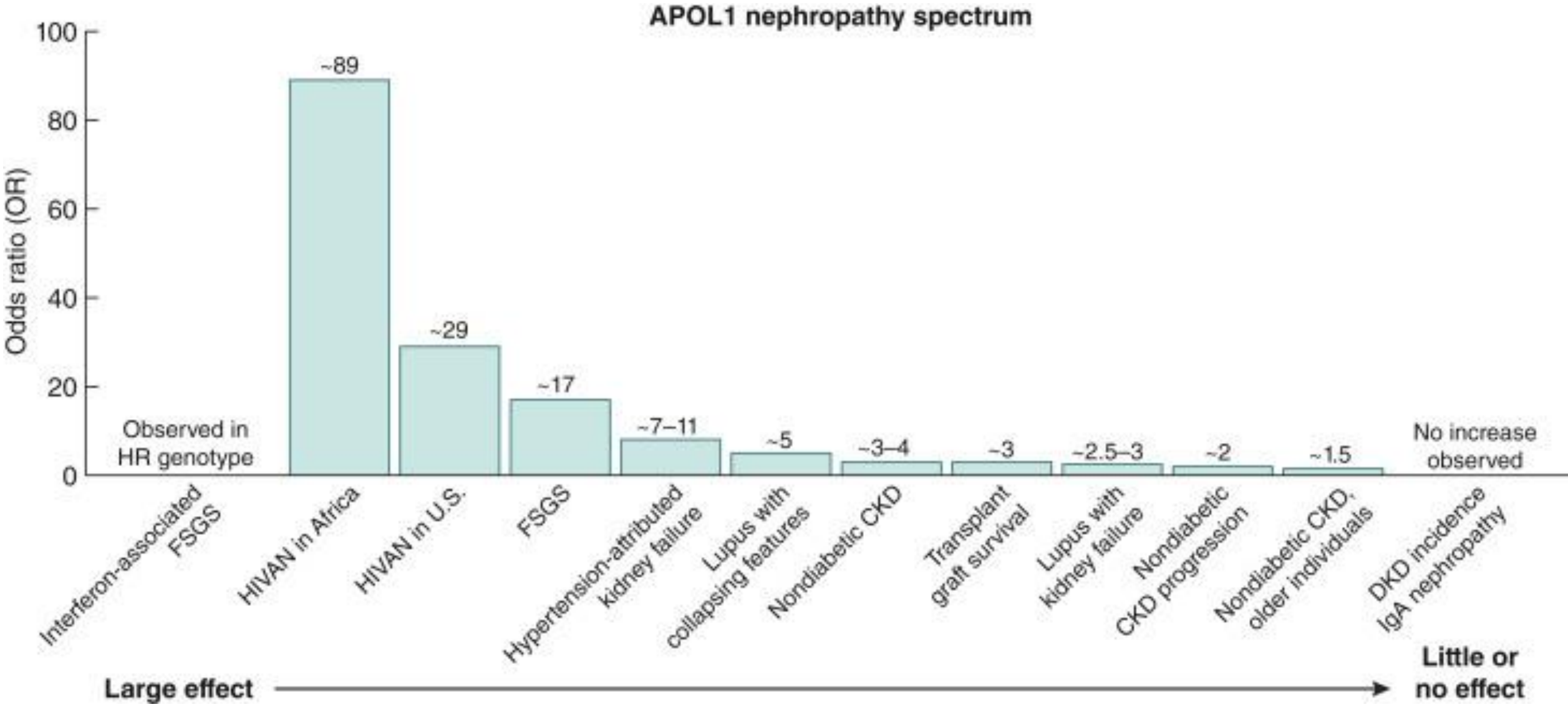
Identification of APOL1-associated sub-phenotypes

Phenotypes associated with *APOL1* high-risk variants

- At first, two main phenotypes, with very different presentations:
  - Collapsing focal segmental glomerulosclerosis (FSGS) – very heavy proteinuria, very rapid loss of kidney function, can be idiopathic or HIV-associated.
  - Hypertension-attributed kidney failure – slow, progressive decline in eGFR, low-grade proteinuria

APOL1 kidney disease spectrum has expanded



Ojo et al. *Kidney International* 2025

Even though *APOL1* effect sizes are large, penetrance is incomplete

- Many individuals with 2 high-risk variants never develop CKD
- Disease risk depends on triggers (“second hits”) and modifiers
- Common ‘hits’/contexts discussed in U.S. cohorts:
  - HIV infection (especially uncontrolled), COVID-19, sepsis
  - Interferon signaling (infection, autoimmunity, IFN therapies)
  - Hemodynamic stress, toxins, socioeconomic and environmental exposures
- Interpretation: *APOL1* is a *susceptibility* genotype

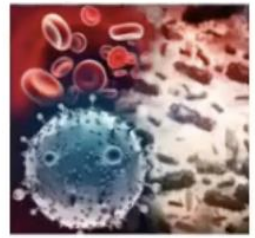
Activating AMKD: the "Second Hit"

For those carrying two *APOL1* risk variants, lifetime risk of developing kidney disease is estimated to be at least 15%[2]

SECOND HIT

Infection[3,4]

- Viral (HIV, COVID-19, CMV, Parvovirus)
- Hemophagocytic (malaria, schistosomiasis)

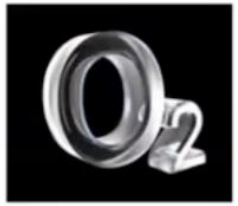


Inflammation[5,6]

- Administered interferons
- Autoimmune disease
- Sepsis

Hypoxia[7]

