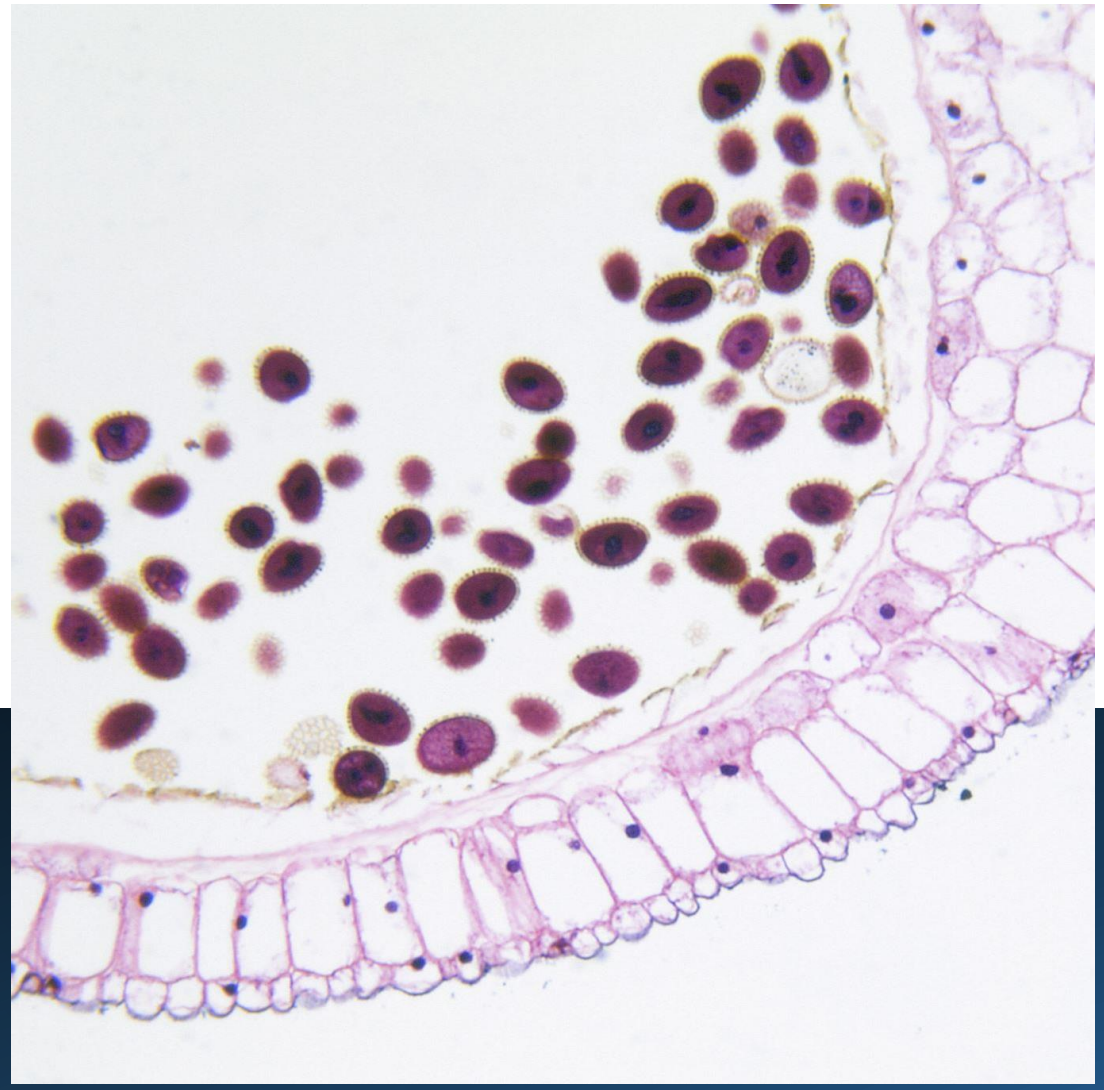
APOL1 and Kidney Disease



Prof. Vincent Boima

MD, MPH, FWACP, FGCP, FISN, Cert Nephrology (SA) phy

University of Ghana Medical School

Cameroon Society of Nephrology Conference 2025, Yaoundé

Outline:

- CKD in Africa
- Frequency and distribution of APOL1 risk variants
- APOL1 kidney disease
- Genetic therapy for APOL1 kidney disease
- Implications for kidney transplantation

CKD OVERVIEW: AFRICANS

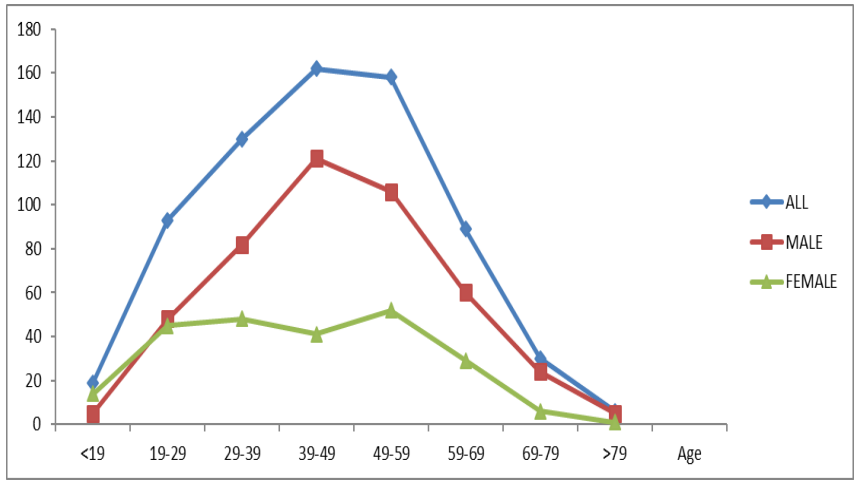
Africans succumb to end-stage renal disease (ESRD) 20 to 30 years earlier Europeans

Kidney replacement therapy is either unavailable or unaffordable, making the development of ESRD a death sentence for many

CKD causes premature mortality, cardiovascular comorbidities

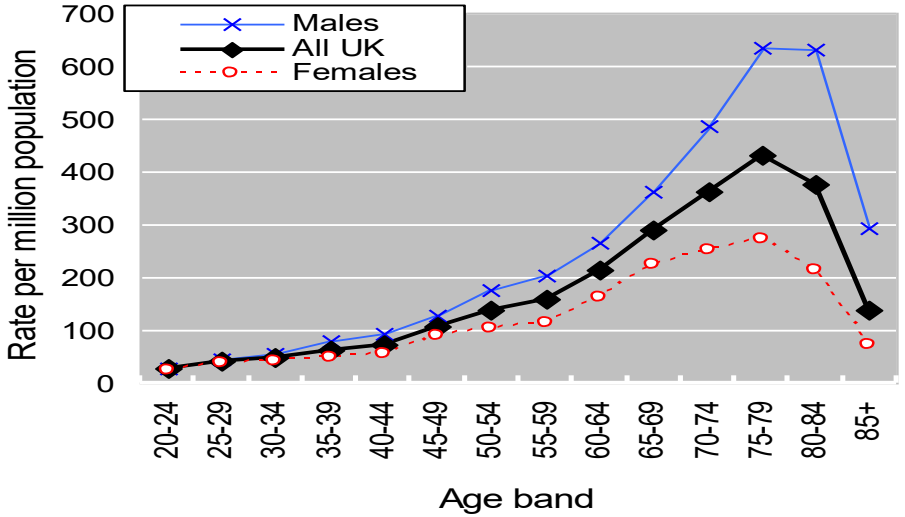
RENAL REGISTRY: GHANA AND UK: AGE AND SEX

Prevalent rates of ESRD by age and sex in 2017



Ghana Renal Registry 2017

Figure 3.5: Incident rates by age and gender in 2007



UK Renal Registry 11th Annual Report 2008

Boima V, Tannor EK, Osafo C. et al., 2021. "The Ghana Renal Registry – a First Annual Report". *African Journal of Nephrology* 24 (1), 19-24. https://doi.org/10.21804/24-1-4545.

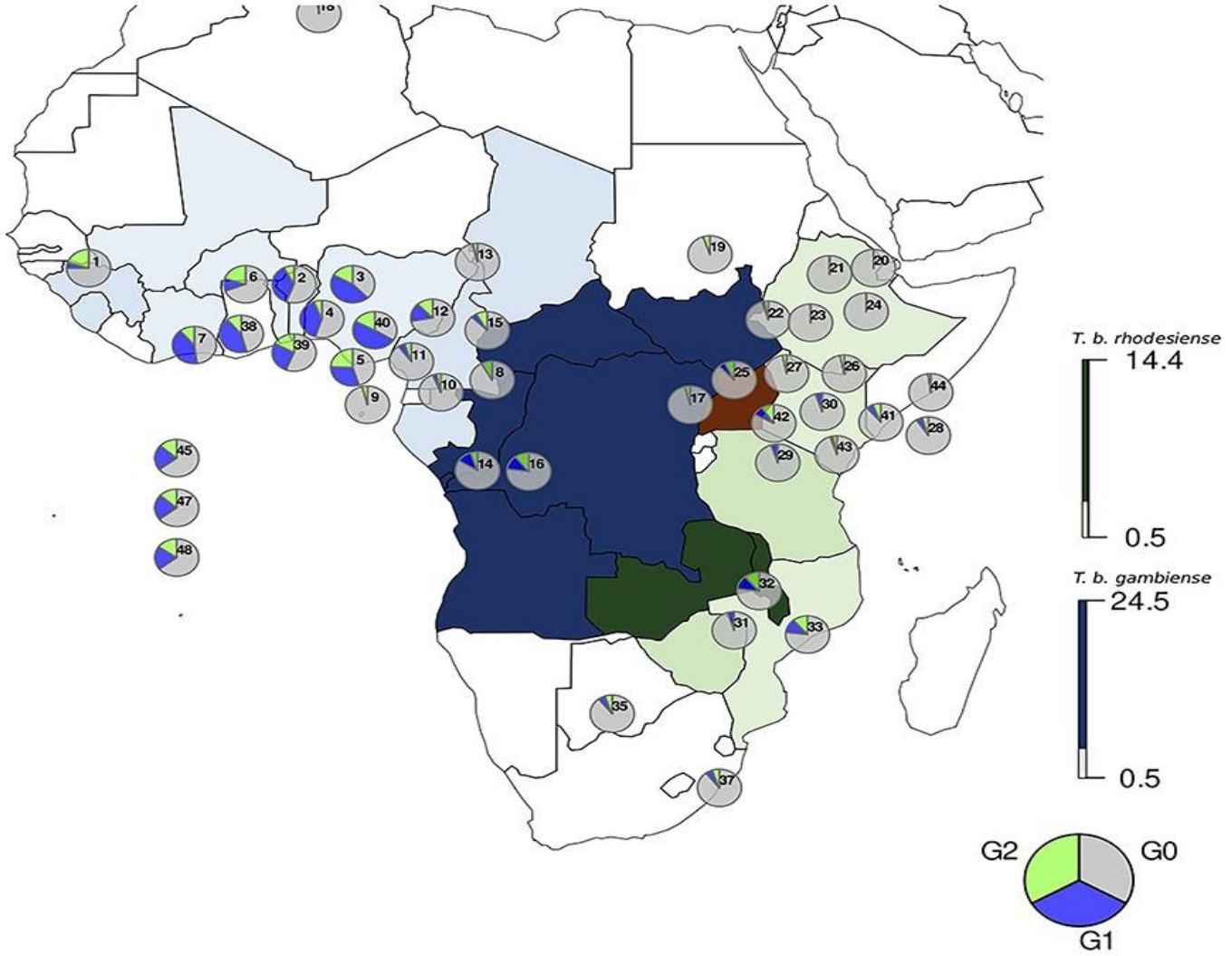
APOL1 variants and trypanosomiasis

1. *APOL1* variants evolved some 10,000 years ago and provided protection against Trypanosoma brucei brucei (cf Sickle haemoglobin and malaria)
2. Therefore, APOL1 variants rose to a high proportion in Africans
3. This was after the out of Africa migration of homo sapiens some 50-80,000 years ago
4. Therefore, APOL1 variants found only in Africans and people of African descent

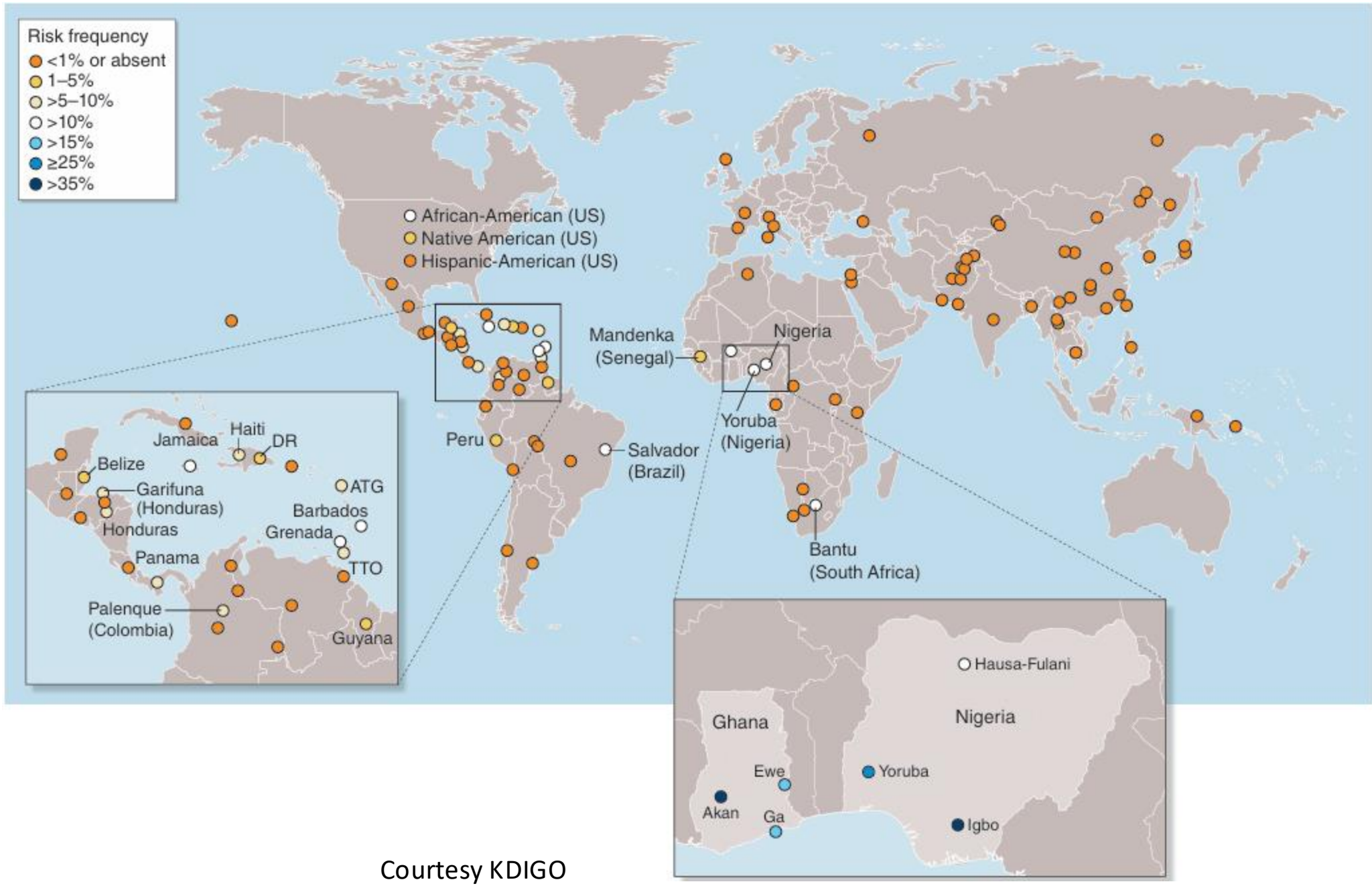
Apol1 risk variants explain excess risk of kidney disease in African Americans

