



Brigham and Women's Hospital

Founding Member, Mass General Brigham

APOL1 and Kidney Disease

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Clinical focus: Adult Nephrology

Research focus: APOL1-Mediate Kidney Disease



Disclosures

- Advisor for Maze Therapeutics and Podium Bio.
- Received research funding from NIH, Alnylam and Icagen.
- APOL1-directed therapies discussed in this presentation are investigational; none is currently FDA-approved.



Objectives

What should you be able to do after this review?

Recognize

the clinical spectrum
of AMKD

01

Explain

genetic risk and
incomplete penetrance

02

Apply

selective testing and
transplant counseling

03

Evaluate

current and emerging
therapies

04



Case Vignette

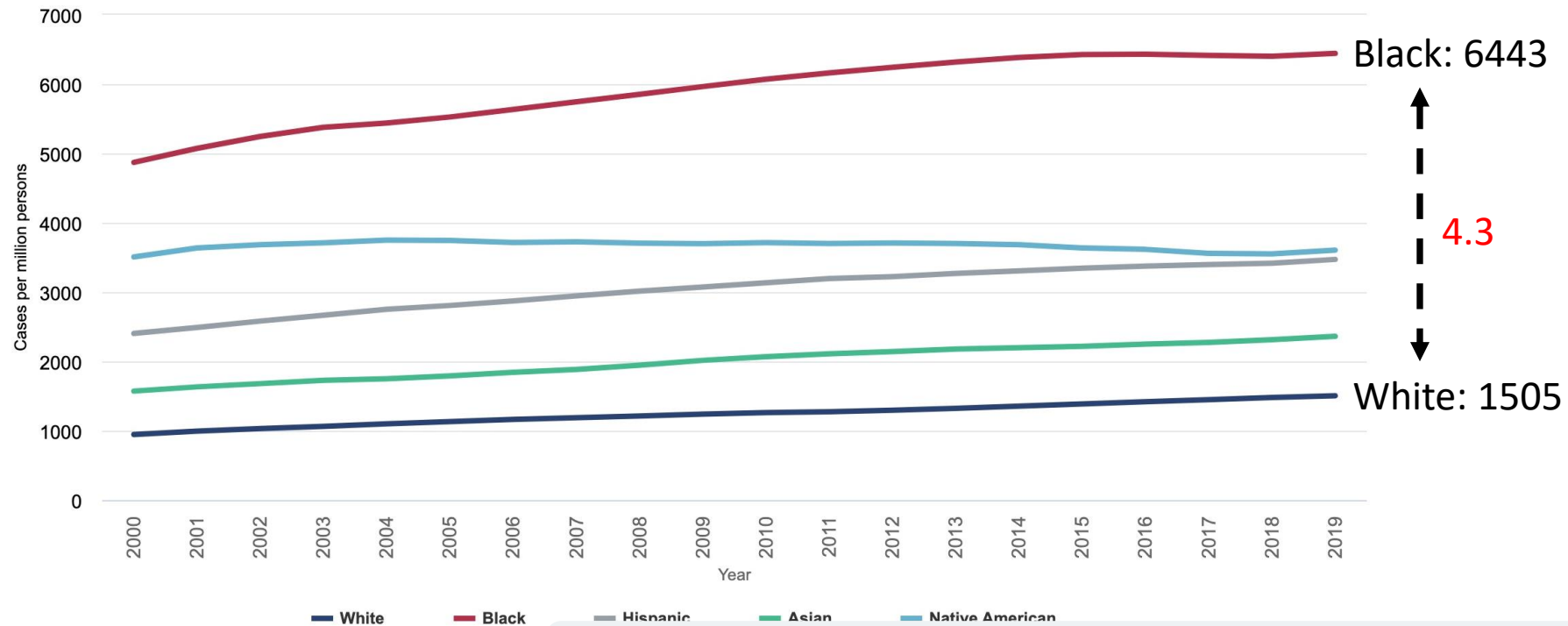
39 year old non-diabetic African American male with history of hypertension and FSGS presents for routine follow up visit. His proteinuria is stable at 0.8g/day. However, his eGFR has been declining over the past 3 years from 45 to 35 despite optimal BP management with lisinopril and chlorthalidone. He asked the following questions:

Questions:

- 1) How likely is an APOL1 high-risk genotype?
- 2) Would you recommend APOL1 genetic testing for him?
- 3) Does APOL1 genotype affect prognosis?
- 4) What should we do now?
- 5) Does donor APOL1 genotype affect kidney allograft outcome?



Black Americans are **4-times** more likely to develop kidney failure than White Americans