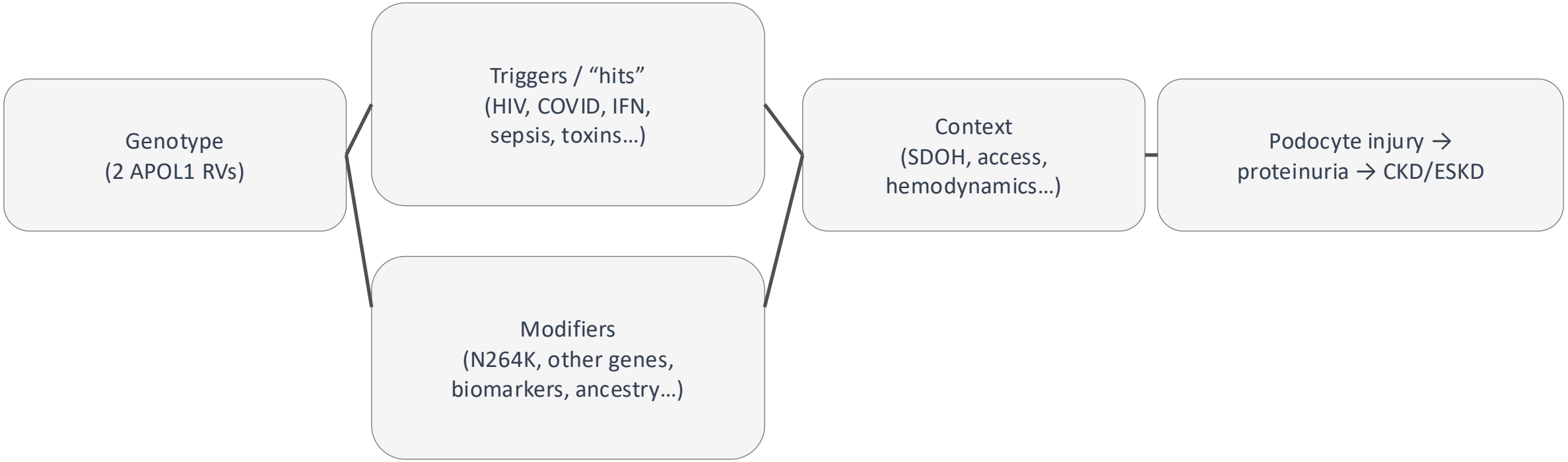
- Sickle Nephropathy
- Post-transplant



AMKD, APOL1-mediated kidney disease; **CMV**, Cytomegalovirus; **COVID-19 (SARS-CoV2)**, severe acute respiratory syndrome coronavirus-2 2019; **HIV**, Human Immunodeficiency Virus

1. Genovese G, et al. *Science* 329: 841–845, 2010; **2**. Dummer PD, et al. *Semin Nephrol.* 2015 May; 35(3):222-36; **3**. Bruggeman LA, et al. *Curr Opin Nephrol Hypertens.* 2021 May 1;30(3):317-323; **4**. Beckerman P, et al. *Trends Mol Med.* 2018;24(8):682-695; **5.** Larsen CP, et al. *J Am Soc Nephrol.* 2013 Apr; 24(5):722-5; **6**. Chaudhary, NS, et al. *CJASN.* Dec 2019; 14(12):p 1733-1740; **7**. Grampp, S, et al. *Kidney International.* April 23, 2023.

Model: APOL1-mediated disease is multi-hit



APOL1 status is *necessary but often not sufficient* — risk is amplified by inflammatory triggers and shaped by social/clinical context.

Second-hit example: COVID-19–associated AKI

Hospitalized patients with African genetic ancestry
(Million Veteran Program):

- APOL1 high-risk genotype associated with more severe AKI stages
- Suggests inflammatory/IFN pathways can precipitate kidney injury in susceptible genotypes

Conceptual link:

- COVAN and other collapsing glomerulopathies may represent a shared 'podocyte stress' pathway

Figure 2. Incidence of Acute Kidney Injury (AKI) and AKI Stages by *APOL1* Risk Group

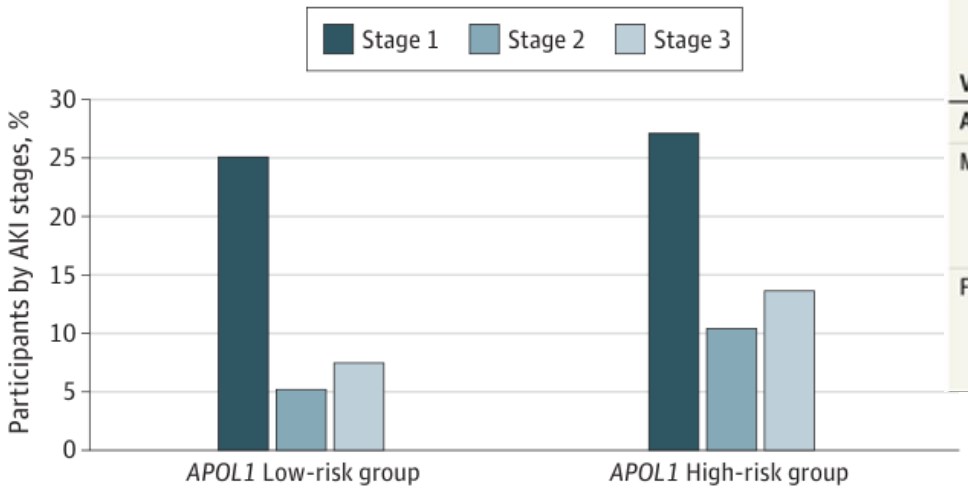


Table 3. Association of *APOL1* High-Risk Group, AKI, AKI Stages, and Death in Veterans With African Ancestry Hospitalized With COVID-19[a]

		Primary outcome, acute kidney injury		Secondary outcomes			
				AKI severity stages		Death	
Variable	No.	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
All patients							
Minimally adjusted							
2 Copies of *APOL1* RVs	125	1.80 (1.21-2.69)	.004	1.88 (1.30-2.71)	.001	1.92 (1.13-3.17)	.01
1 Or 0 copies of RVs	865	1 [Reference]		1 [Reference]		1 [Reference]	
Fully adjusted model							
2 Copies of *APOL1* RVs	121	1.95 (1.27-3.02)	.002	2.03 (1.37-2.99)	<.001	2.15 (1.22- 3.72)	.007
1 Or 0 copies of RVs	812	1 [Reference]		1 [Reference]		1 [Reference]	