- Apolipoprotein L1 (*APOL1*) gene located chromosome 22
- APOL1 produced in the liver and circulates with HDL3
- Two renal risk variants of *APOL1*: G1 (S342G and I384M substitutions) & G2 (deletion of two amino acid residues, N388 and Y389)
- Explain ≈70% excess risk of CKD in African Americans
- Strongest risk factor for CKD

Distribution of human African trypansomiasis (T.b. gambiense and T.b. rhodesiense) and APOL1 G1 and G2 allele ...



Hum Mol Genet, Volume 30, Issue R1, 1 March 2021, Pages R129–R137, https://doi.org/10.1093/hmg/ddab024



Courtesy KDIGO

	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

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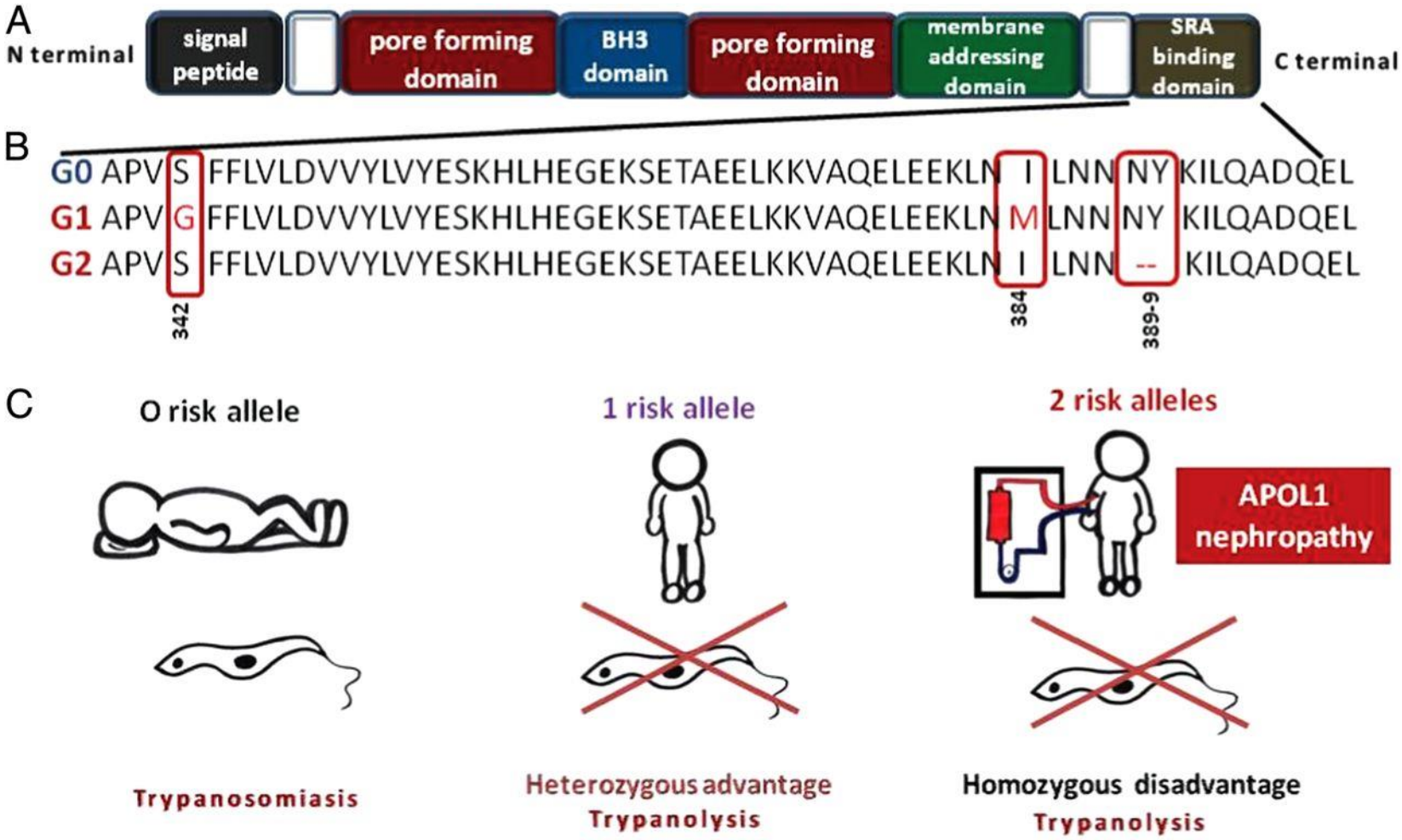
Freq. of 2RRV – 29% vs CTRL – 13.9%: Ashuntantang et al – unpublished

Courtesy KDIGO

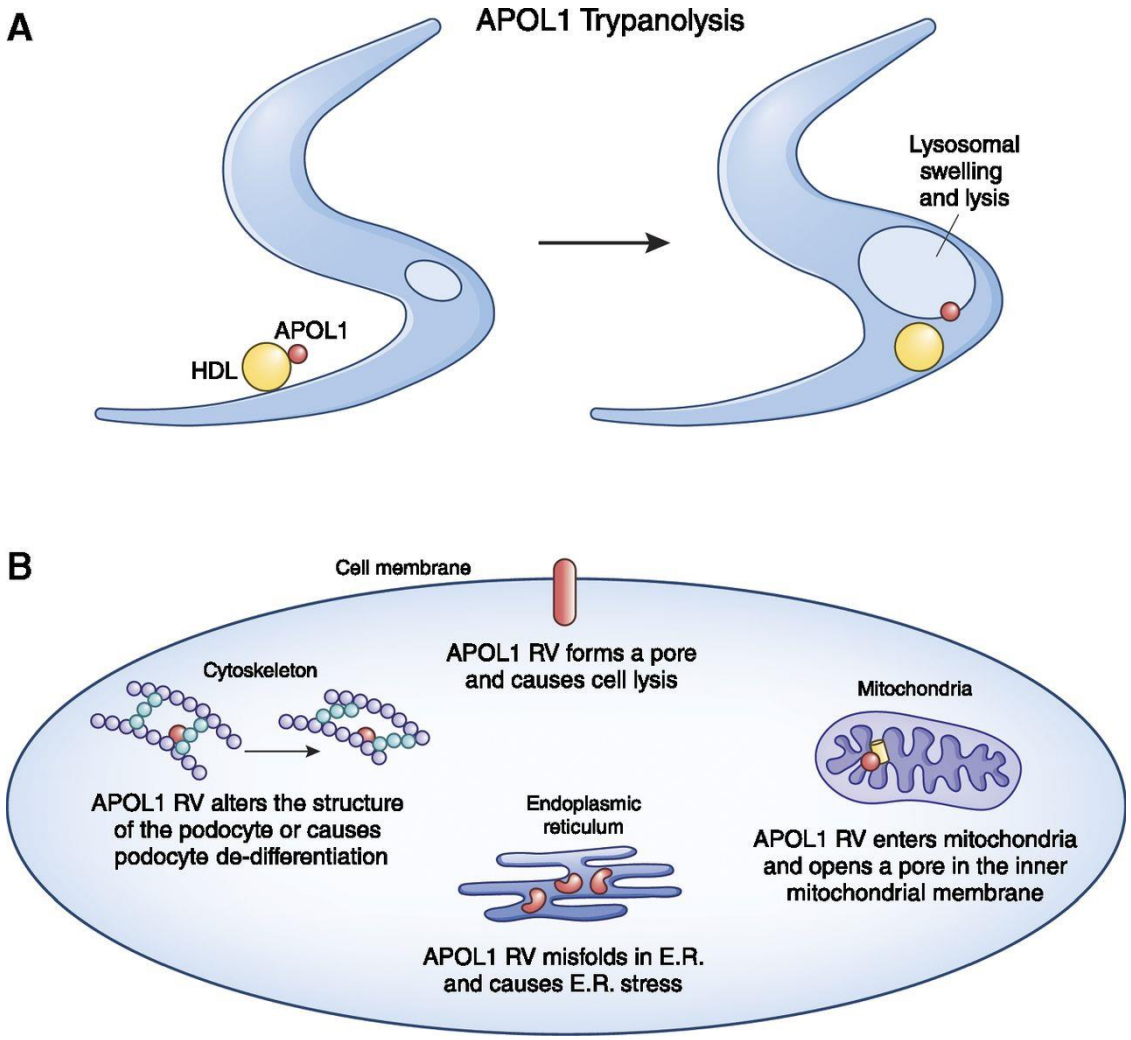
The structure of APOL1 with annotated domains



Etty Kruzel-Davila et al. Nephrol. Dial. Transplant. 2016;31:349-358

NDT
Nephrology Dialysis Transplantation

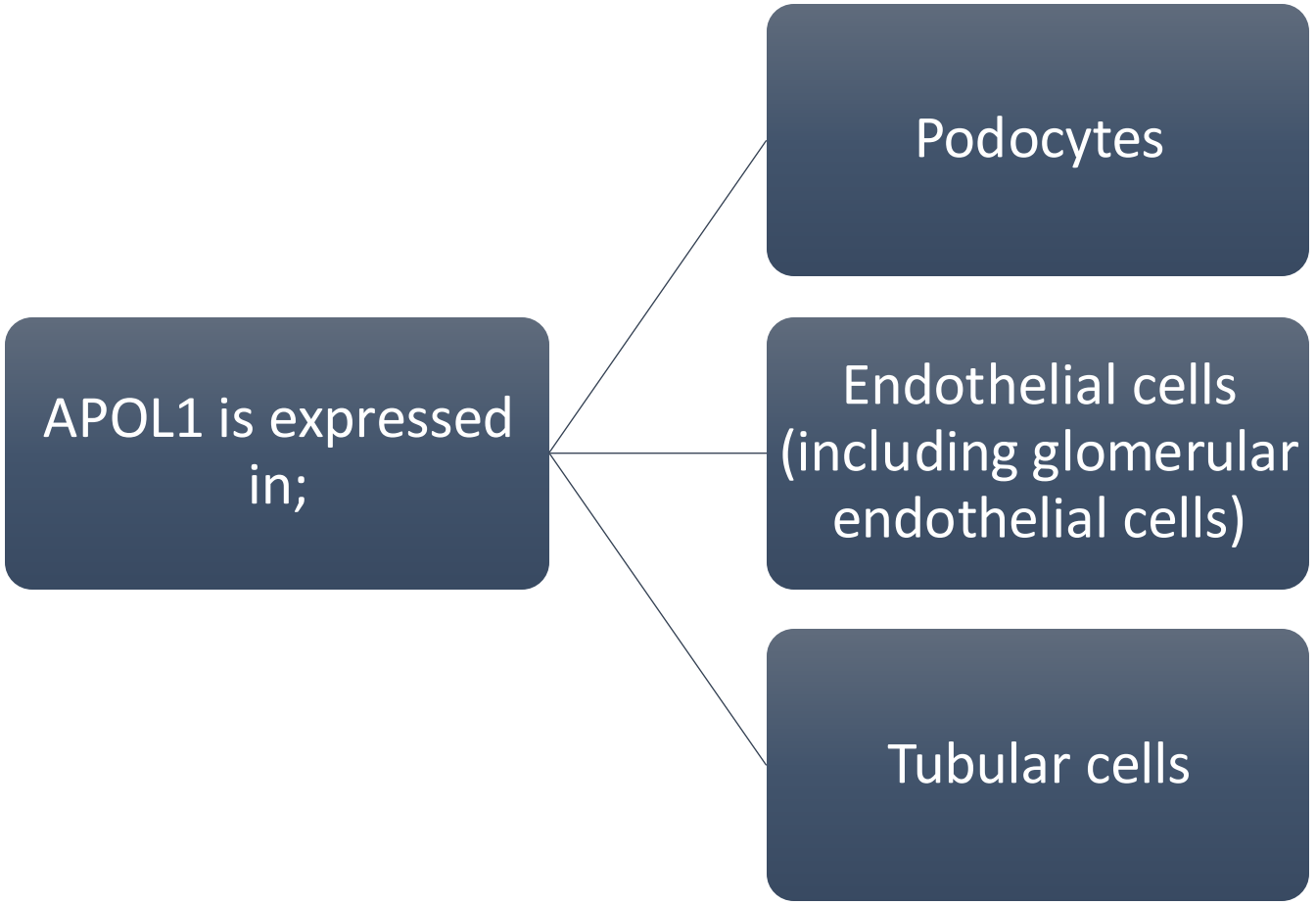
APOL1 mechanisms in health and disease.