Data Source: 2021 United States Renal Data System Annual Data Report

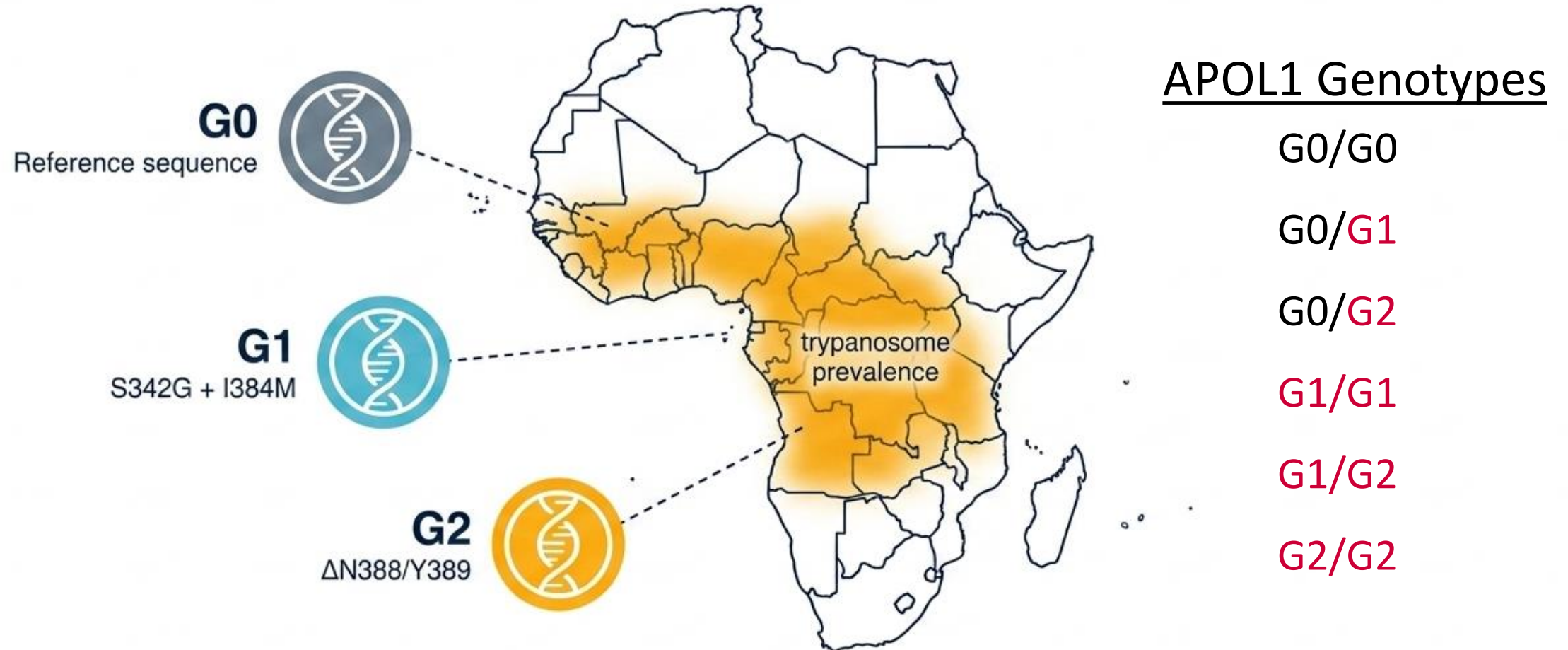
The disparity is multifactorial

- Structural and social determinants of health
- Unequal access to preventive and specialty care
- Hypertension, diabetes, and environmental exposures
- Genetic susceptibility, including APOL1



G1 and G2 link trypanolytic advantage to kidney risk

Selection by trypanosomal exposure increased frequencies in parts of sub-Saharan Africa. The same variants increase susceptibility to kidney disease.

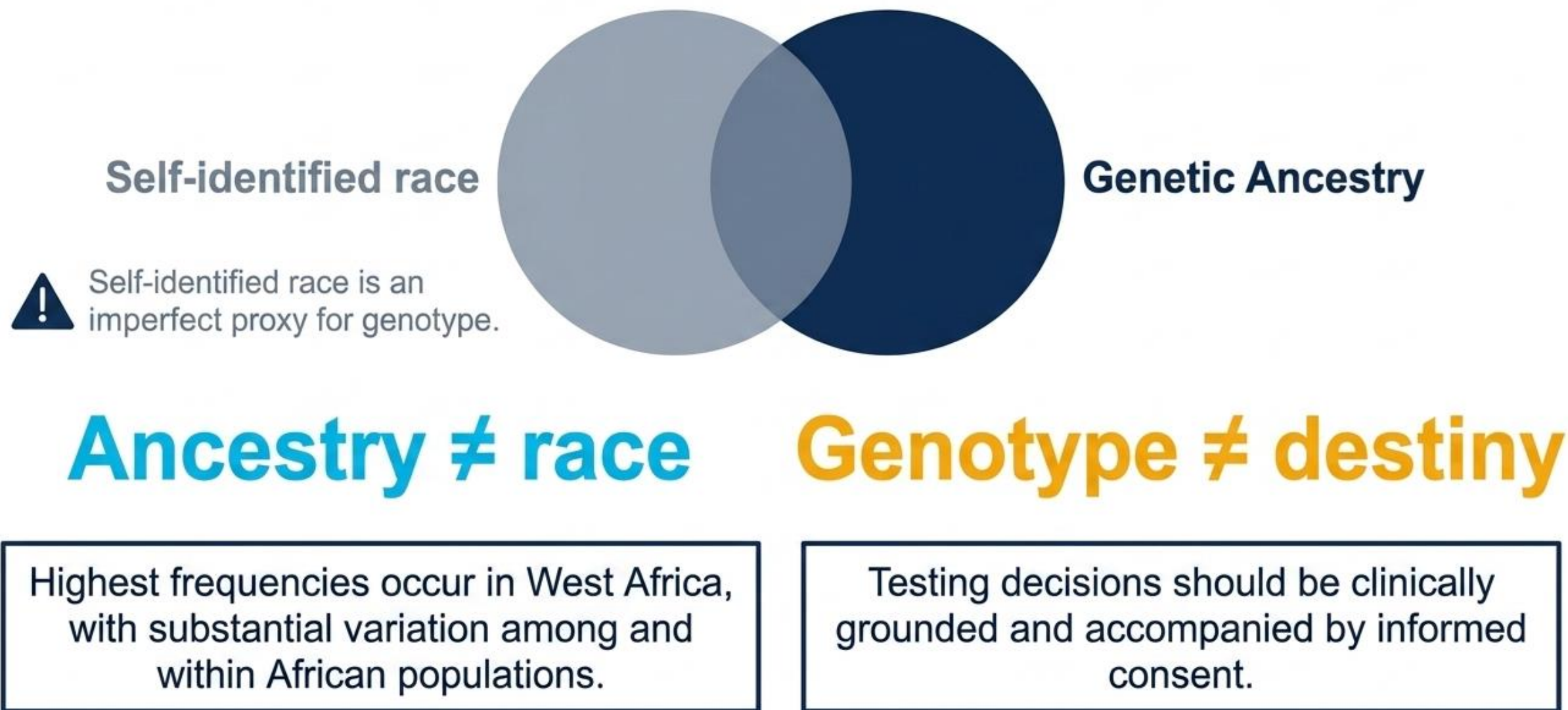


APOL1 risk variants track recent African ancestry—not race



Ancestry ≠ race

***APOL1* risk variants track recent African ancestry—not race**



Precision medicine must advance equity—not geneticize inequity

Say

“Recent African ancestry”
“Risk variant”
“Incomplete penetrance”