Hung et al. *JAMA Intern Med* 2022

Genetic Second Hits in APOL1-Mediated Kidney Disease

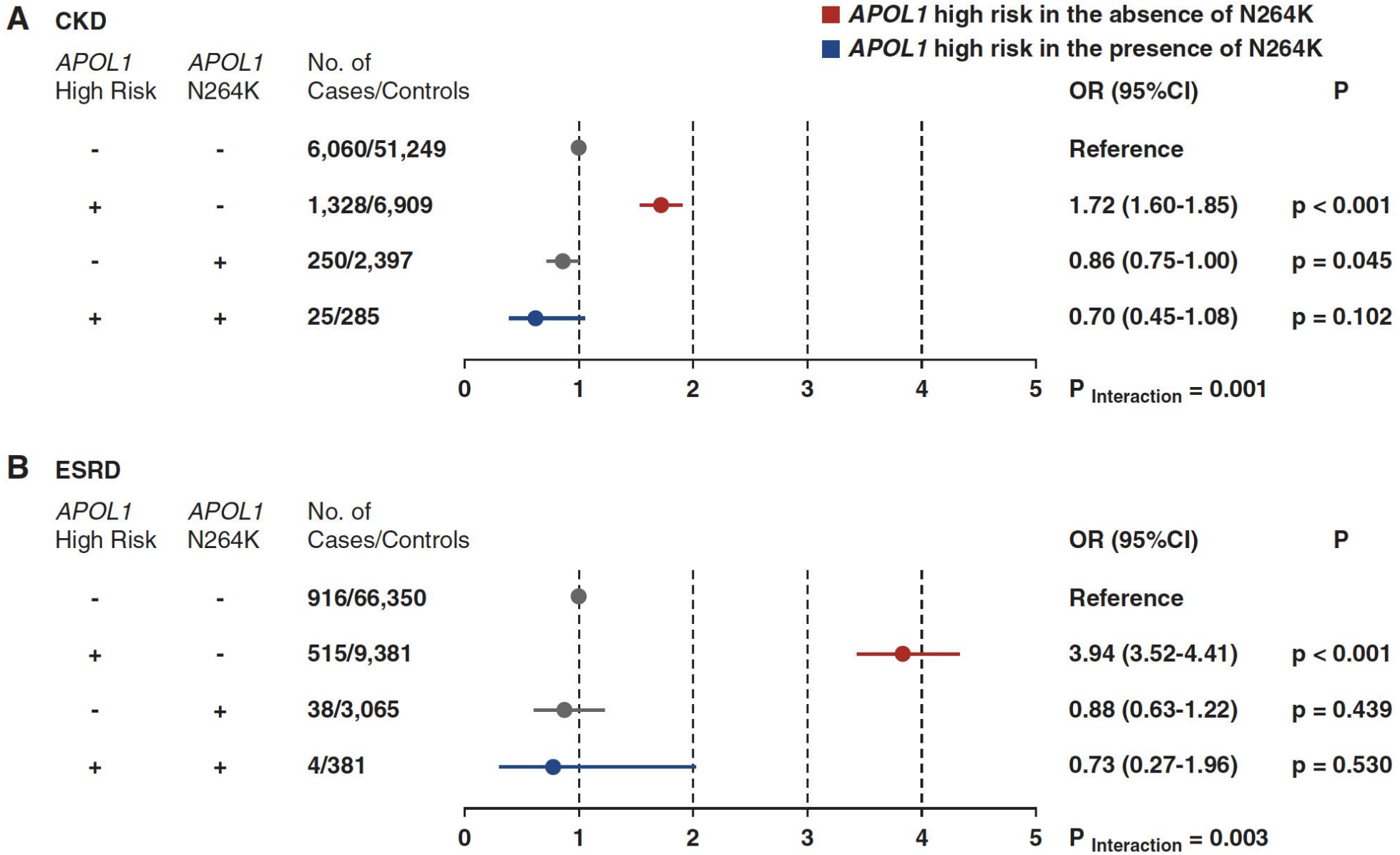
- APOL1 high-risk genotype alone is insufficient to cause disease
  - Additional genetic modifiers influence penetrance and severity
  - Examples include UBD, GSTM1 null, SMOC2, APOL3 truncating variants
  - Protective modifiers (e.g., p.N264K/M1) reduce toxicity
  - Overall evidence favors gene–environment interactions over strong gene–gene effects