David J. Friedman, and Martin R. Pollak CJASN
2021;16:294-303

CJASN®
Clinical Journal of the American Society of Nephrology

APOL1-mediated kidney disease (AMKD)



1. Tzur S et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet 128: 345–350, 2010

- GWAS- the presence of 2 APOL1 mutations explain up to 70% of the cause for non-diabetic kidney disease

- The presence of G1/G1, G2/2 or G1/G2 leads to;

  - 3 times to 17 times greater risk of kidney disease development
  - 2 to 3 times greater risk of progression to ESKD

1. Pays E et al. Human innate immunity against African trypanosomes. Curr Opin Immunol 21: 493–498, 2009
2. Vanhollebeke B et al. Human Trypanosoma evansi infection linked to a lack of apolipoprotein L-I. N Engl J Med 355: 2752–2756, 2006
3. Johnstone DB et al. APOL1 null alleles from a rural village in India do not correlate with glomerulosclerosis. PLoS One 7: e51546, 2012
4. Taylor HE et al. The innate immune factor apolipoprotein L1 restricts HIV-1 infection. J Virol 88: 592–603, 2014

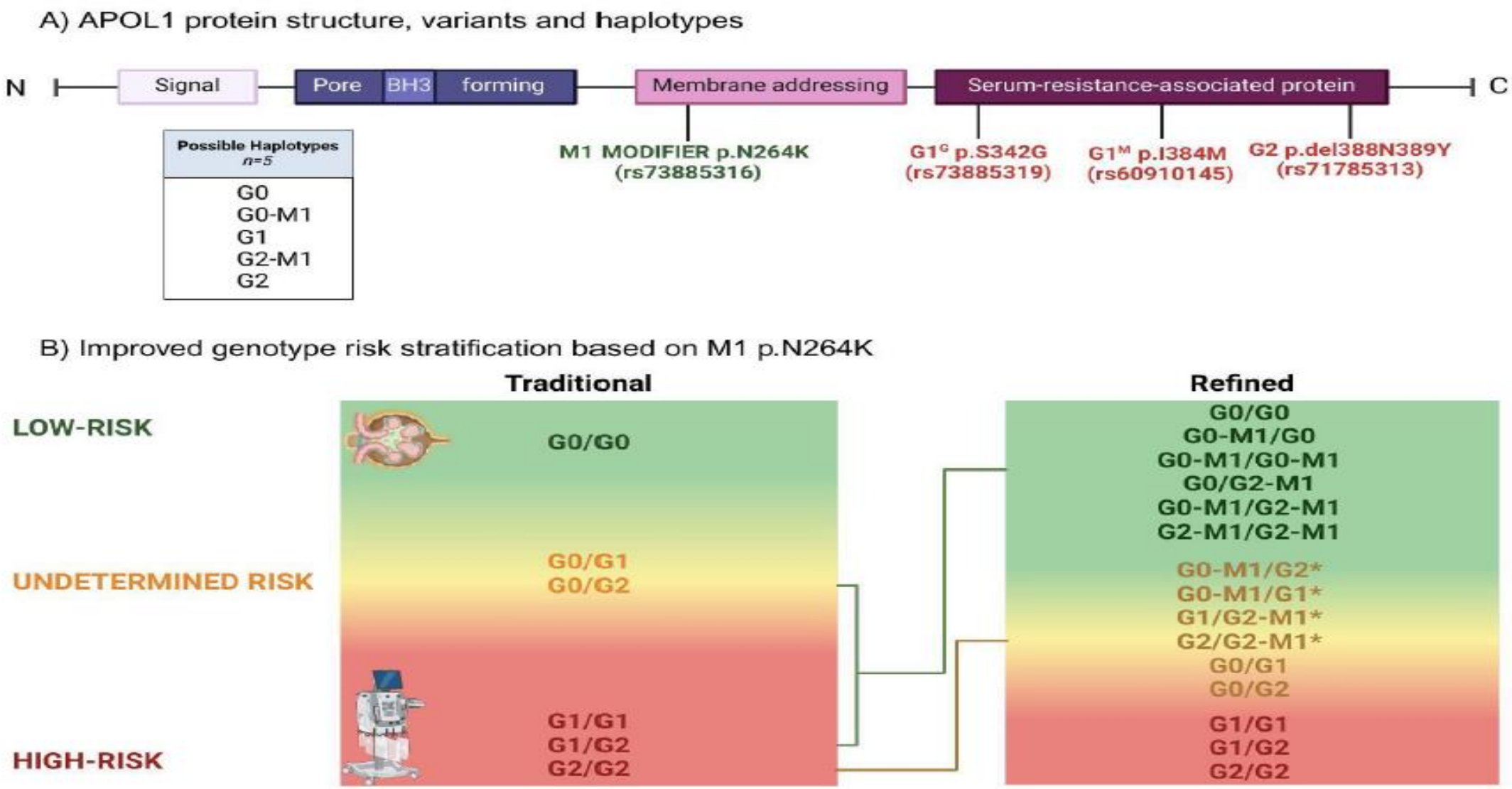
Apol1 high-risk variants require a “second hit” for CKD

- Not all African Americans or Africans with APOL1 high-risk variants develop CKD
- Etiologic Second Hits
  - Gene-gene

  or
  - Gene-environment interaction
- Interferon
- HIV: strongest correlate for CKD

Freedman et al *CJASN* 2015, Nichols B et al. *Kidney Int.* Feb 2015;87(2):332-342, Divers et al Kidney International 2013, Kopp JB et al. *Journal of the American Society of Nephrology.* Nov 2011; Nichols *Kidney Int. 2014*

APOL1 protective M1 p.264K Variant



Gbadegesin et al. Glomerular Dis 2024

One gene, many phenotypes

High-risk APOL1 genotype

Sudden onset/insidious

Nephrotic/non-proteinuric

Rapid/slow GFR loss

Glomerular/vascular

<u>Explanations</u>

Genetic Modifiers?

Different Triggers?

Cell types?

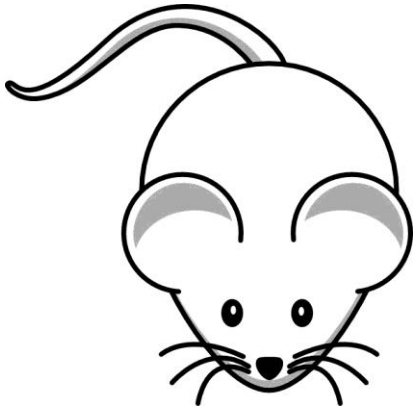
Organelles?

Pathways?

Multiple mechanisms?

BAC-transgenic APOL1 Mouse

Mouse with full human APOL1 seq.



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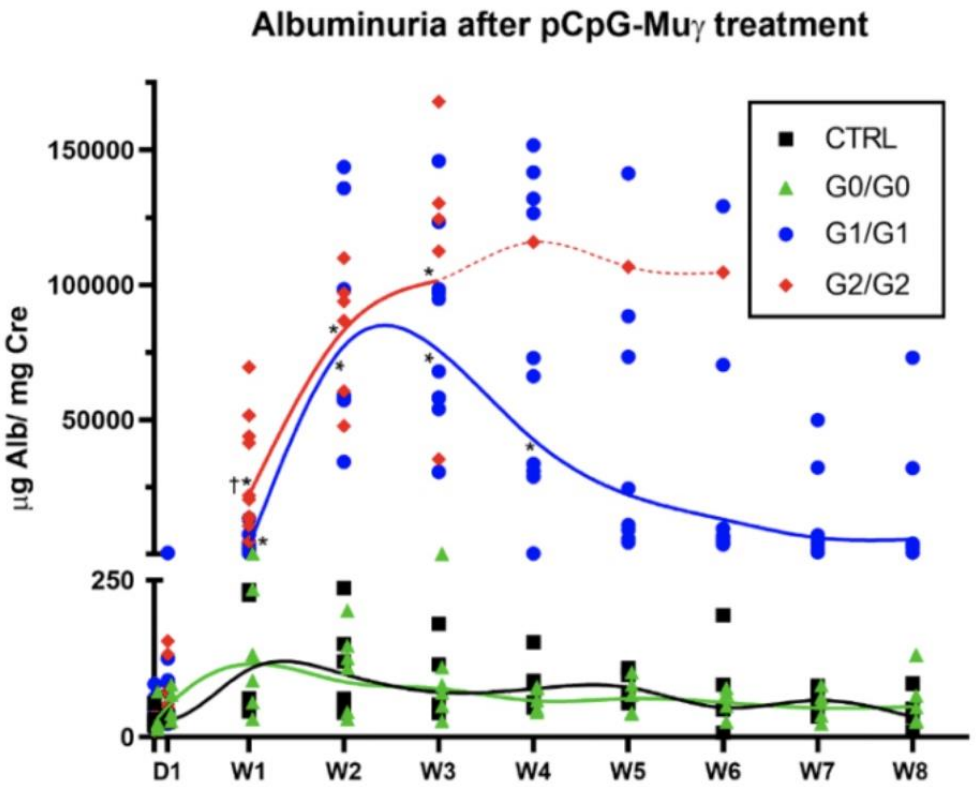
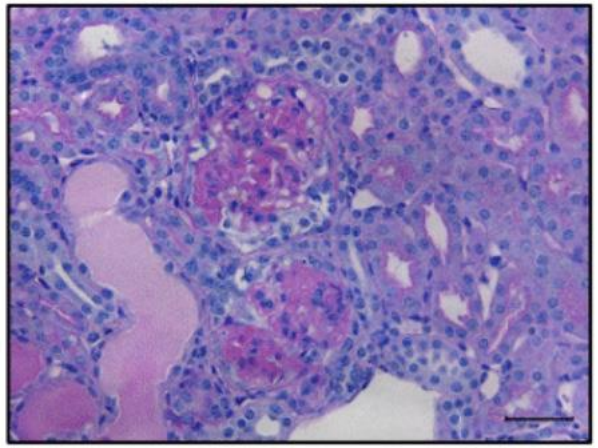
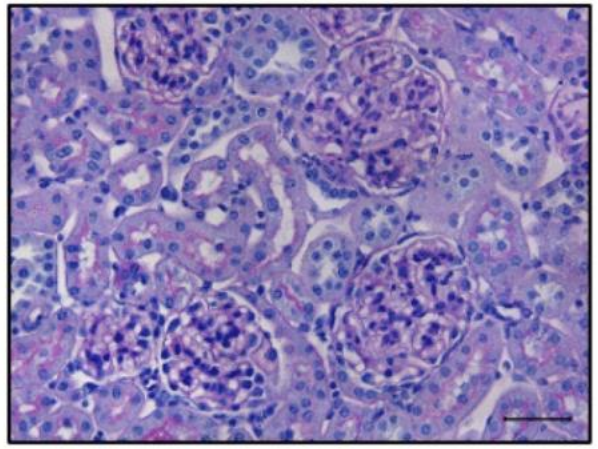
Plasmid for interferon-γ





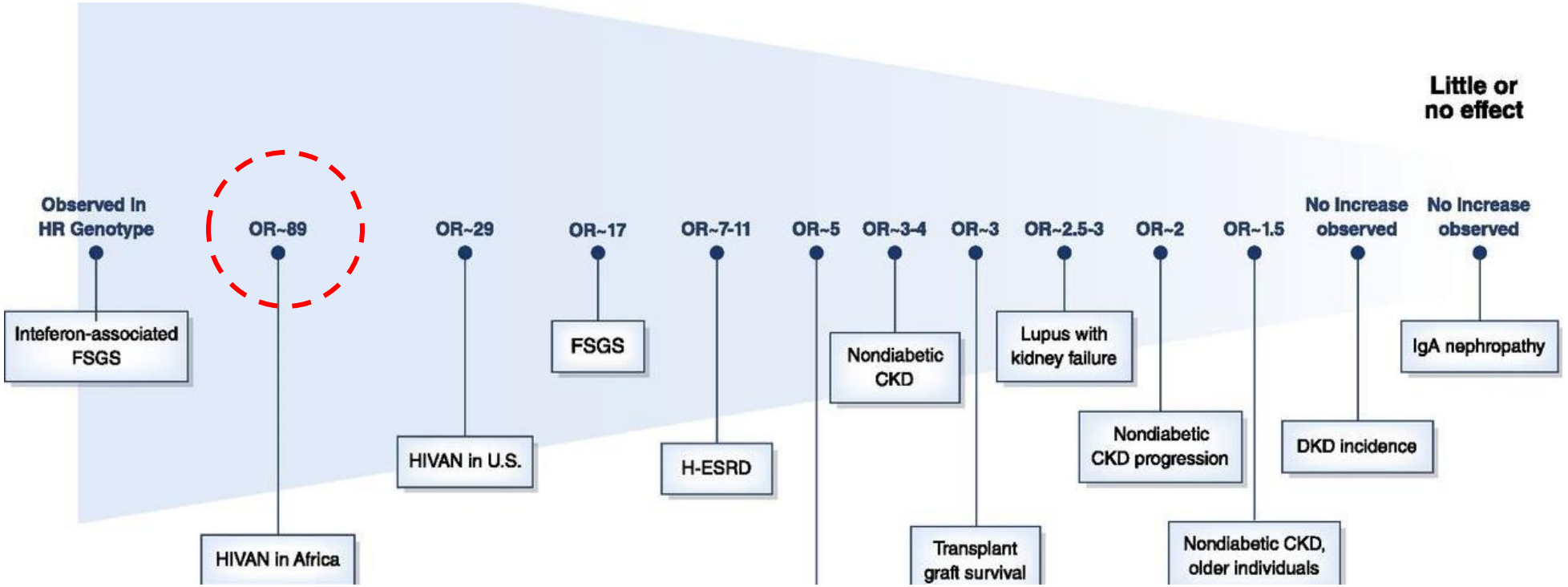
G2/G2 mouse



G0/G0 mouse

Gizelle McCarthy/Angelo Blasio, DMM 2021

APOL1 Nephropathy: From Genetics to Clinical Applications



Friedman, David J.; Pollak, Martin R. Clinical Journal of the American Society of Nephrology16(2):294-303, February 2021. doi: 10.2215/CJN.15161219