Avoid

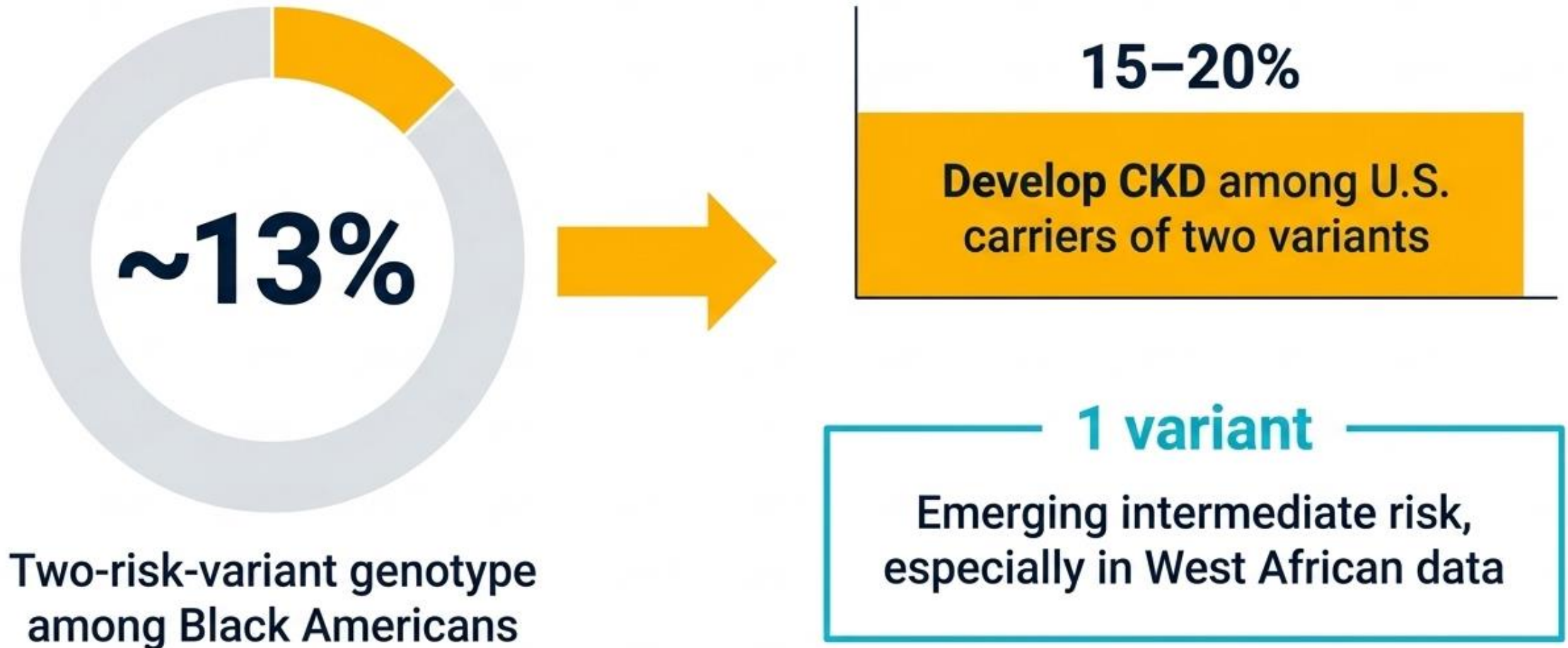
“Black gene”
Genetic determinism
Testing without consent

Remember

**APOL1 explains only part of
disparity**
**Access to testing and trials
matters**



Two variants confer the greatest risk—but one may not be neutral



Board-level shorthand remains “recessive risk,” but the biologic model is more nuanced.

Knowledge Check 1:

Which of the following forms is NOT associated with APOL1 high-risk genotype?

- A. Hypertension-attributed kidney disease
- B. Increased incidence of diabetic kidney disease
- C. COVID-19 associated collapsing nephropathy
- D. HIV associated collapsing nephropathy
- E. Lupus associated collapsing nephropathy



The *APOL1* Clinical Spectrum: Beyond a Single Lesion

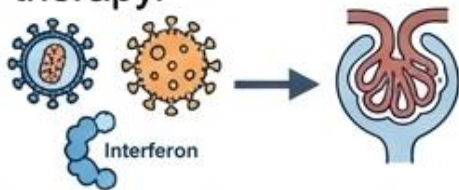
Focal Segmental Glomerulosclerosis (FSGS)

- 40–60% of African-American patients with primary FSGS have two risk variants.
- **Caveat:** Drastically alters pretest probability (relevant to our Case).



Collapsing Glomerulopathy

- **Triggers:** Highly associated with HIV (HIVAN), COVID-19 (COVAN), and interferon therapy.

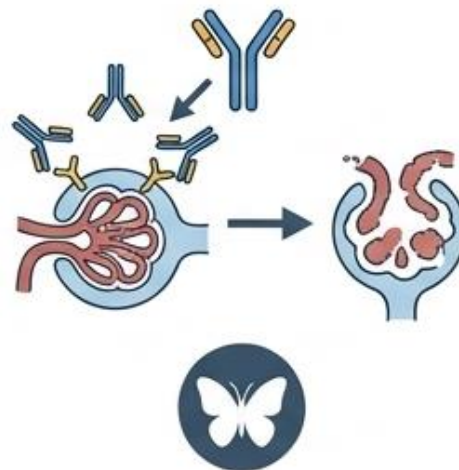


- **Presentation:** Often features rapid progression.



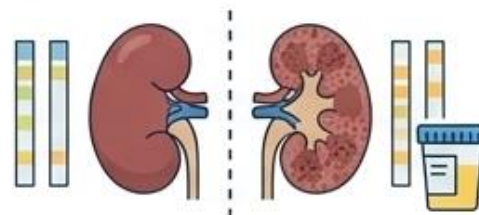
Lupus Nephritis

- **Caveat:** Particularly associated with collapsing lesions in the context of autoimmune inflammation.



Nondiabetic CKD

- **Caveat:** Frequently mislabeled as “hypertensive CKD.” Histology is not genotype-specific; proteinuria can be variable.