APOL1 and *N264K, case study*

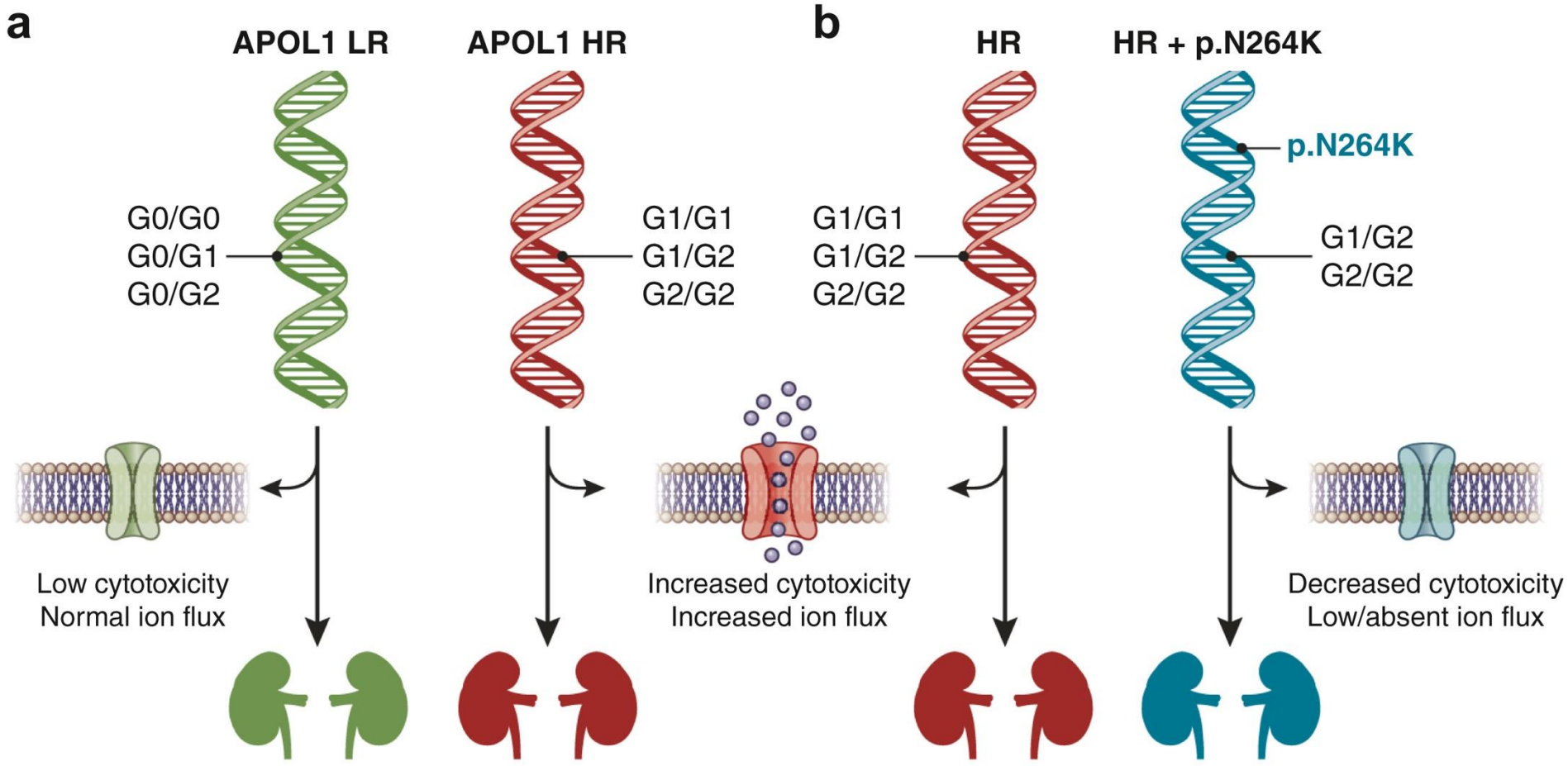
- Ghanaian patient presented with trypanosomiasis infection
- No cases had been reported in 10 years
- WGS performed
- Patient had two copies of *APOL1* high-risk variants (G2/G2) but also homozygous missense substitution (N264K), which knocked down the trypanolytic activity of *APOL1*, allowing the trypanosome to avoid ApoL1-mediated immunity.