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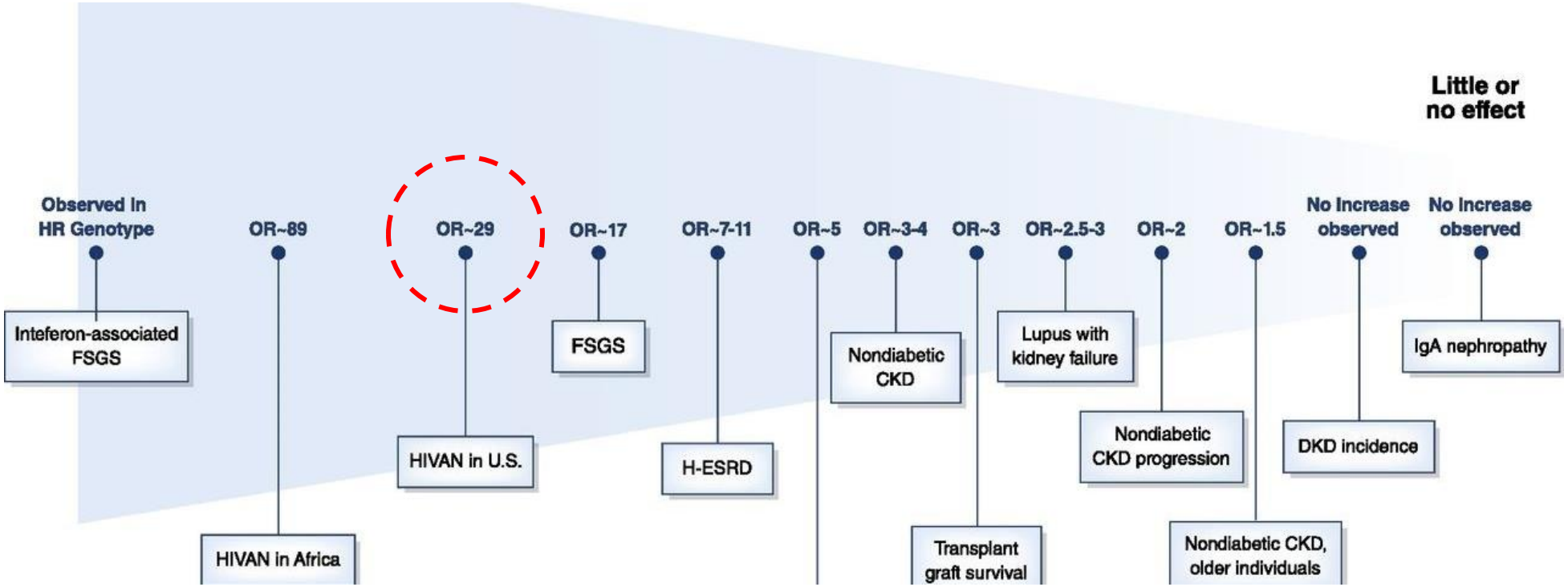

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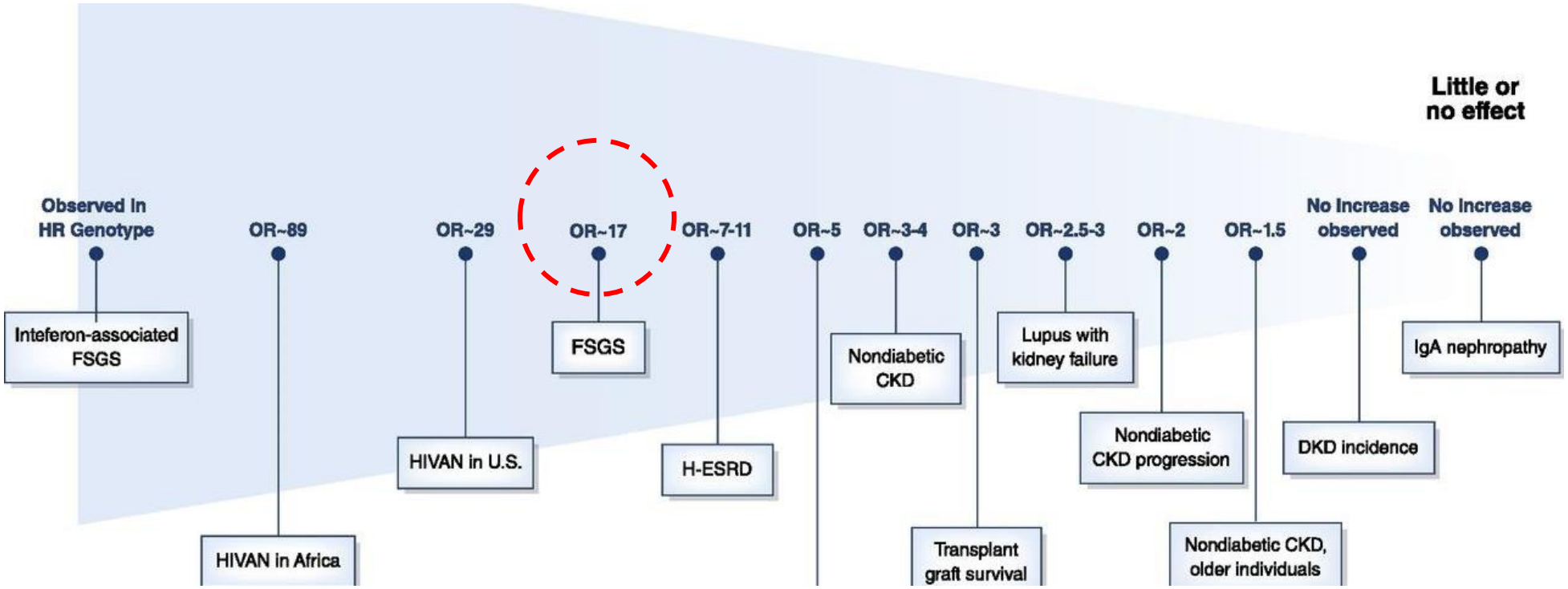

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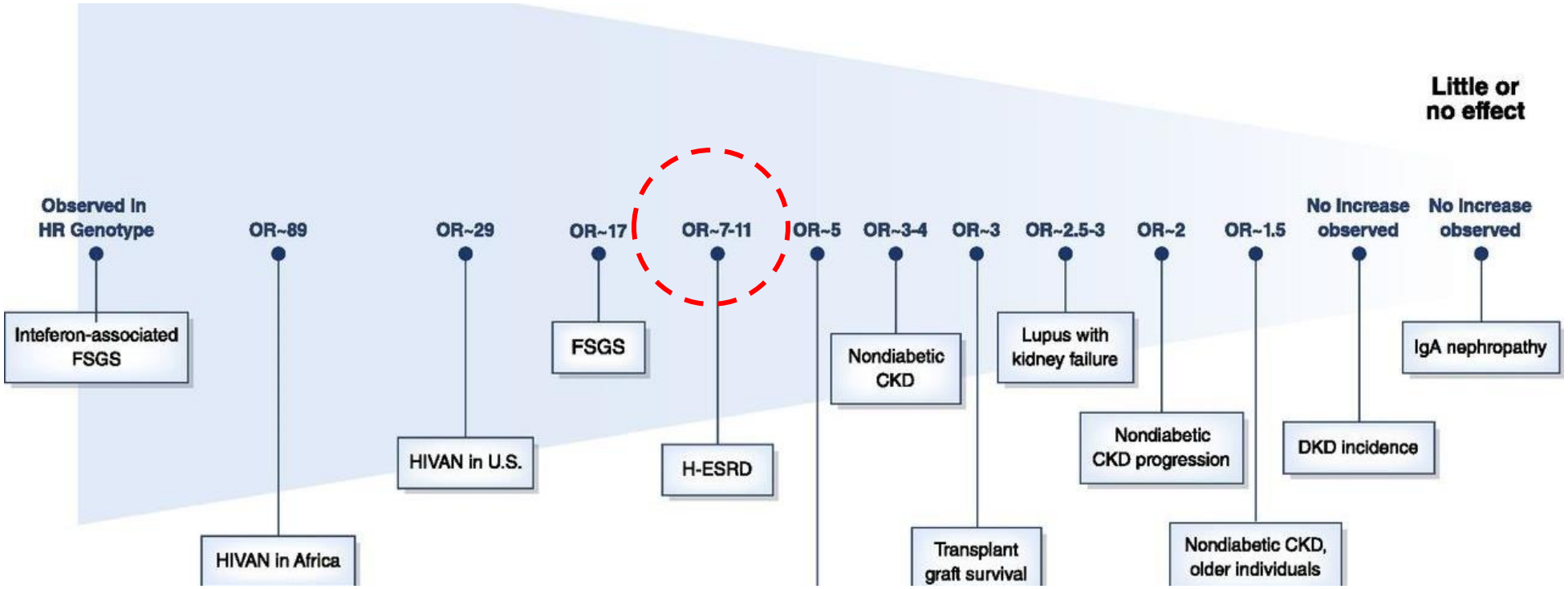
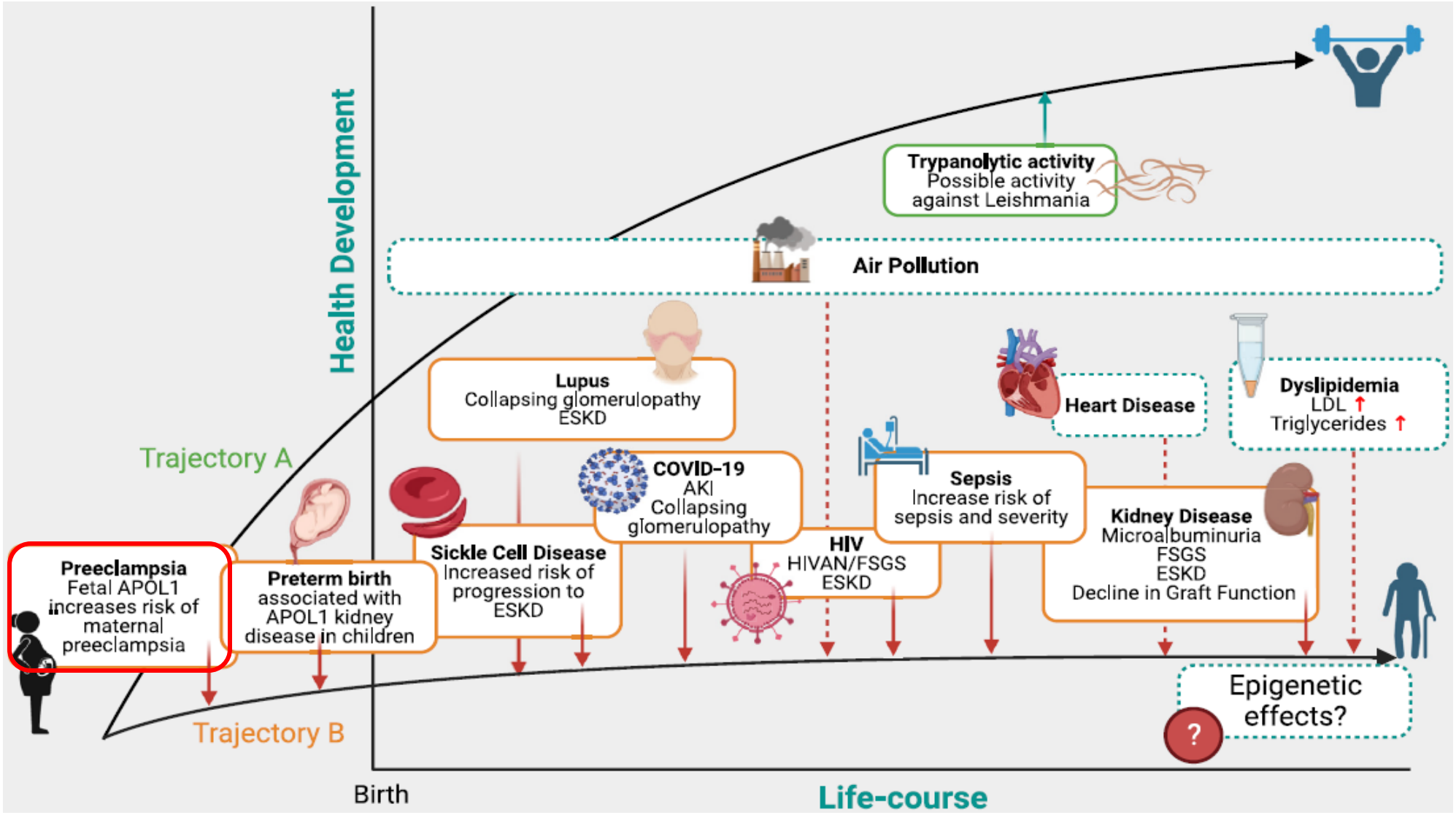
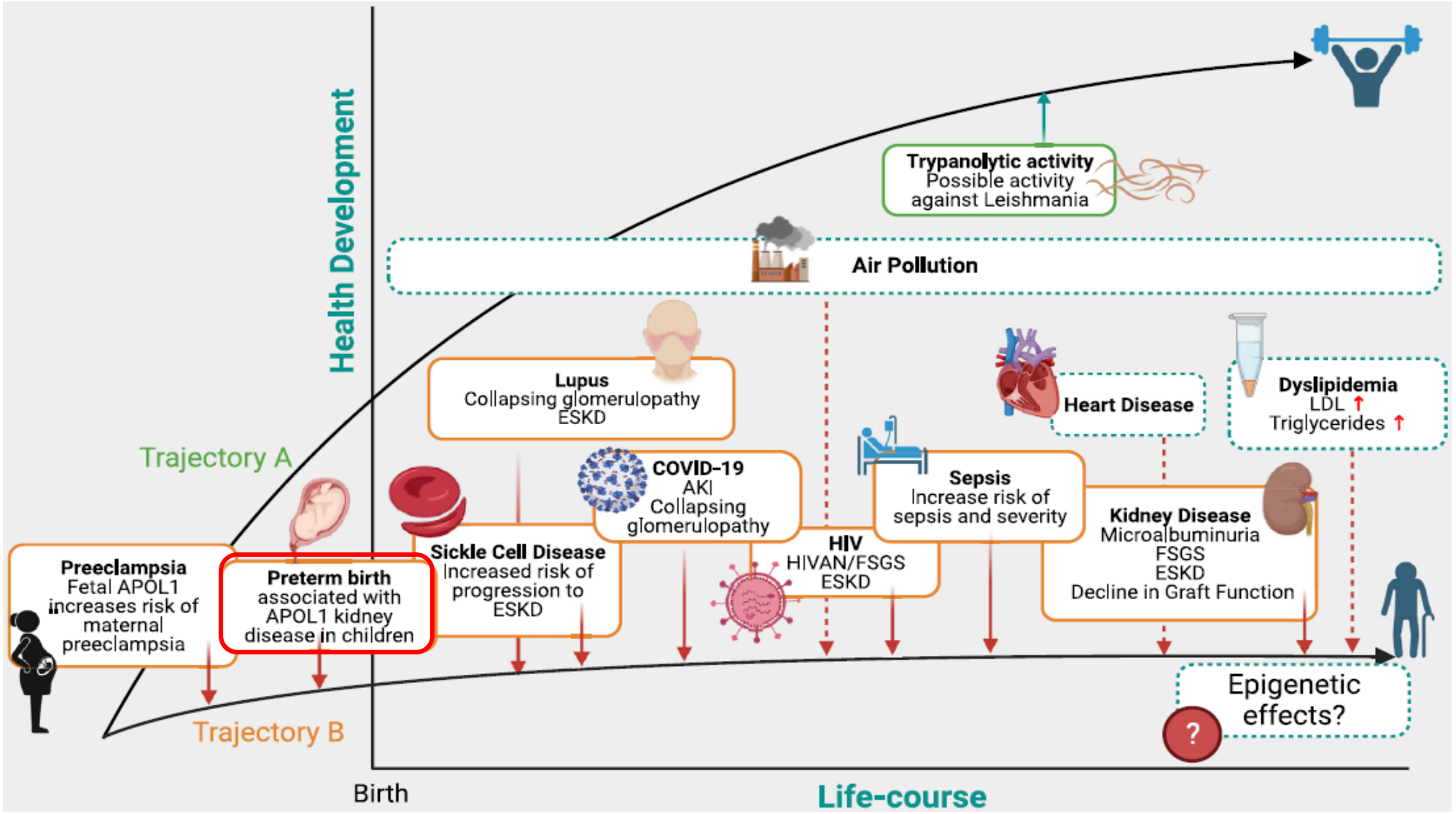
APOL1 Nephropathy: From Genetics to Clinical Applications