~~Hypertensive CKD~~ ? *APOL1*-associated CKD

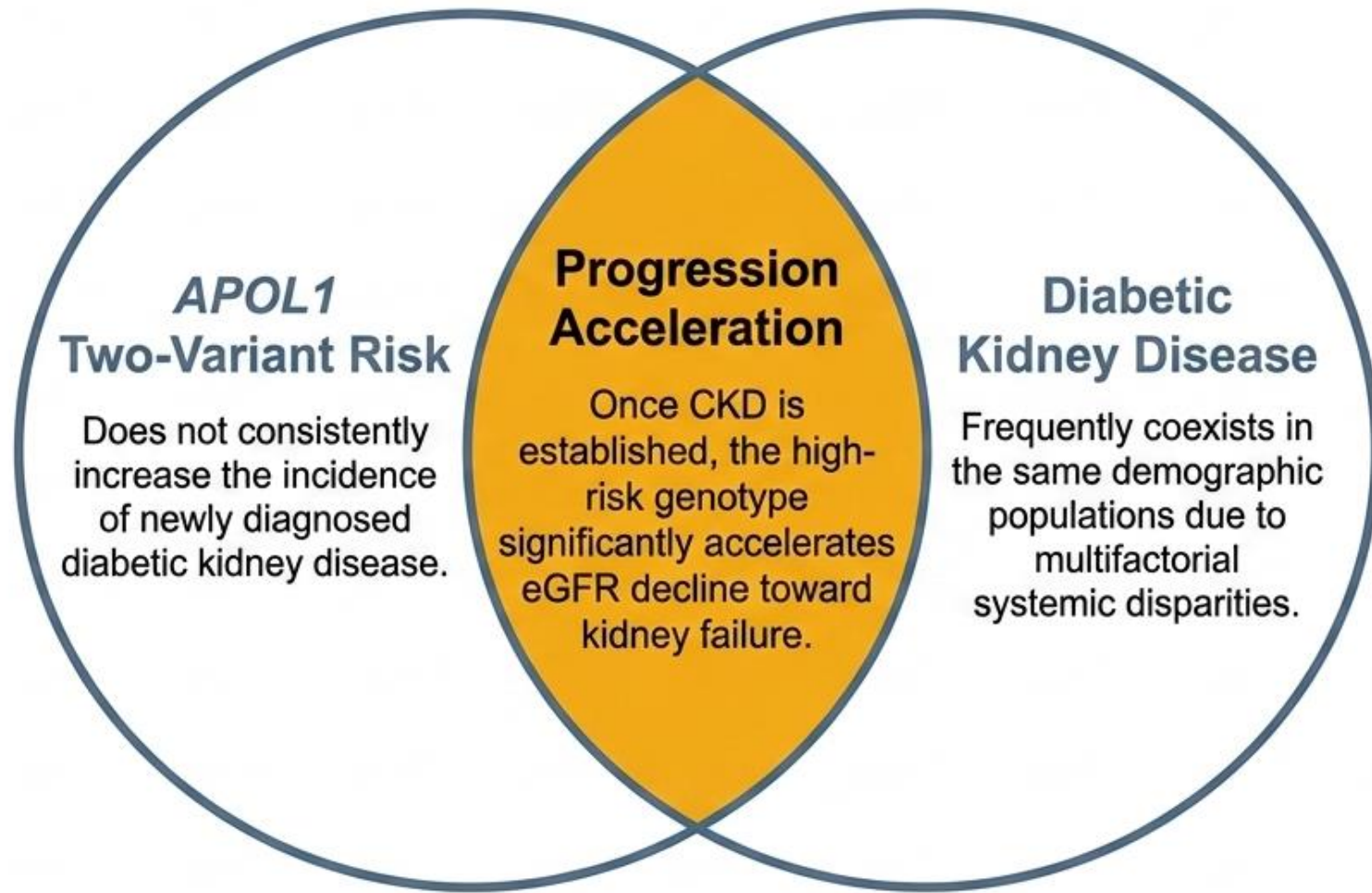
Knowledge Check 1:

Which of the following forms is NOT associated with high-risk APOL1 genotype?

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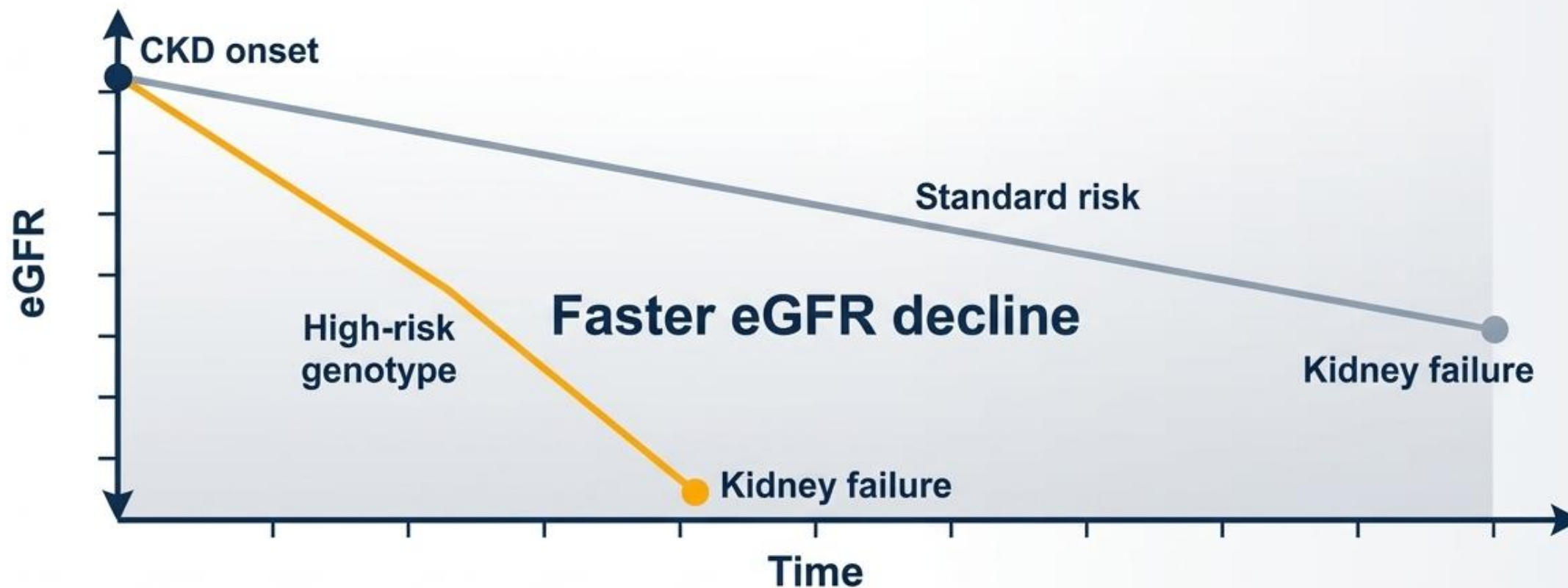


Clarifying Diabetic Kidney Disease: Incidence vs. Progression



Clinical Rule: Do not automatically attribute CKD in a person with diabetes to diabetic nephropathy. Look for the accelerated trajectory.