Cuypers et al. mBio 2016

APOL1 and *N264K*, *across the population*



Hung et al. *JASN 2023*



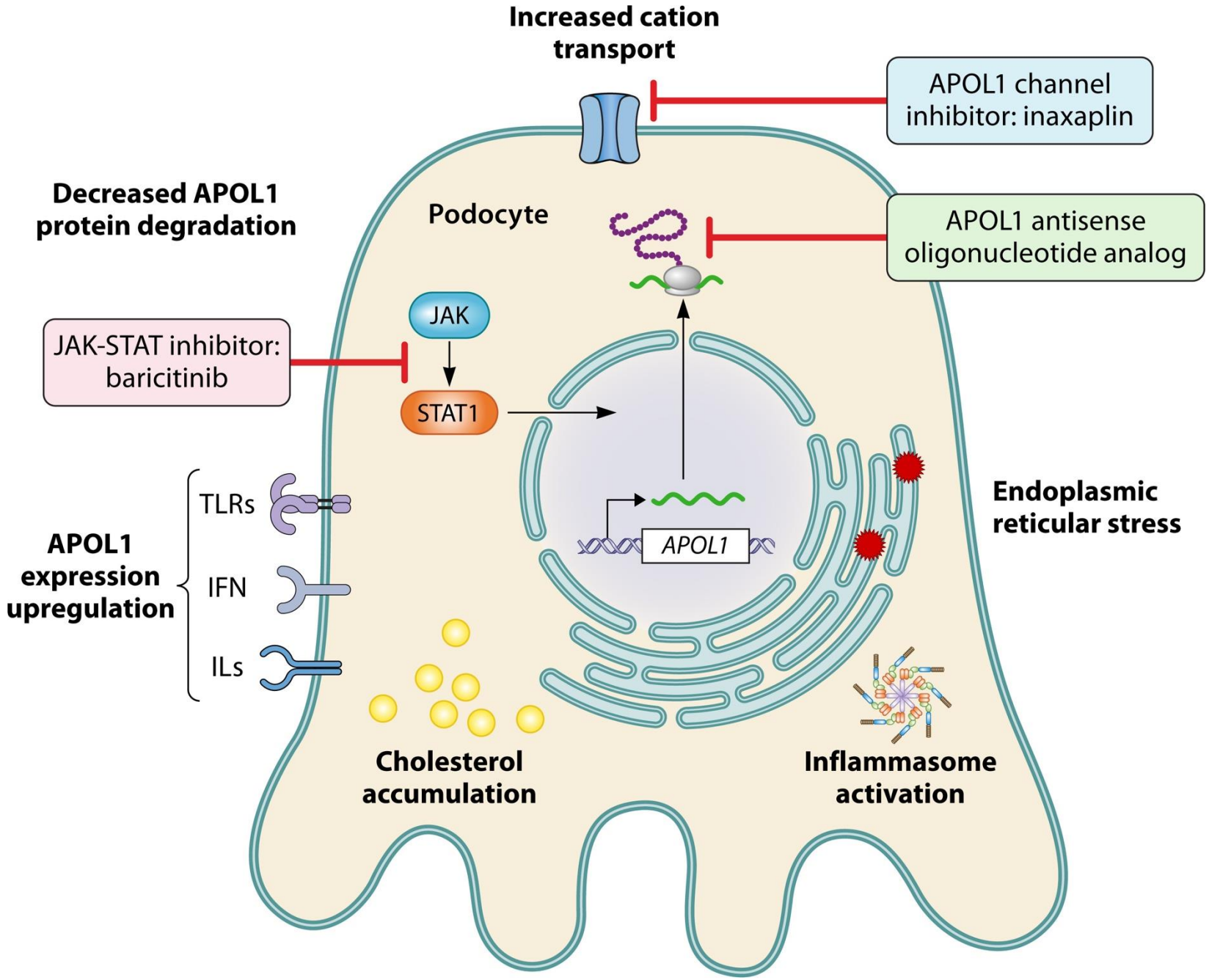
Increased risk of kidney disease

Hung *et al.* (MVP)
APOL1 HR vs. LR, no p.N264K
CKD OR: 1.7 (CI 1.60–1.85, $P < 0.001$)
ESKD OR: 3.9 (CI 3.52–4.41, $P < 0.001$)

Decreased risk of kidney disease

Hung *et al.* (MVP + BioVU + All of Us)
HR + p.N264K vs. HR, no p.N246K
CKD OR: 0.43 (CI 0.30–0.61, $P < 0.001$)
ESKD OR: 0.19 (CI 0.08–0.43, $P < 0.001$)

Gupta *et al.*
HR + p.N264K vs. HR, no p.N246K
FSGS OR: 0.07 (CI 0.008–0.25, $P = 3.4 \times 10^{-9}$)
CKD 3+ OR: 0.29 (CI 0.10–0.79, $P = 0.016$)


Increased cation transport
APOL1 channel inhibitor: inaxaplin
Decreased APOL1 protein degradation
Podocyte
APOL1 antisense oligonucleotide analog
JAK
JAK-STAT inhibitor: baricitinib
STAT1
TLRs
APOL1 expression upregulation
IFN
ILs
APOL1
Endoplasmic reticular stress
Cholesterol accumulation
Inflammasome activation

Precision-informed targets: where can we intervene?

Reduce APOL1 expression

- ASO / siRNA
- Transcriptional control
- Treat IFN drivers

Block pore/channel function

- Small-molecule inhibitors
- “Genetic inhibition” (N264K)
- Structure-guided drug design

Modulate downstream injury

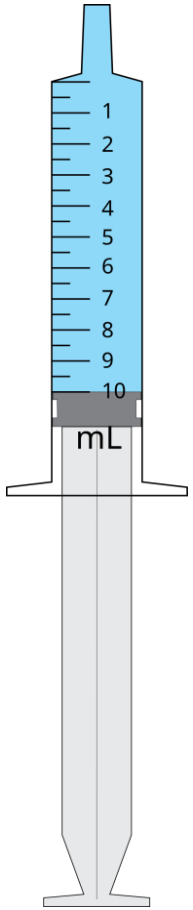
- JAK/STAT inhibition
- STING / NLRP3
- suPAR–integrin axis

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	Injection (s.c.)	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 adults	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
			NCT06794996	Adults with proteinuric *APOL1*-mediated kidney disease with or without either type 2 diabetes mellitus, sickle cell disease, HIV, or lupus nephritis	2b	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; HIV, human immunodeficiency virus; JAK-STAT, Janus kinase/signal transducer and activator of transcription; NCT, National Clinical Trial.

Therapeutics: APOL1 inhibition as precision nephrology



Inaxaplin (VX-147)

- Small proof-of-concept trial showed reduced proteinuria over 13 weeks
- Precision approach: target APOL1 channel function
- Ongoing adaptive Phase 2/3 studies aim to confirm efficacy and safety
- SSA discussion prompt: how will trial access, diagnostics, and follow-up shape translation?

Safety considerations in drug development: APOL1 sits at the intersection of kidney & immunity

Because *APOL1* evolved in an innate immunity context, therapeutic inhibition raises key questions:

- Infection risk: does *APOL1* inhibition meaningfully alter host defense (especially in high-infection settings)?
- Pregnancy: emerging links between fetal *APOL1* genotype and preeclampsia/SGA (causality still debated)
- Off-target biology: endothelial and immune cell effects; extra-renal phenotypes
- Long-term outcomes: CKD progression, cardiovascular events, transplant outcomes

Transplantation: donor vs recipient APOL1 genotype

Evidence summary

• Deceased donor genotype: 2 RVs in donors is associated with higher allograft failure risk in multiple cohorts
• Living donors: *APOL1* testing can inform counseling, but policies vary and data are still evolving
• Recipient genotype: mixed data; may influence rejection and graft survival in some studies