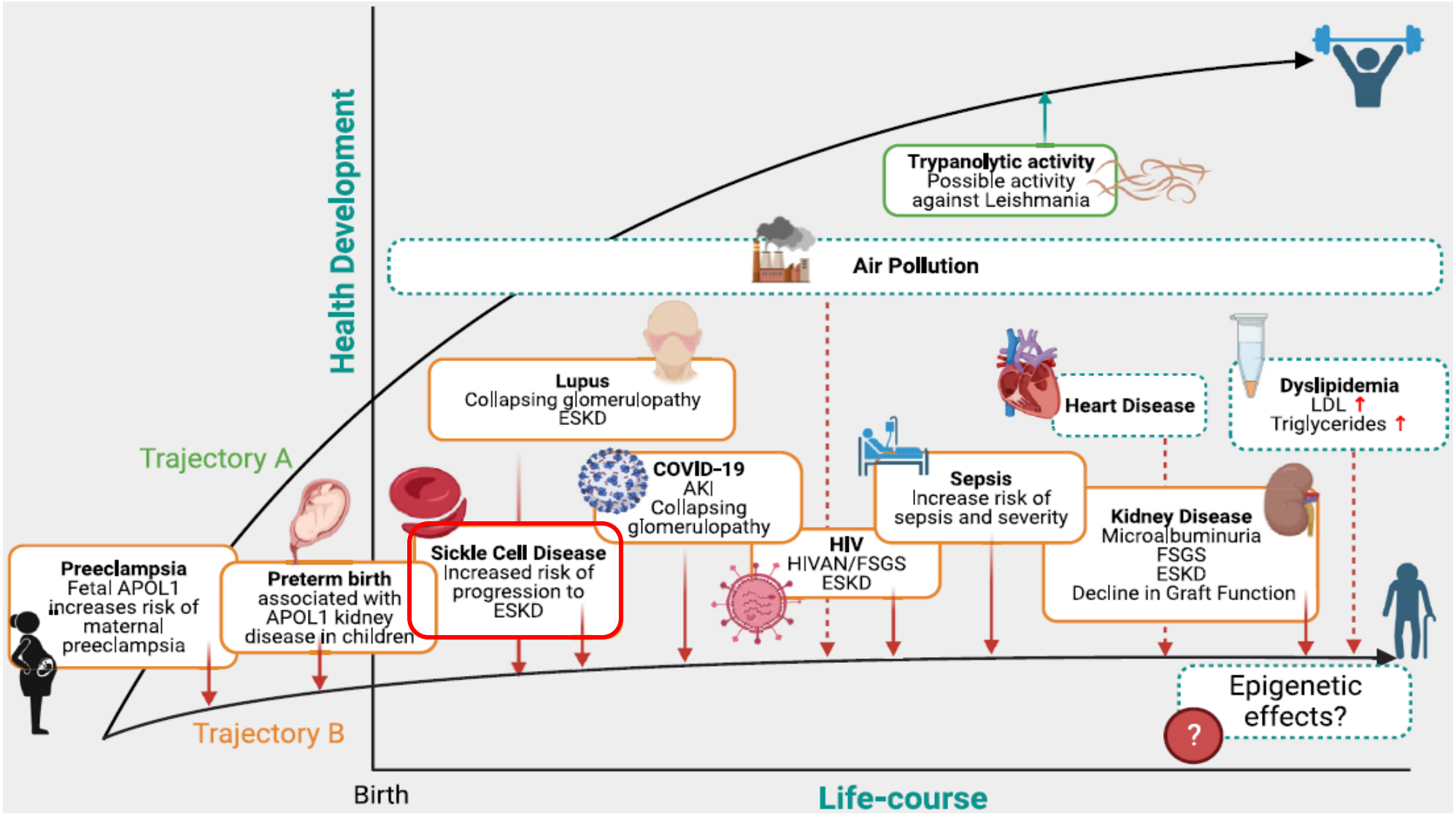
Friedman, David J.; Pollak, Martin R. Clinical Journal of the American Society of Nephrology16(2):294-303, February 2021. doi: 10.2215/CJN.15161219



American Journal of Kidney Diseases 2024 84102-110DOI: (10.1053/j.ajkd.2023.12.014)



American Journal of Kidney Diseases 2024 84102-110DOI: (10.1053/j.ajkd.2023.12.014)



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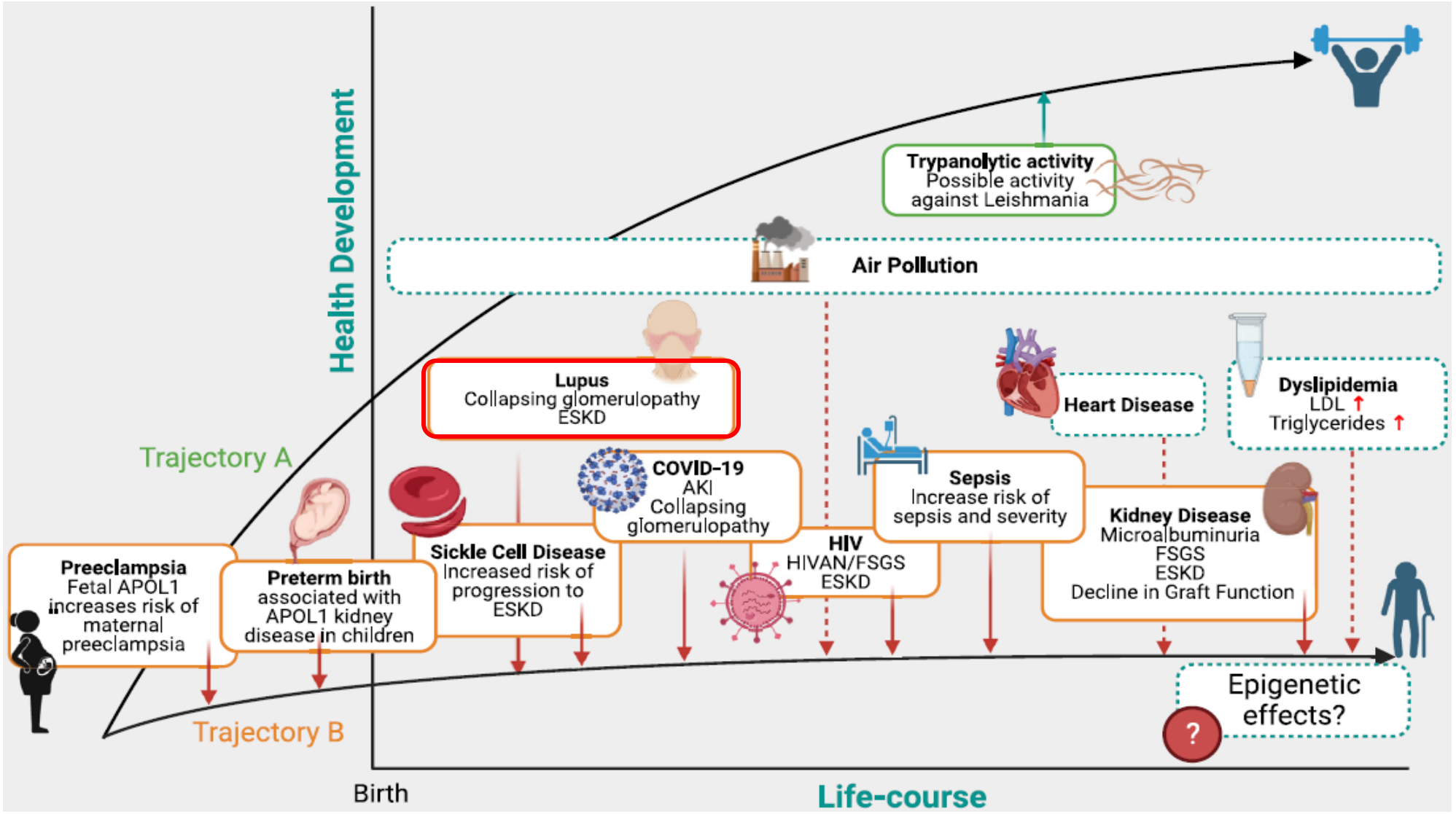

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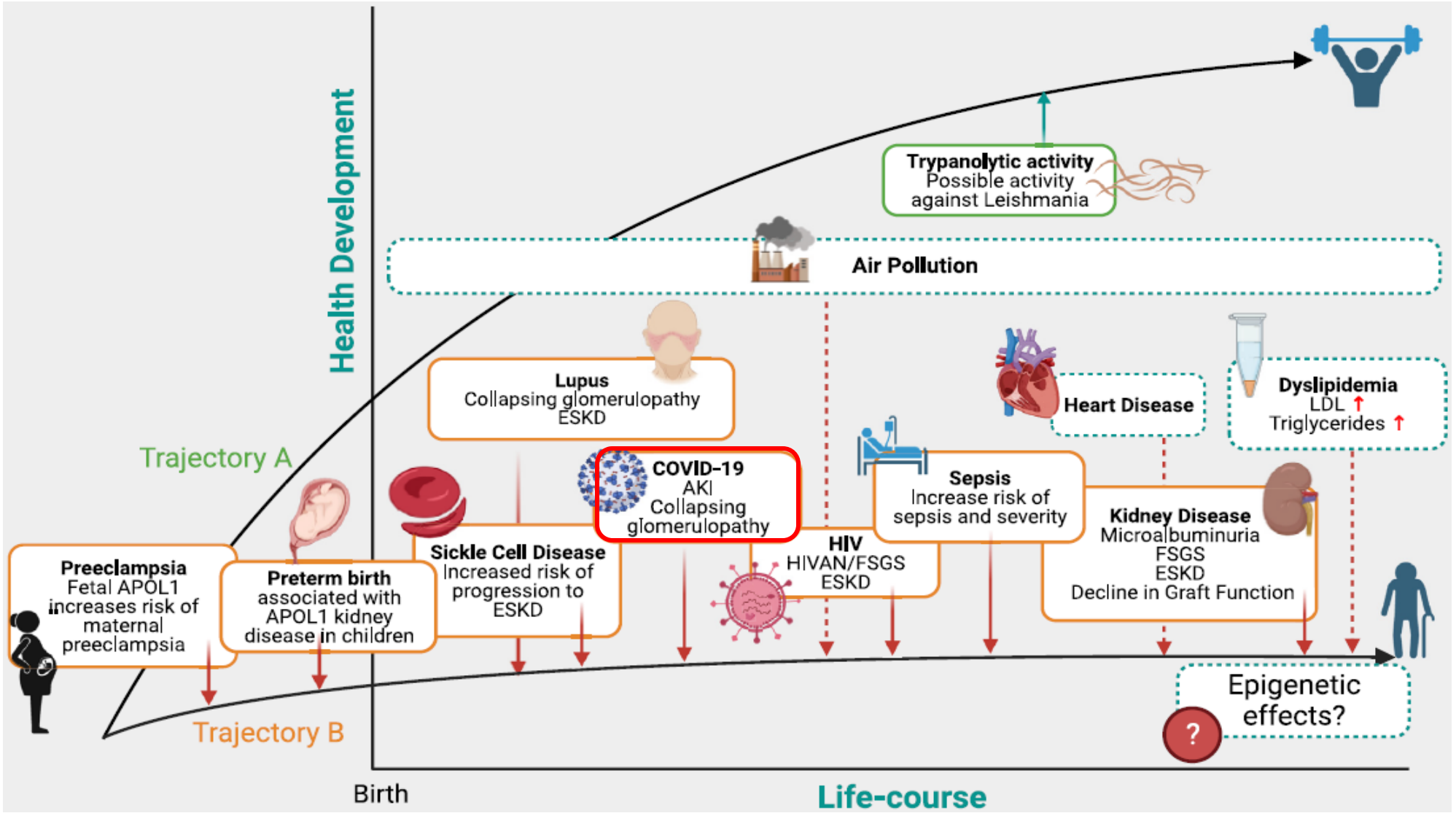
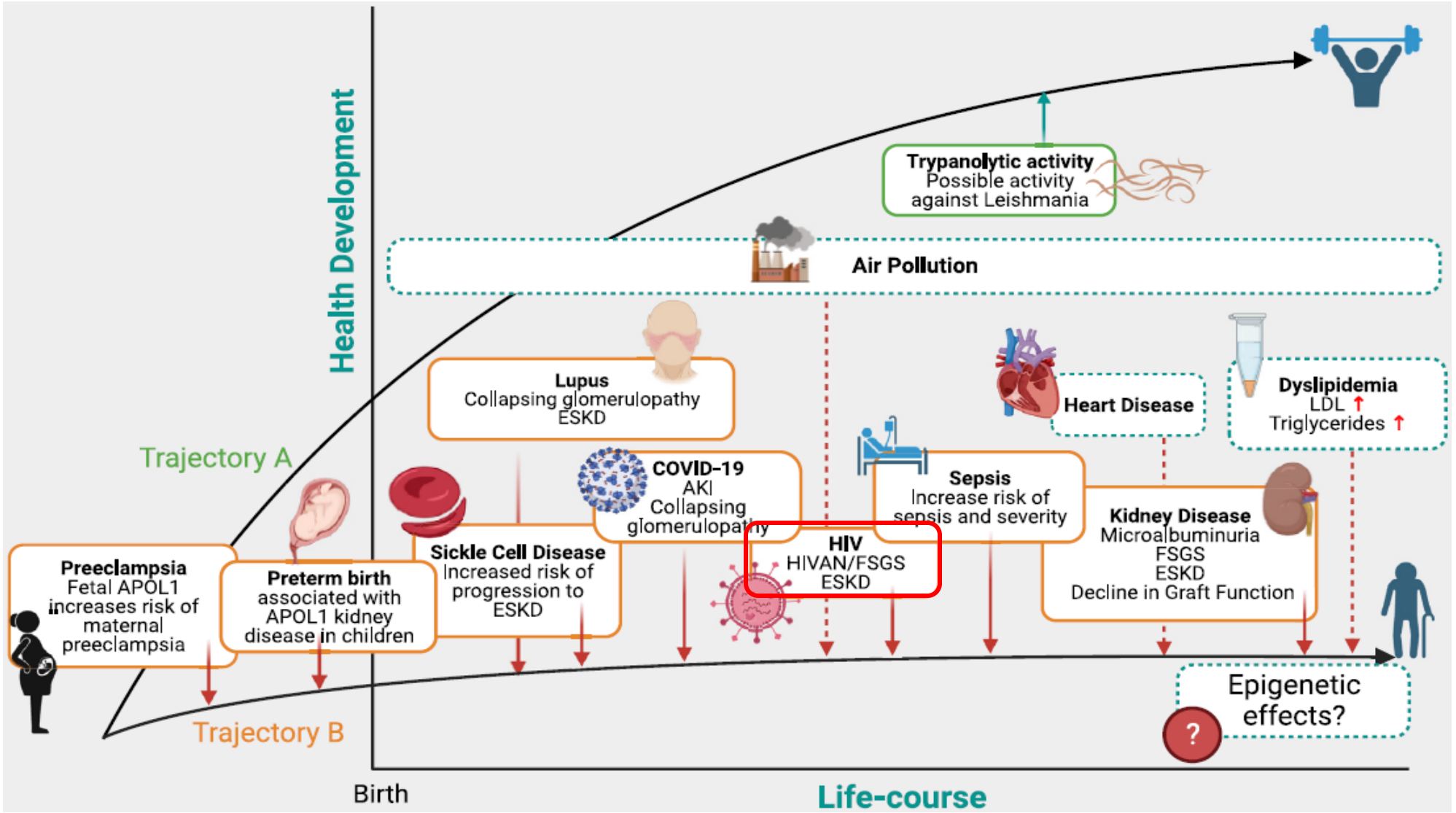