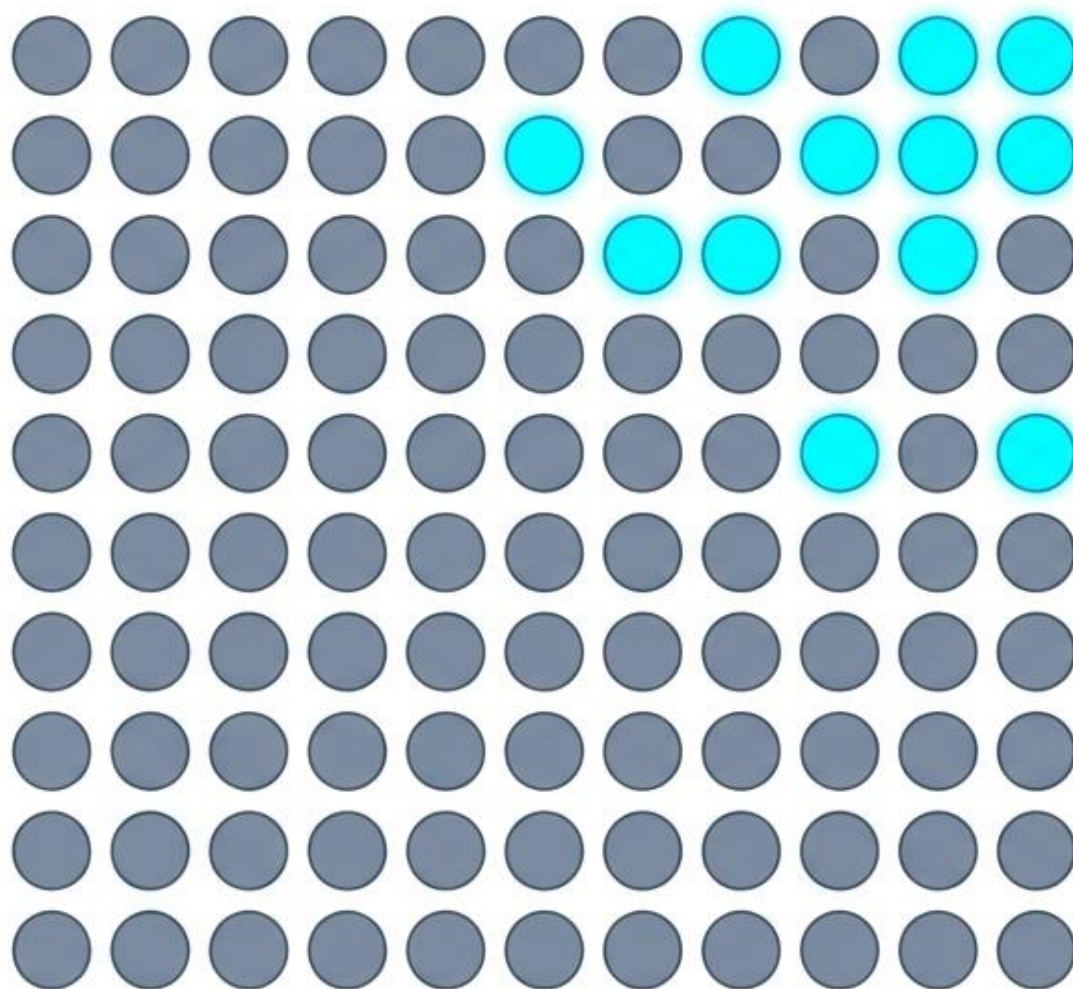
High-risk genotype accelerates established CKD



Genotype adds prognostic information, but albuminuria, eGFR, BP, family history, and clinical context remain essential.

Most carriers never develop kidney disease

Genotype identifies susceptibility—not active disease.