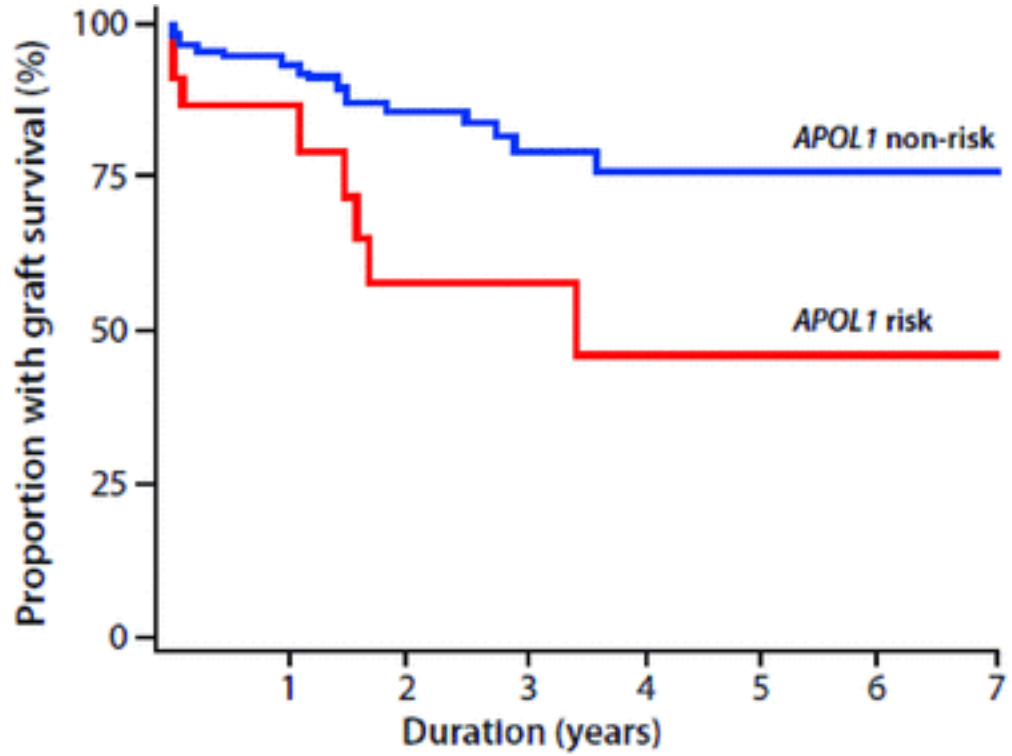
Equity tension:
• APOL1 testing may improve risk prediction, but could reduce access if used to exclude donors without supportive systems

Bottom line: genotype information should support *shared decision-making* not become a new barrier.

APOL1 high risk variants in the donors

Table 1. Demographic characteristics of renal allograft donors and recipients

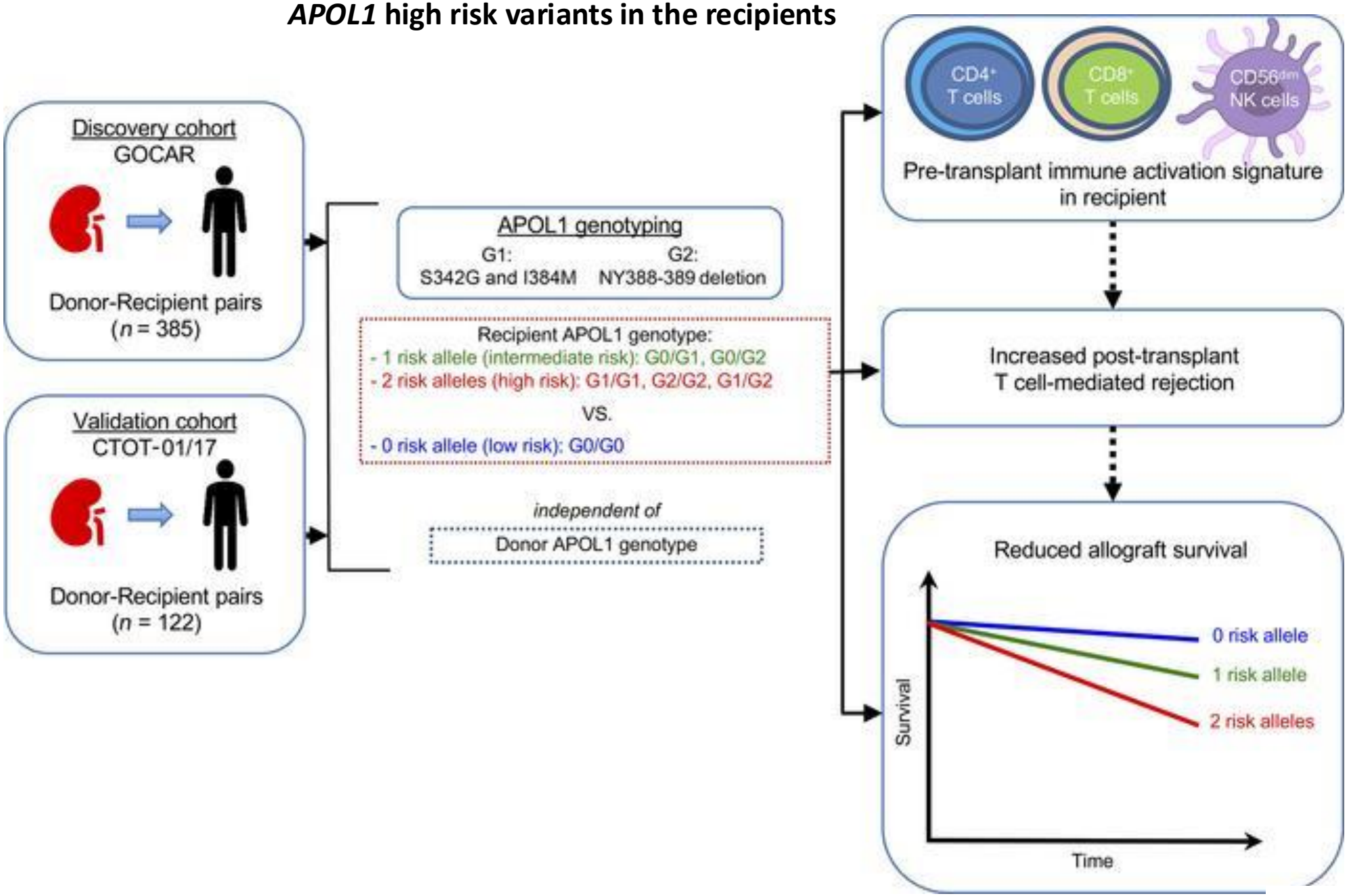
Variables	Number of *APOL1* G1-G2 nephropathy risk variants from kidney donor		
	Two N = 22	Zero or 1 N = 114	p Value
Donor age (years)	43.7 ± 16.8	47.7 ± 15.8	0.27
Donor gender (% male)	66.3	60.0	0.26
Terminal serum creatinine (mg/dL)	1.34 ± 0.8	1.19 ± 0.7	0.51
PRA* at transplant (%)	13.4 ± 27.6	19.7 ± 31.3	0.48
PRA * > 0 (%)	31.6	38.7	0.56
Donor African ancestry (%)	0.77 ± 0.10	0.72 ± 0.21	0.53
Cold ischemia time (hours)	22.5 ± 7.9	23.2 ± 8.0	0.82
HLA mismatch (N)	4.2 ± 1.4	3.8 ± 1.5	0.29
Recipient gender (% male)	77.3	53.5	0.04
Recipient age (years)	45.2 ± 16.9	47.1 ± 16.2	0.72
Standard criteria donor (%)	81.8	79.8	0.83
Recipient race (% African American)	50.0	50.9	0.94