American Journal of Kidney Diseases 2024 84102-110DOI: (10.1053/j.ajkd.2023.12.014)



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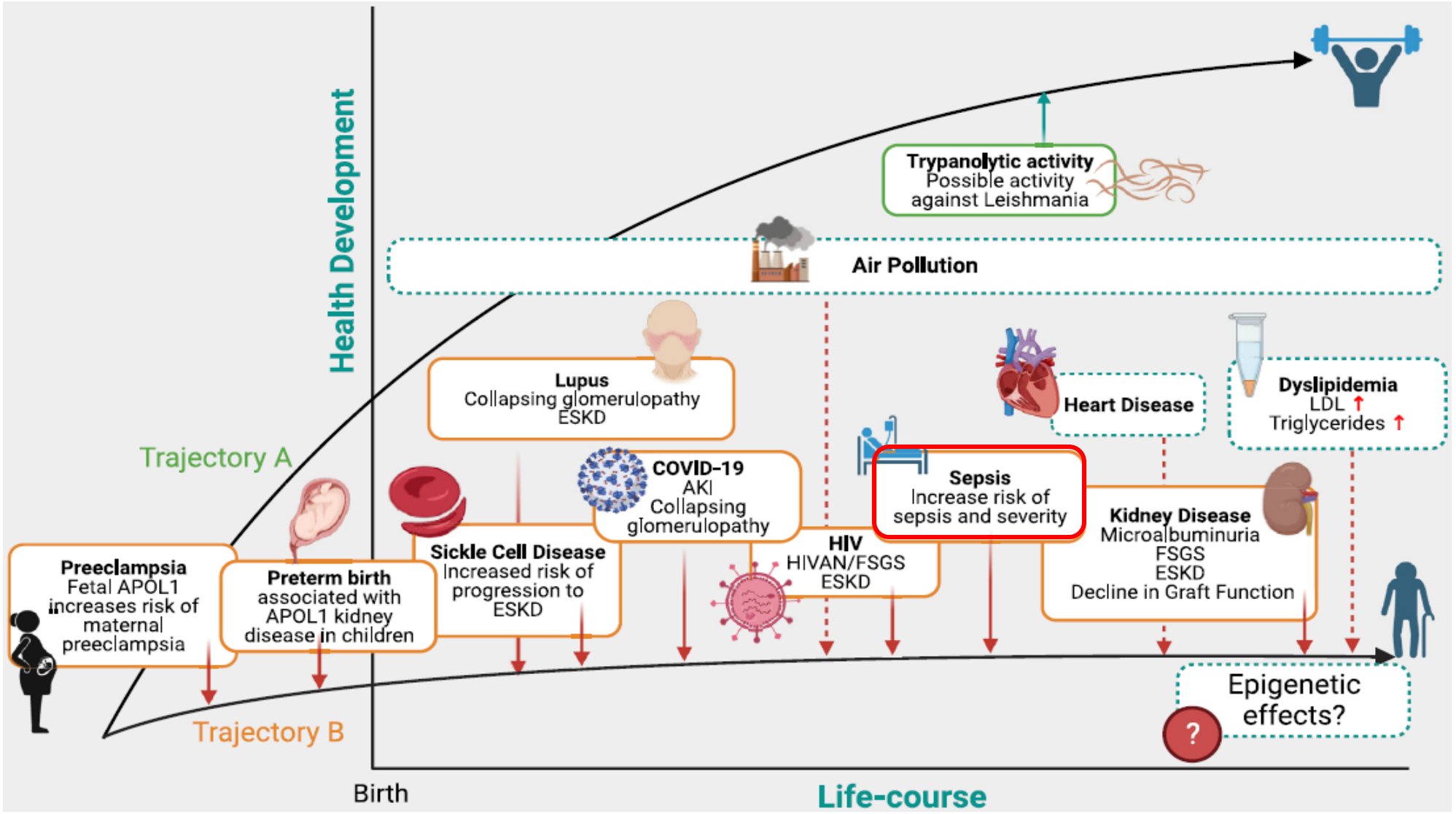

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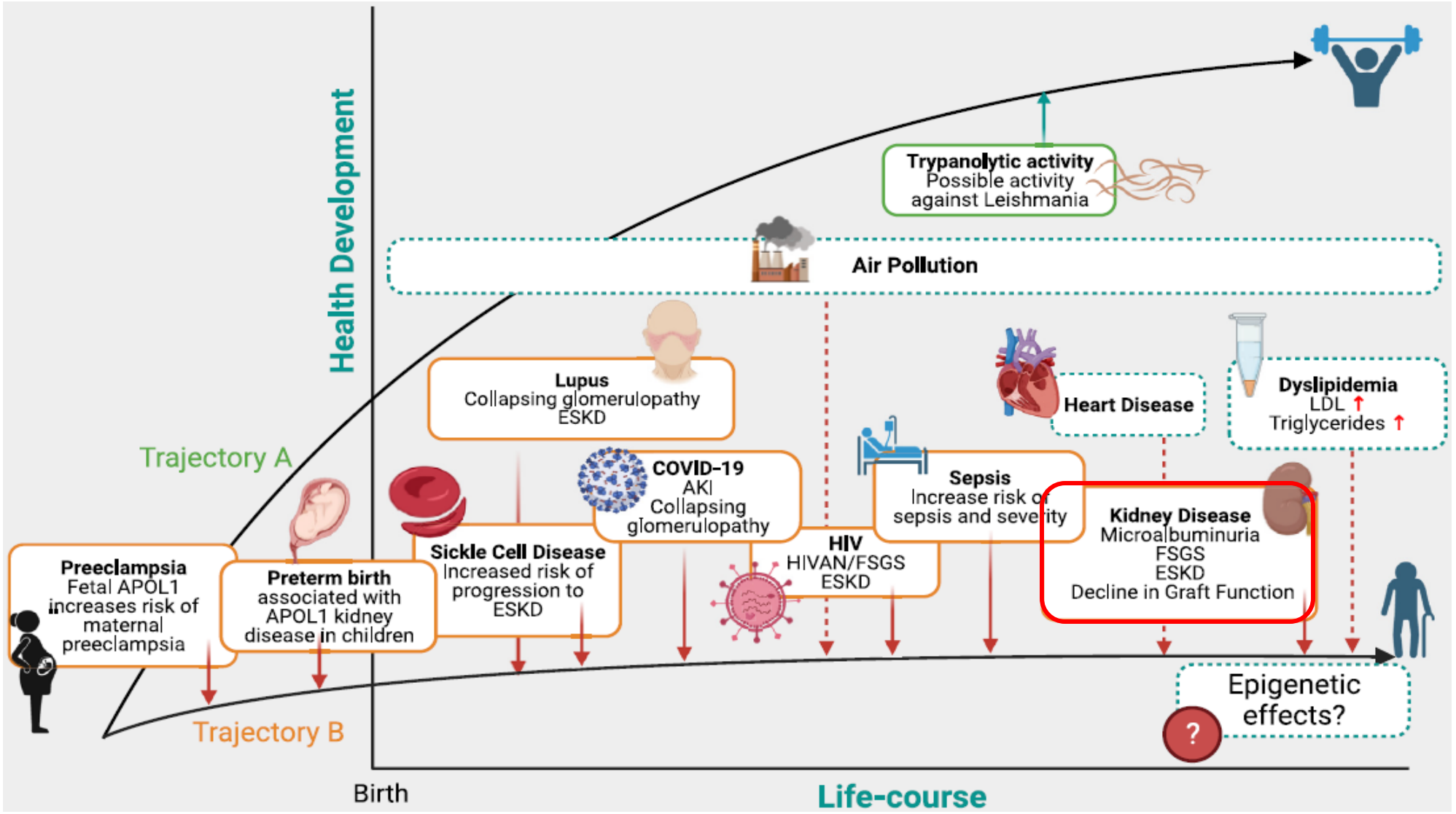


American Journal of Kidney Diseases 2024 84102-110DOI: (10.1053/j.ajkd.2023.12.014)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 5, 2013 VOL. 369 NO. 23

APOL1 Risk Variants, Race, and Progression of Chronic Kidney Disease

Two studies, examined the variants in APOL1 gene on progression of CKD.

AASK- evaluated 693 black patients with CKD attributed to hypertension.

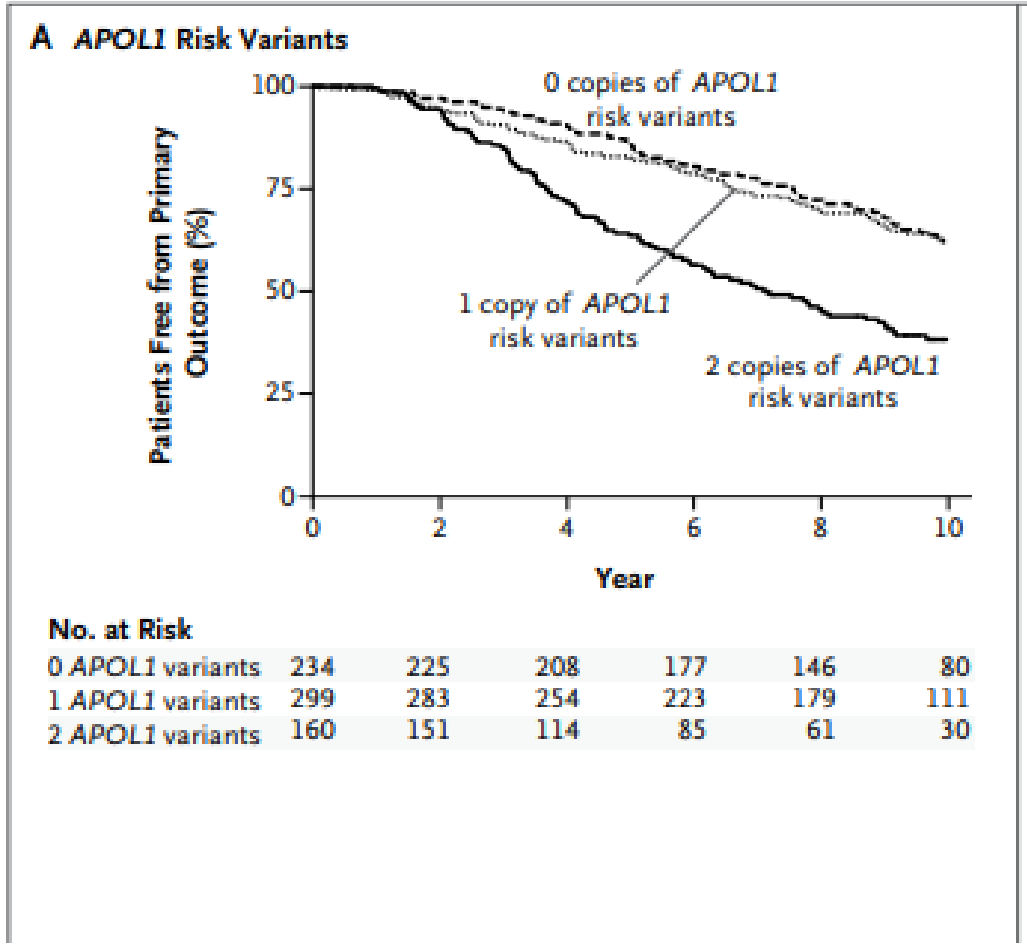
CRIC- study- evaluated 2955 white patients and black patients with CKD

2 copies of high-risk APOL1 variants (APOL1 high-risk group) or 0 or 1 copy (APOL1 low-risk group).