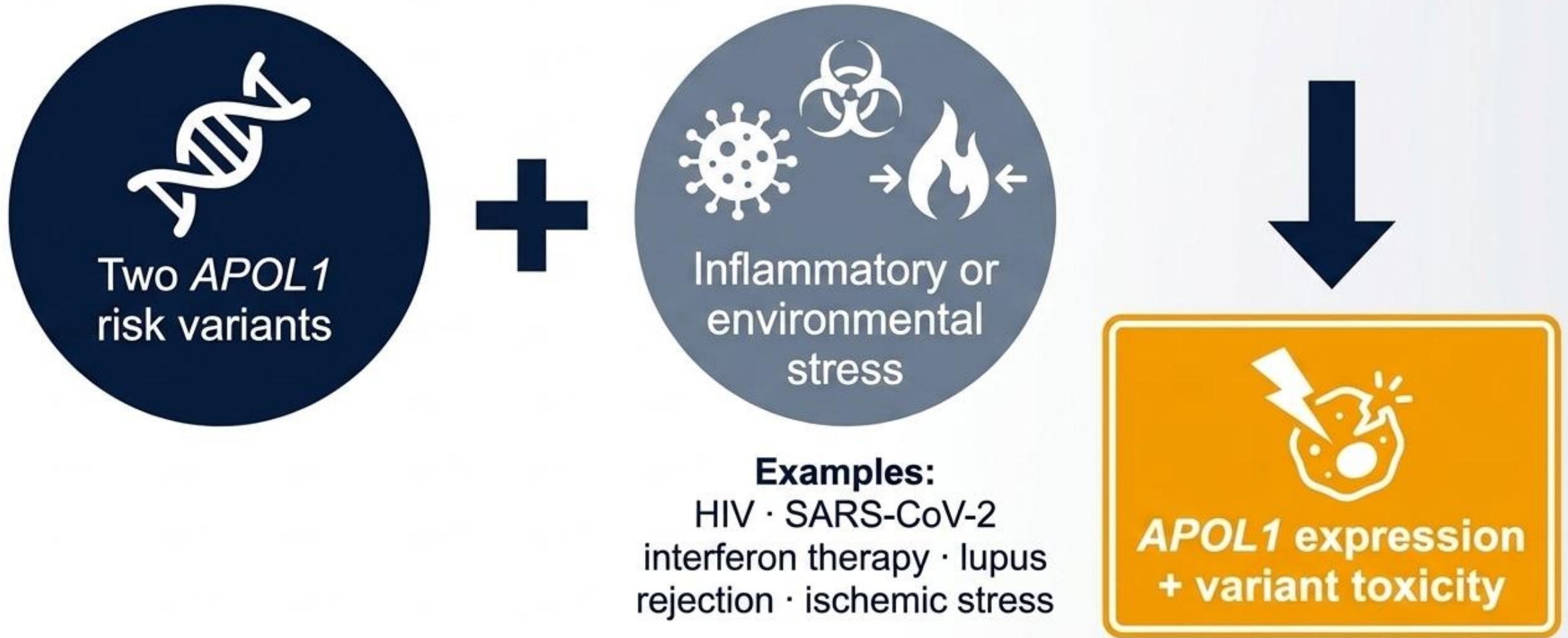
~15%

Estimated lifetime
kidney-failure risk
among people with
two risk variants.

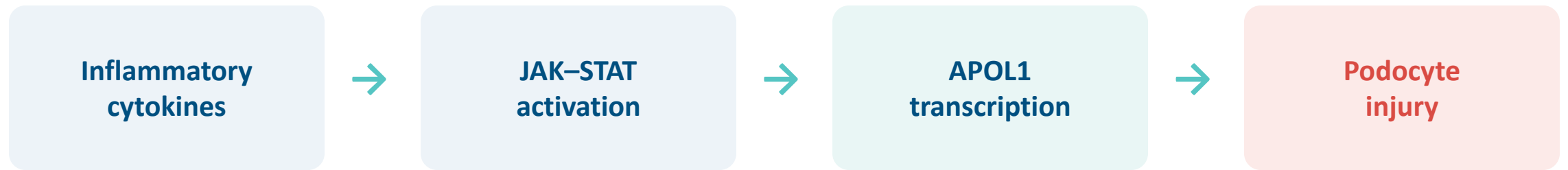
Most

Remain free of APOL1
kidney disease.

Disease often requires genetic susceptibility plus a second hit



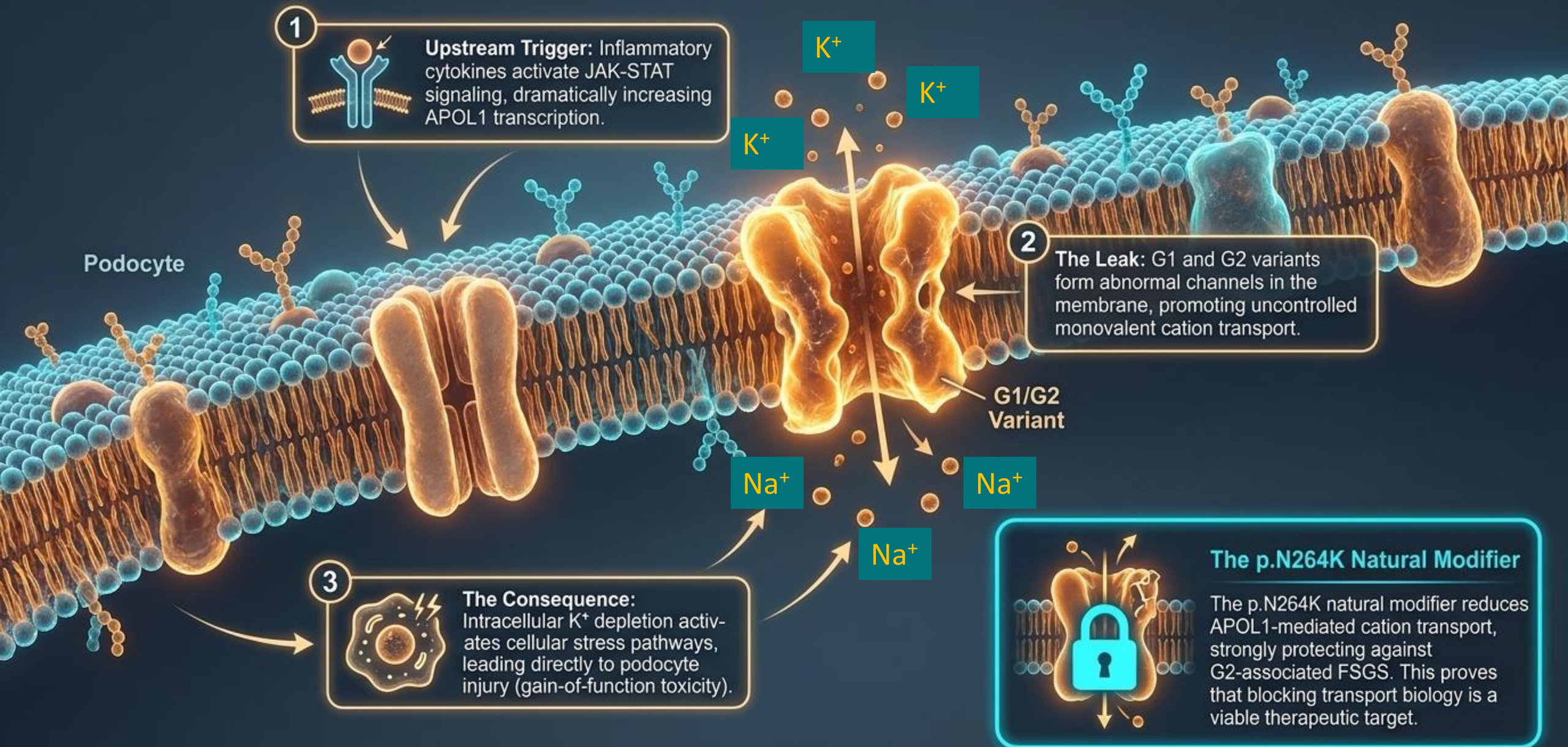
Interferon–JAK–STAT signaling turns susceptibility into expression



Therapeutic implication: suppress APOL1 expression upstream or inhibit APOL1 function downstream.