***APOL1* non-risk**								
No. at risk	114	82	52	35	18	7	6	3
No. with graft loss (%)	–	7 (6%)	13(11%)	16 (14%)	17 (15%)	17 (15%)	17 (15%)	17 (15%)
No. censored	–	25	49	63	79	90	91	94
***APOL1* risk**								
No. at risk	22	12	8	5	2	1	1	0
No. with graft loss (%)	–	3 (14%)	7 (32%)	7 (32%)	8 (36%)	8 (36%)	8 (36%)	8 (36%)
No. censored	–	7	7	10	12	13	13	14

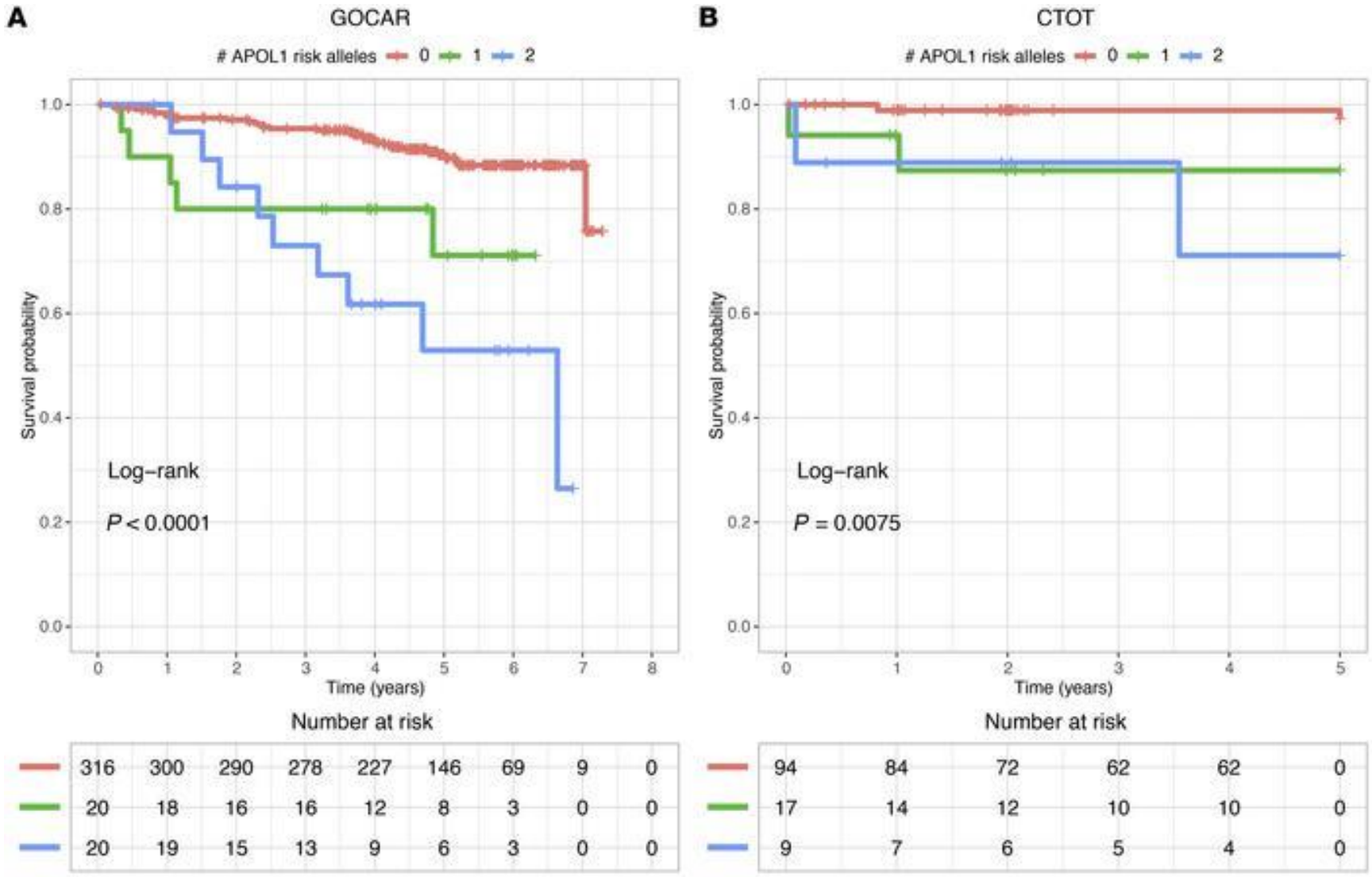
Reeves-Daniel et al. *AJT* 2011

APOL1 high risk variants in the recipients



Zhang et al. *JCI* 2021

Recipient APOL1 risk alleles associate with death-censored renal allograft survival and rejection episodes