Primary outcome:

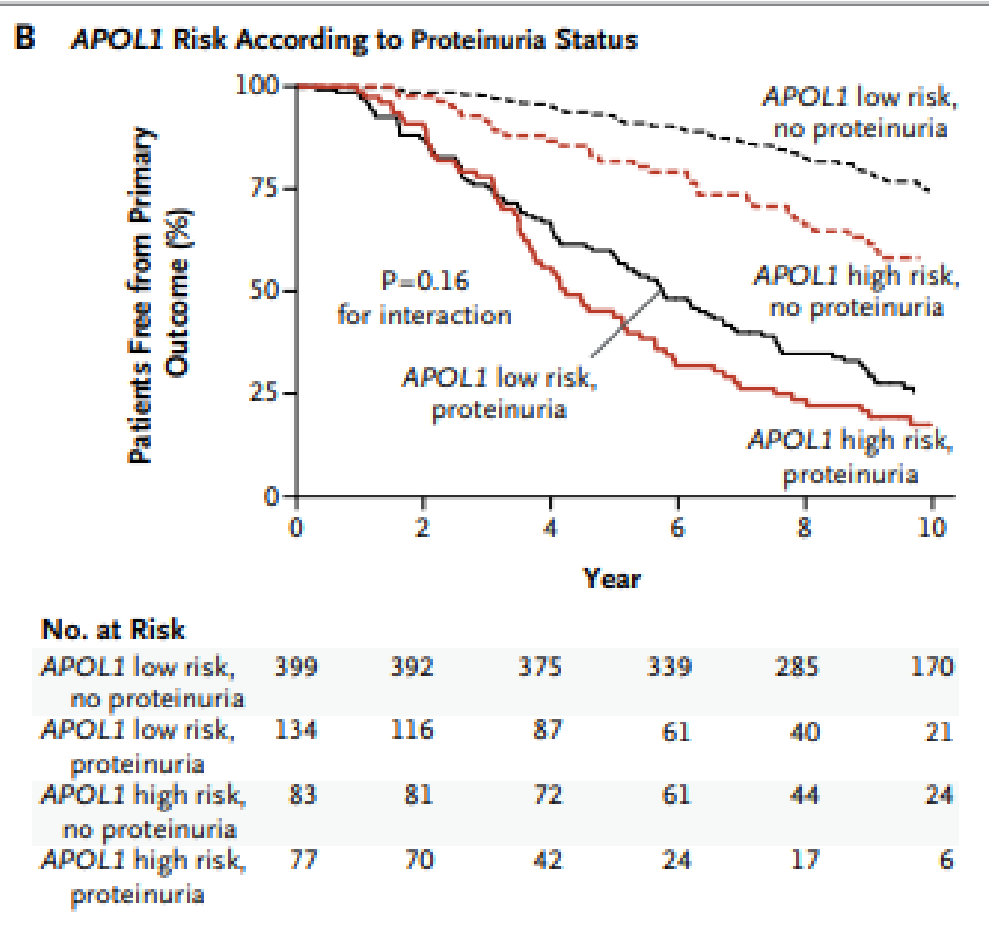
AASK - composite of end-stage renal disease or a doubling of the serum creatinine level

CRIC study- the slope in the eGFR and the composite of end-stage renal disease or a reduction of 50% in the eGFR from baseline.



No. at Risk

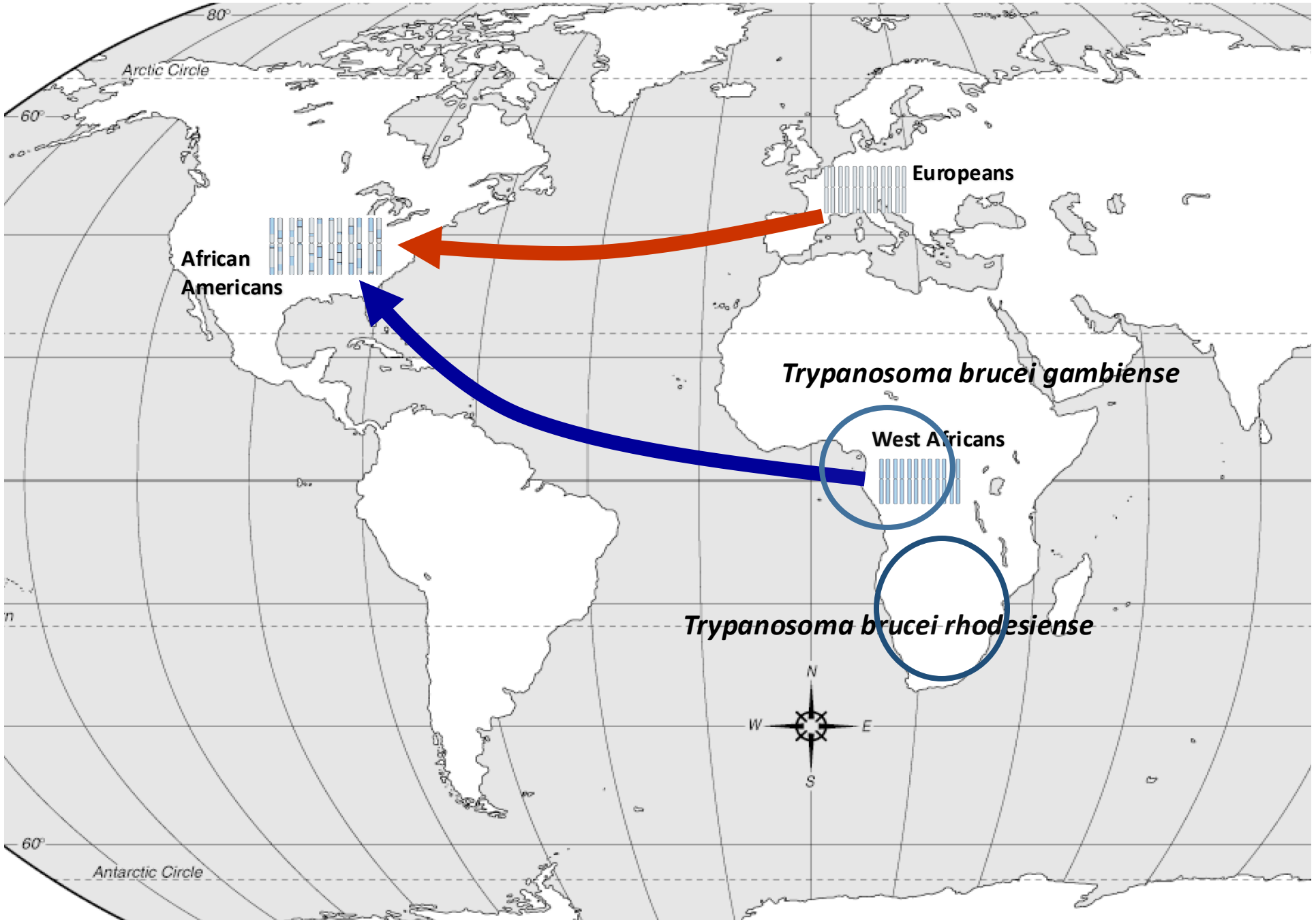
0 *APOL1* variants	234	225	208	177	146	80
1 *APOL1* variants	299	283	254	223	179	111
2 *APOL1* variants	160	151	114	85	61	30



No. at Risk

APOL1 low risk, no proteinuria	399	392	375	339	285	170
APOL1 low risk, proteinuria	134	116	87	61	40	21
APOL1 high risk, no proteinuria	83	81	72	61	44	24
APOL1 high risk, proteinuria	77	70	42	24	17	6

Parsa, A. et al. (2013). APOL1 Risk Variants, Race, and Progression of Chronic Kidney Disease. *New England Journal of Medicine, 369(23), 2183-2196. doi:10.1056/NEJMoa1310345*


80°
Arctic Circle
60°
Europeans
African
Americans
Trypanosoma brucei gambiense
West Africans
Trypanosoma brucei rhodesiense
N
W
E
S
60°
Antarctic Circle

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

APOL1 Bi- and Monoallelic Variants and Chronic Kidney Disease in West Africans

R.A. Gbadegesin, I. Ulasi, S. Ajayi, Y. Raji, T. Olanrewaju, C. Osafo, A.D. Ademola, A. Asinobi, C.A. Winkler, D. Burke, F. Arogundade, I. Ekem, J. Plange-Rhule,* M. Mamven, M. Matekole, O. Amodu, R. Cooper,* S. Antwi, A.A. Adeyemo, T.O. Ilori, V. Adabayeri, A. Nyarko, A. Ghansah, T. Amira, A. Solarin, O. Awobusuyi, P.L. Kimmel, F.C. Brosius, M. Makusidi, U. Odenigbo, M. Kretzler, J.B. Hodgin, M.R. Pollak, V. Boima, B.I. Freedman, N.D. Palmer, B. Collins, M. Phadnis, J. Smith, C.I. Agwai, O. Okoye, A. Abdu, J. Wilson, W. Williams, B.L. Salako, R.S. Parekh, B. Tayo, D. Adu, and A. Ojo, for the H3Africa Kidney

APOL1 Genotypes	Odds Ratio (95% CI)	
	Unadjusted	Adjusted†
2 *APOL1* risk alleles vs. <2	1.34 (1.21–1.49)	1.25 (1.11–1.40)
G0/G1 vs. G0/G0	1.16 (1.03–1.31)	1.19 (1.04–1.35)
G0/G2 vs. G0/G0	1.18 (1.01–1.38)	1.19 (1.00–1.41)
G0/G1 and G0/G2 vs. G0/G0	1.17 (1.05–1.30)	1.18 (1.04–1.33)
G1/G1 vs. G0/G0	1.46 (1.26–1.69)	1.37 (1.16–1.61)
G1/G2 vs. G0/G0	1.40 (1.18–1.65)	1.34 (1.12–1.61)
G2/G2 vs. G0/G0	2.25 (1.52–3.34)	2.05 (1.35–3.13)

*

Values are odds ratios for CKD among West African participants with the indicated *APOL1* genotypes. G1 and G2 are *APOL1* risk variants. G2/G2 indicates the presence of two risk alleles, G0/G1 or G0/G2 a single risk allele, and G0/G0 no risk alleles.

†

These odds ratios were adjusted for the following covariates: age, sex, BMI, mean arterial pressure, HIV status, diabetes status, clinical site, tobacco use, and language group (Akan, Ewe, Ga-Adangbe, Hausa/Fulani, Igbo, Yoruba, or other). Confidence intervals are not adjusted for multiplicity and may not be used in place of hypothesis testing.

Summary:

Prevalence:

- Monoallelic APOL1 variants was 43.0%
- Biallelic APOL1 variants was 29.7%

2 APOL1 risk alleles:

- 25% higher risk of CKD
- 84% higher risk of FSGS

1 APOL1 risk allele:

- 18% higher risk of CKD
- 61% higher risk of FSGS

The inclusion of covariates

- Did not modify these associations

So What Next?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2023 VOL. 388 NO. 11

Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

A single-group, open-label, phase 2a clinical study

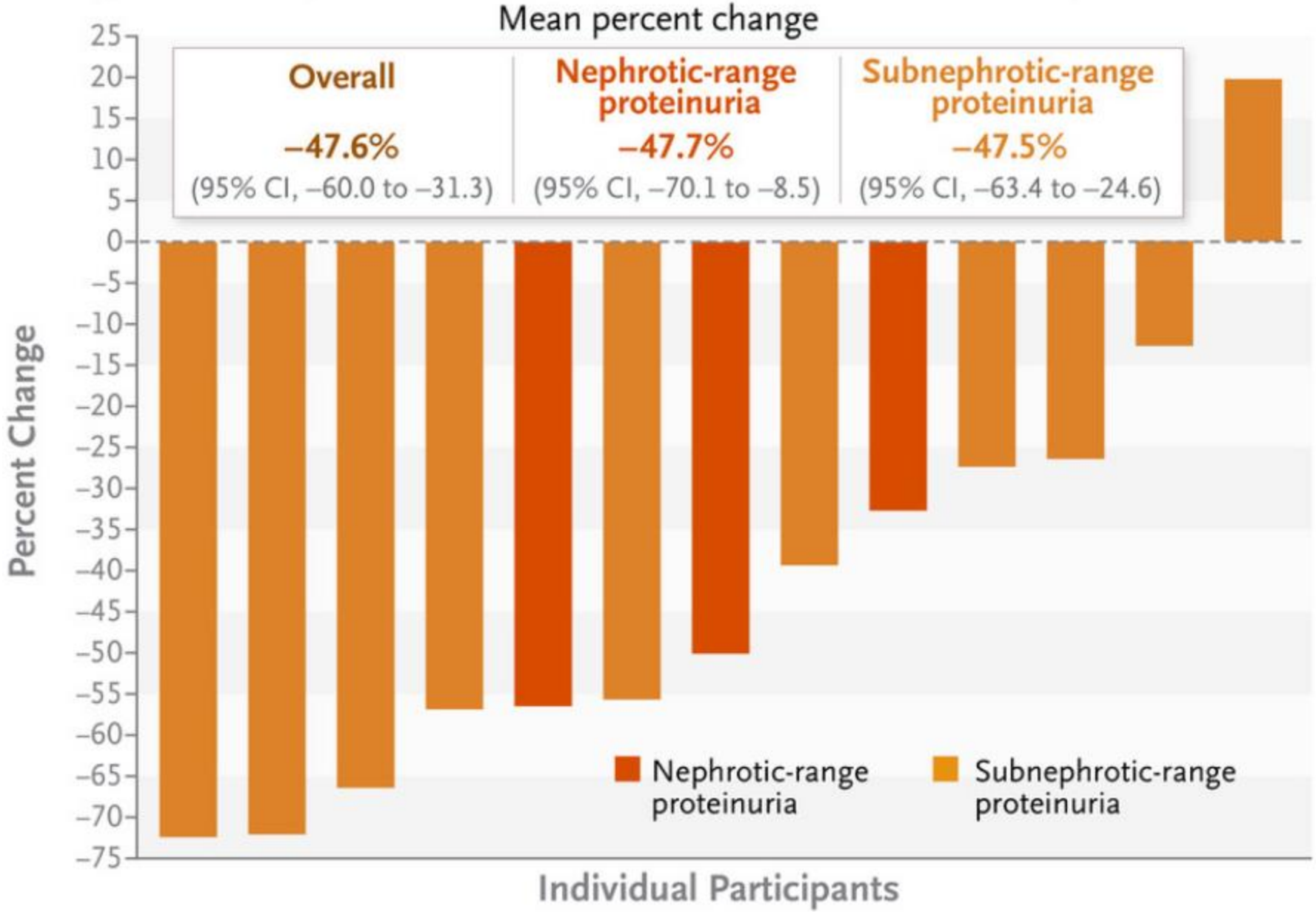
Inaxaplin was administered to participants who had two APOL1 variants with