The Toxic Cation Channel Mechanism



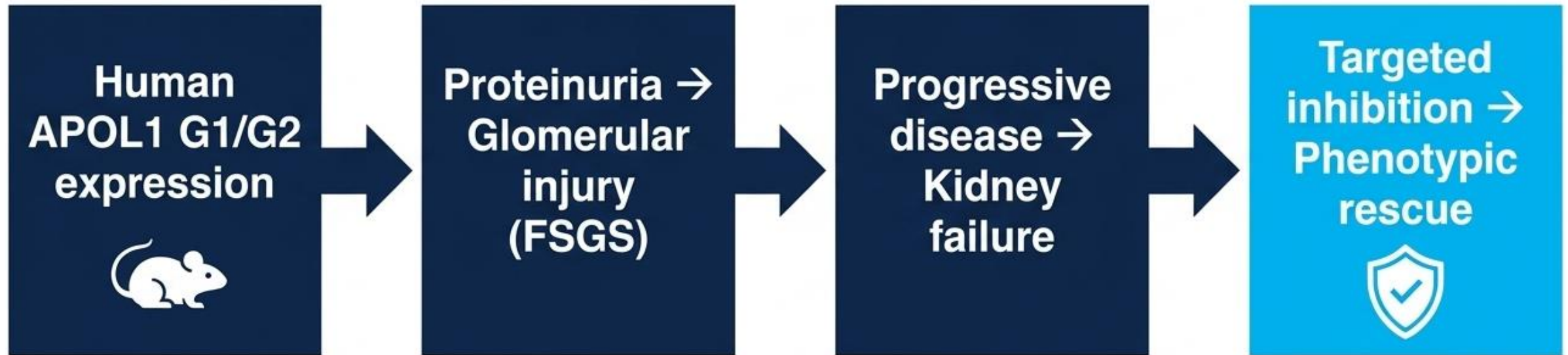
p.N264K is a natural experiment supporting causal transport biology



**Reduced
G2-associated
risk**

N264K reduces APOL1-mediated cation transport and strongly protects against G2-associated FSGS and kidney disease.

Humanized models establish causality and test rescue



Models are strongest when APOL1 expression level, cell type, genotype, and inflammatory context resemble human disease.

When should APOL1 kidney disease enter the differential?



CLINICAL CLUES

Young-onset nondiabetic CKD

FSGS or collapsing glomerulopathy

Rapid progression or family history

HIV-, COVID-, lupus-, or
interferon-associated collapse



CAUTION

Proteinuria can be variable or absent.

Histology is not genotype-specific.

“Hypertensive CKD” may conceal
APOL1 disease.

Genotype alone does not establish
causality.

KDIGO supports selective—not routine population—testing



Testing may inform

- Diagnostic interpretation
- Risk stratification and follow-up
- Living-donor counseling
- Clinical-trial eligibility



Evidence remains insufficient for

- Routine population screening
- Testing without informed consent
- Predicting disease from genotype alone
- Automatic exclusion from donation

Testing is a counseling process—not just a laboratory order

Before

Clarify purpose, alternatives,
privacy, family implications

Result

Explain 0, 1, or 2 variants and
incomplete penetrance

After

Link the result to follow-up,
family discussion, or trial
options

Avoid deterministic language: “increased susceptibility” is more accurate than “you have the disease.”



In transplantation, the kidney donor's genotype matters most

2 variants

Shorter allograft survival on average

Second hits

Rejection, viral infection, and inflammation may precipitate collapse

1 variant

2025 signal of risk requires replication before policy change

Genotype informs risk; it does not determine the fate of an individual kidney.



Transplantation Dynamics: Donors vs. Recipient Risk

RECIPIENT GENOTYPE

- Donor's genotype matters most. Deceased donor HR APOL1 → poorer transplant outcomes.
- Associations with rejection and graft loss are inconsistent.
- Recipient immune-cell APOL1 biology is plausible but not yet management-defining.

LIVING DONATION

- Offer informed, individualized counseling when relevant ancestry is present.
- Age, family history, kidney phenotype, and uncertainty matter.
- Two variants associated with risk of post donation eGFR decline + proteinuria in some donors. However, two variants should not be presented as an automatic universal exclusion.



Knowledge check 2

Which statement best reflects current guidance on APOL1 testing?

- A. Screen every person who self-identifies as Black.
- B. A two-risk-variant genotype proves APOL1 caused the CKD.
- C. Use selective testing when results may inform diagnosis, prognosis, donation, or trial access.
- D. Exclude every potential living donor with two risk variants.



Knowledge check 2

Which statement best reflects current guidance on APOL1 testing?