Zhang et al. *JCI* 2021

APOLLO: generating evidence for equitable transplant policy

APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO): Design and Rationale

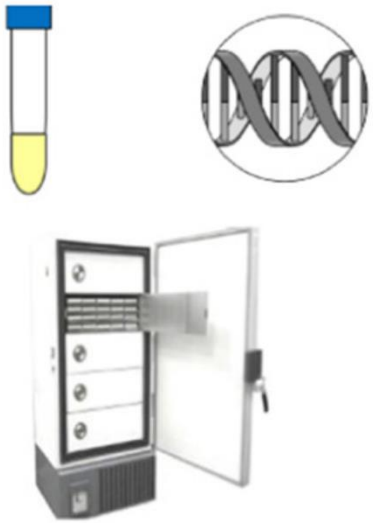
APOLLO

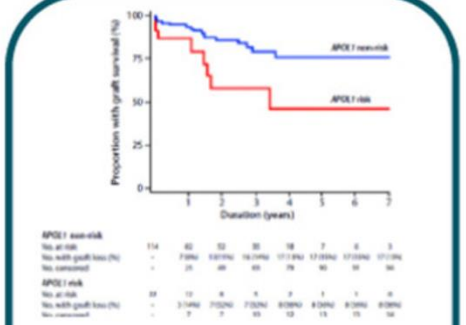
DNA extraction for *APOL1* testing & bio-sample collection

Transplant outcomes based on UNOS data

***APOL1* effects on kidney transplant recipients & donors**

- **2,614 DDKT pairs**
- **550 LD pairs**
- 260 Transplant Programs
- 58 OPOs
- 66 HLA labs





Reprinted with permission from Reeves-Daniel AM, DePalma JA, Bleyer AJ, et al. The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant*. 2011;11:1025–1030. Copyright © 2011 The Authors Journal compilation. Copyright © 2011 The American Society of Transplantation and the American Society of Transplant Surgeons.

CONCLUSION:

The NIH APOLLO Consortium including 260 transplant programs, 58 OPOs and 66 HLA labs will assess effects of *APOL1* in deceased and living donor kidney transplantation.

KI REPORTS
KIReports.org

Freedman BI *et al.*, KI Reports

Ethics & equity: the “double bind” in APOL1 testing

- Protect potential living donors from avoidable long-term kidney risk
- Protect transplant candidates (often Black patients) from reduced donor availability and longer wait times

Key safeguards:

- Community-engaged policy development (trust, transparency, cultural humility)
- Non-discrimination protections (insurance/employment), privacy and data governance
- Equitable access to testing + genetic counseling
- Avoid genetic determinism: APOL1 is a susceptibility genotype with incomplete penetrance

Ethics lens: aim for *risk-informed choice*, not categorical exclusion.

KDIGO living donor guidance (2017) re: *APOL1*

- Use individualized risk assessment rather than race-based assumptions
- Provide clear counseling about long-term kidney risk and follow-up responsibilities
- APOL1 testing: not mandated universally; may be considered for donors with African ancestry and/or family history, depending on local practice

Practical counseling points:

- Clarify what APOL1 can and cannot predict (risk ≠ certainty; context matters)
- Discuss alternatives for recipients if a donor is high-risk
- Ensure donor autonomy and avoid coercion

Implementation varies widely across transplant centers → need evidence + harmonized guidance.

KDIGO APOL1 conference report (2025): key takeaways

- Context-specific testing rather than population screening
- Pre-/post-test counseling and shared decision-making as non-negotiables
- Avoidance of policies that inadvertently worsen inequities in transplant access
- Research priorities: penetrance, modifiers (e.g., protective variants), biomarkers, and implementation science

Interpretation for the diaspora:

- Don’t export one-size-fits-all policies; local disease triggers and health system realities matter.

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 a 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.

APOL1, apolipoprotein L1; CKD, chronic kidney disease.

Ojo AO et al. *KI* 2025

Interpreting KDIGO guidance in African realities

African settings differ in ways that directly affect APOL1 interpretation:

- Epidemiology: infectious burden (HIV, sepsis), variable APOL1 frequencies, different comorbidity profiles
- Resources: limited access to APOL1 testing, dialysis and transplantation
- Ethics: competing priorities when treatment options are constrained

Diaspora connection:

- African immigrants may have high-risk genotypes but different exposure histories
- Guidance should integrate ancestry, triggers, and care access—not assume uniform risk

Equity principle: testing without access to effective interventions can widen disparities → pair testing with care pathways.

Equitable implementation: a practical checklist

To implement APOL1 testing and therapies without worsening disparities:

Access & infrastructure
- Affordable testing + genetic counseling (including tele-genetics) for diaspora communities
- Clear clinical pathways for follow-up and referral

Communication
- Explain ancestry vs race; avoid genetic determinism; use culturally appropriate materials

Governance & policy
- Privacy, data stewardship, and community oversight
- Non-discrimination protections; avoid using APOL1 to restrict transplant access without evidence

Research
- Include diverse diaspora subgroups (African American, Afro-Caribbean, African immigrants, Afro-Latino)
- Study modifiers, triggers, and implementation outcomes

Summary

1) U.S. CKD/ESKD disparities are real and multi-causal — APOL1 is one important biological contributor embedded in social context.

2) APOL1 kidney risk is largely recessive and *context-dependent* (multi-hit) → most people with 2 RVs remain healthy.

3) Human genetics (e.g., protective N264K) supports APOL1 as a *druggable* target; multiple precision strategies are advancing.

4) Transplant and testing policies must balance donor safety with recipient equity; counseling and community engagement are essential.

5) Interpreting KDIGO guidance requires local realism: testing should be paired with pathways to care and equitable access to interventions.

Thank you!

Collaboration opportunities

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