A. Screen every person who self-identifies as Black.

B. A two-risk-variant genotype proves APOL1 caused the CKD.

C. Use selective testing when results may inform diagnosis, prognosis, donation, or trial access.

D. Exclude every potential living donor with two risk variants.



Treat the CKD now—even without an approved APOL1-specific drug

RAAS blockade

Maximally tolerated

SGLT2 inhibitor

When eligible

Blood pressure

Individualized target

Sodium + risk factors

Comprehensive care

Cause-specific care

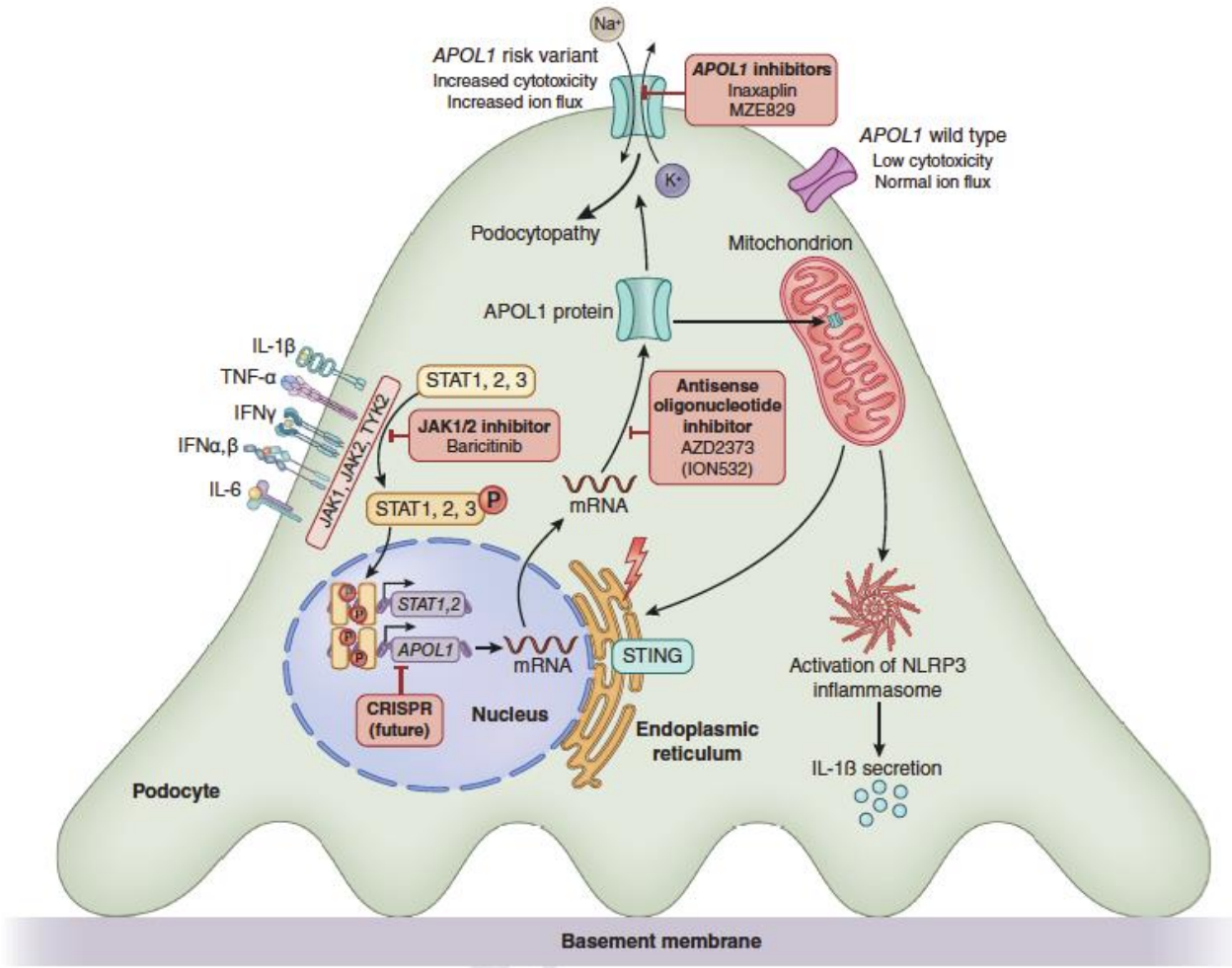
HIV, lupus, triggers

Clinical trial

Offer when appropriate



Investigational Therapies for APOL1-Mediated Kidney Disease



- **Inaxaplin and MZE829:** Blocks APOL1 cation transport function → reduced proteinuria
- **JAK inhibitors:** Suppress interferon-induced APOL1 expression
- **AZD2373:** antisense oligonucleotides → block APOL1 protein expression
- Other

The therapeutic pipeline now attacks APOL1 at multiple levels

STRATEGY	EXAMPLE	2026 STATUS
Direct function	Inaxaplin	Phase 2/3
Direct function	MZE829	Phase 2
Reduce expression	AZD2373 antisense	Early phase
Upstream signaling	JAK inhibitors	Investigator-initiated
Supportive care	RAAS / SGLT2	Clinical standard



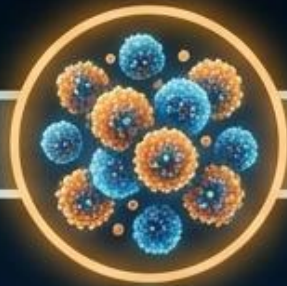
Beyond Genotype: Next-Generation Risk Stratification

Identifying which high-risk carriers will actually progress.

Genetic Susceptibility



Proteomic Signature



Clinical Outcome



The Biomarker Breakthrough (*Li et al. Nat Med 2026*)

- **The Cohort:** 851 high-risk genotype participants who currently have preserved eGFR.
- **The Tool:** APOL1 Proteomic Risk Score (based on 9 distinct proteins).
- **The Efficacy:** Achieved an 86.5% time-dependent AUC for predicting composite progression outcomes (External validation tAUC 82–85%).

Clinical Takeaway

Genotype defines the baseline susceptibility, but emerging proteomics will act as the “radar” to detect active biological transition before irreversible eGFR decline occurs. (Note: Promising research, not yet routine care).

Case revisited: what would you do now?

Likelihood

Very high. FSGS changes the pretest probability to ~ 40–60% in this demographic.

Testing

Reasonable if accompanied by counseling and linked to prognosis or trial eligibility.

Management

Maximize RAAS blockade; add SGLT2 inhibition if eligible; optimize CKD care. Monitor pipeline trial eligibility

Prognosis

Two variants raise progression risk but do not determine the individual outcome.

Transplant

Donor-kidney genotype is more established than recipient genotype*.



Board Peals

- G1 and G2 increase risk for FSGS, COVAN, HIVAN and certain non-diabetic CKD
- Two variants confer the greatest risk; penetrance is incomplete, and one variant may confer intermediate risk.
- Donor-kidney genotype is the clearest transplant-related genetic determinant.
- High-risk genotype accelerates CKD progression
- Donor-kidney genotype is the clearest transplant-related genetic determinant.



Three take-home messages

1 **Genotype identifies susceptibility—not destiny.**

2 **Test selectively, counsel carefully, and treat CKD comprehensively.**

3 **APOL1-directed therapy is moving from mechanism to clinical validation.**



Key References

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