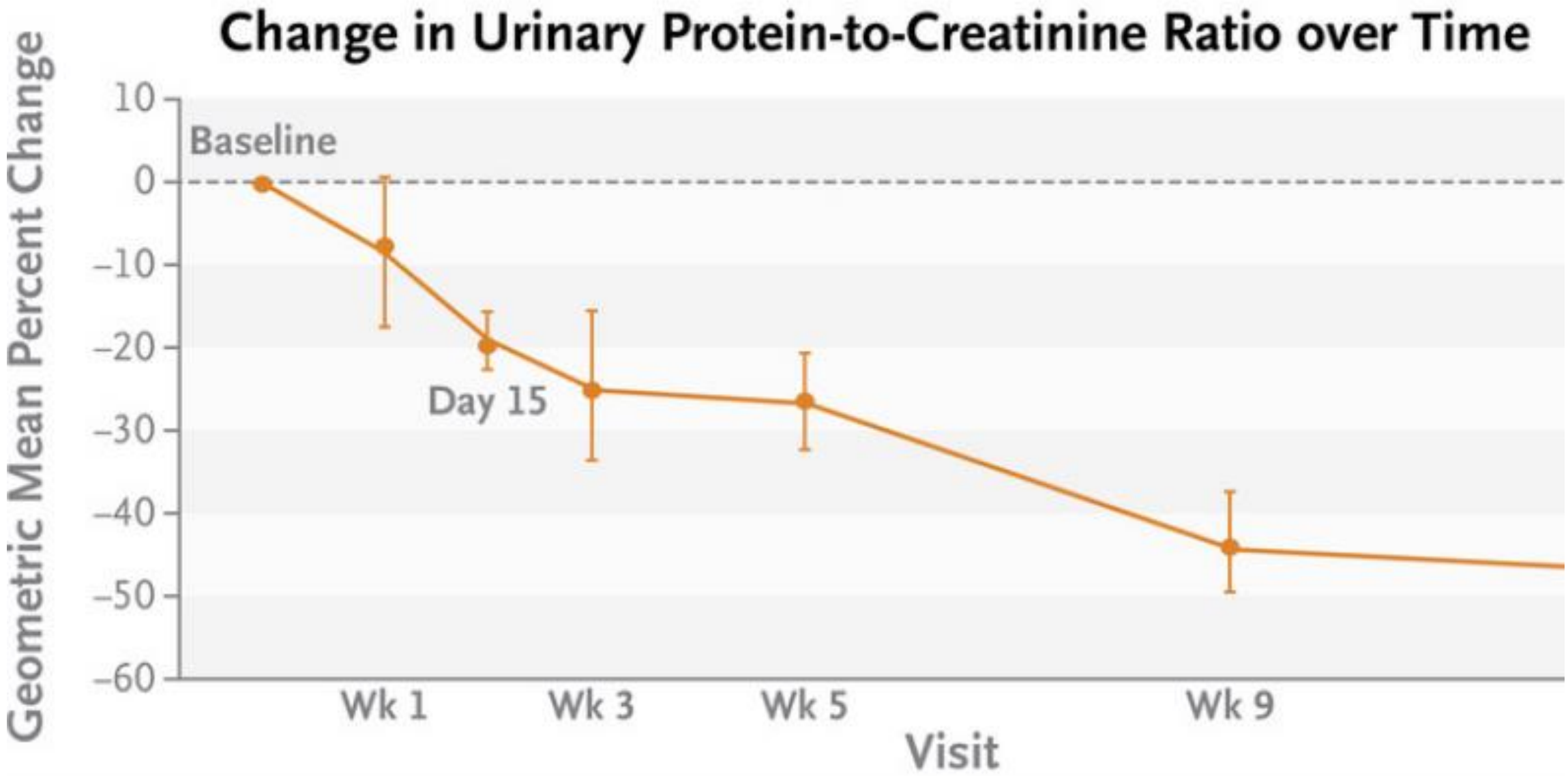
I. biopsy-proven focal segmental glomerulosclerosis
II. proteinuria (urinary protein-to-creatinine ratio of ≥0.7 to <10g/
III. eGFR of ≥27 ml per minute per 1.73 m2)
IV. participants received inaxaplin daily for 13 weeks
V. 15 mg for 2 weeks and 45 mg for 11 weeks) along with standard care.

Primary outcome:

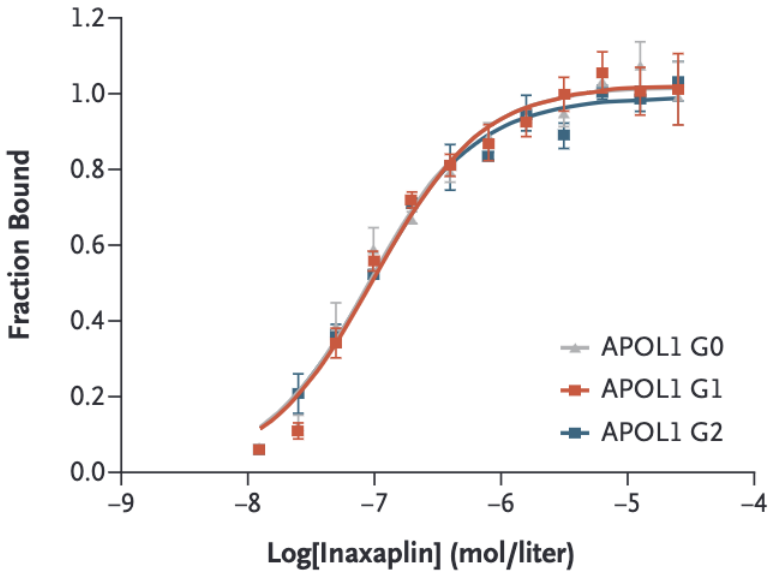
% change from the baseline UPCR at week 13 in participants who had at least 80% adherence to inaxaplin therapy

Change in Urinary Protein-to-Creatinine Ratio in Each Participant at Wk 13

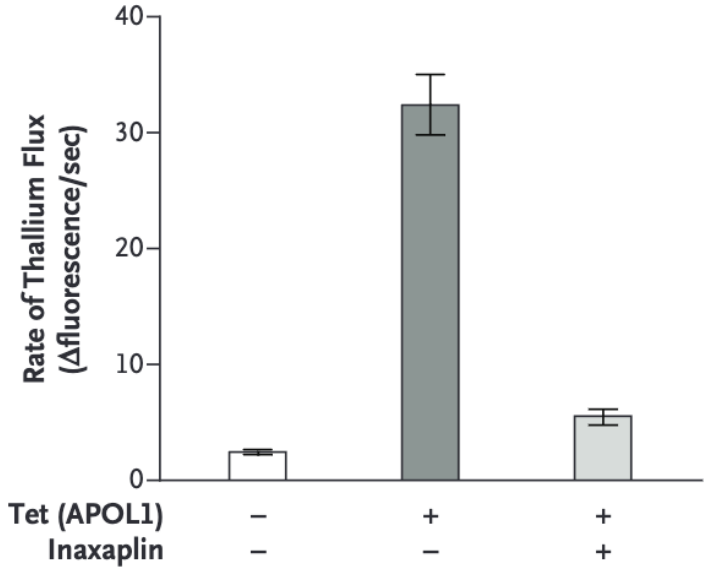



Change in Urinary Protein-to-Creatinine Ratio over Time
Geometric Mean Percent Change
10
0
−10
−20
−30
−40
−50
−60
Baseline
Day 15
Wk 1
Wk 3
Wk 5
Wk 9
Visit

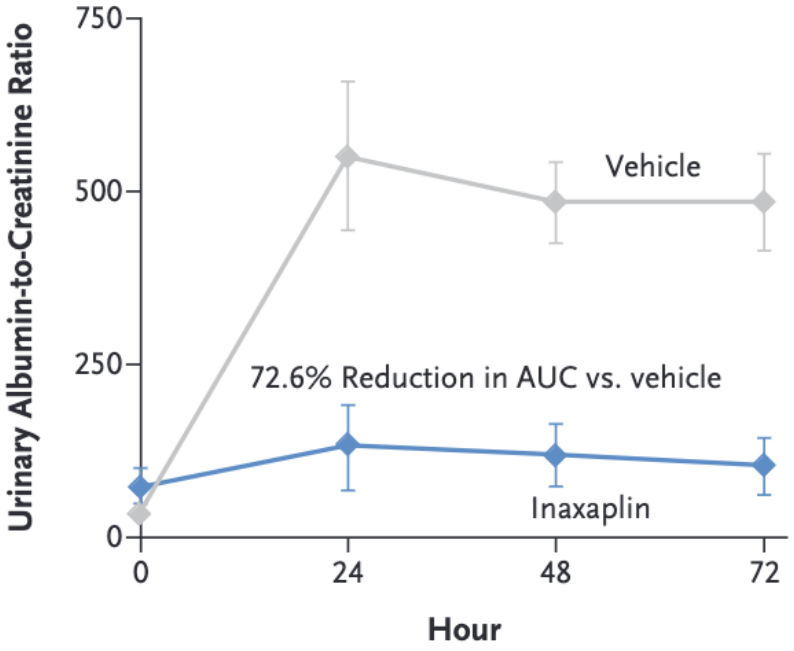
Inaxaplin:



Binds APOL1



Blocks Cation Flux



Reduces Proteinuria

Egbuna et al., NEJM 2023

AMPLITUDE (VERTEX 301)

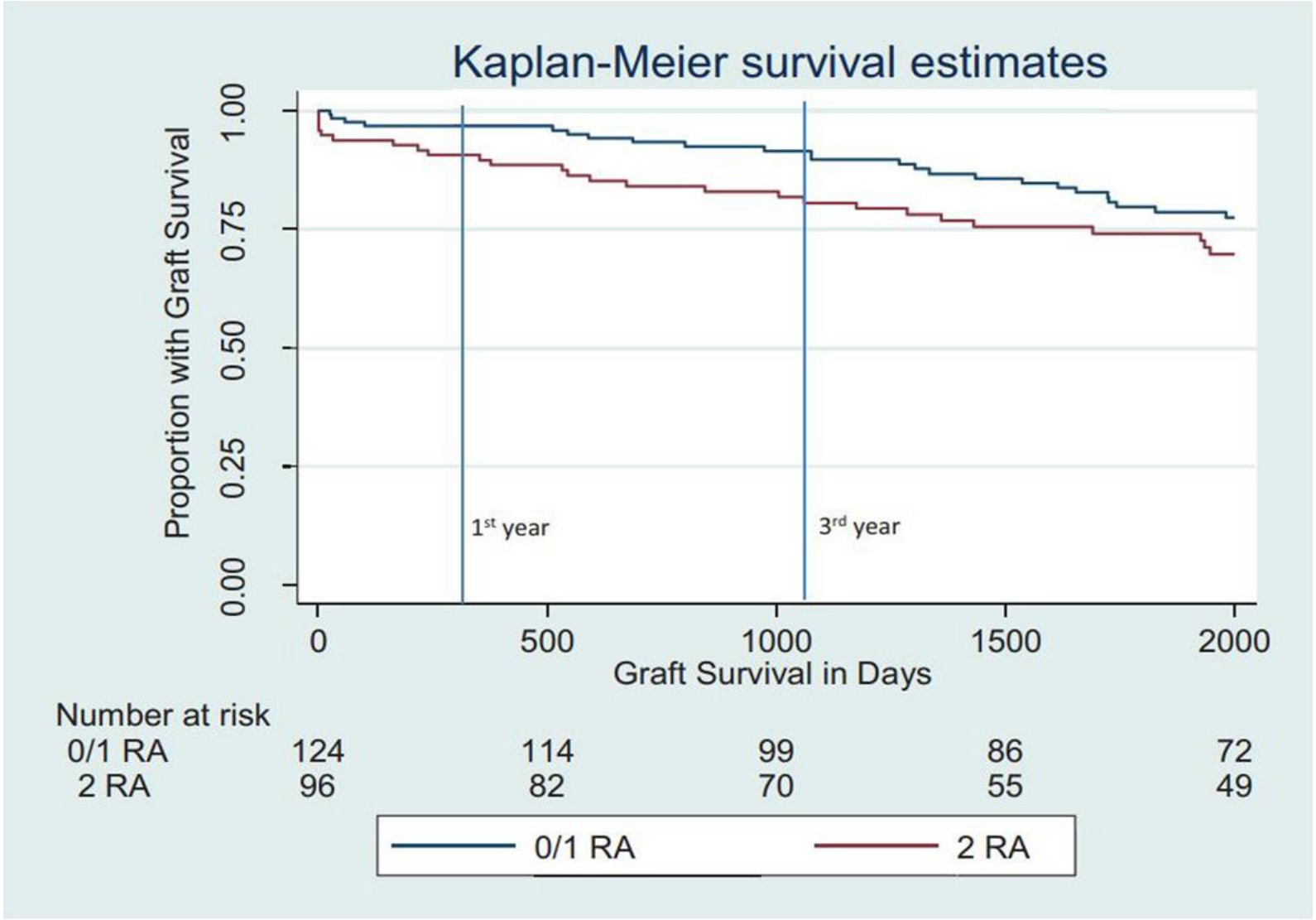
- A Phase 2/3 Adaptive, Double-blind, Placebo-Controlled Study
- Evaluate the Efficacy and Safety of VX-147 in Subjects Aged 12 Years and Older
- With APOL1-mediated Proteinuric Kidney Disease.
- The purpose of this study is to
- Evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of VX-147

Implications for transplantation?

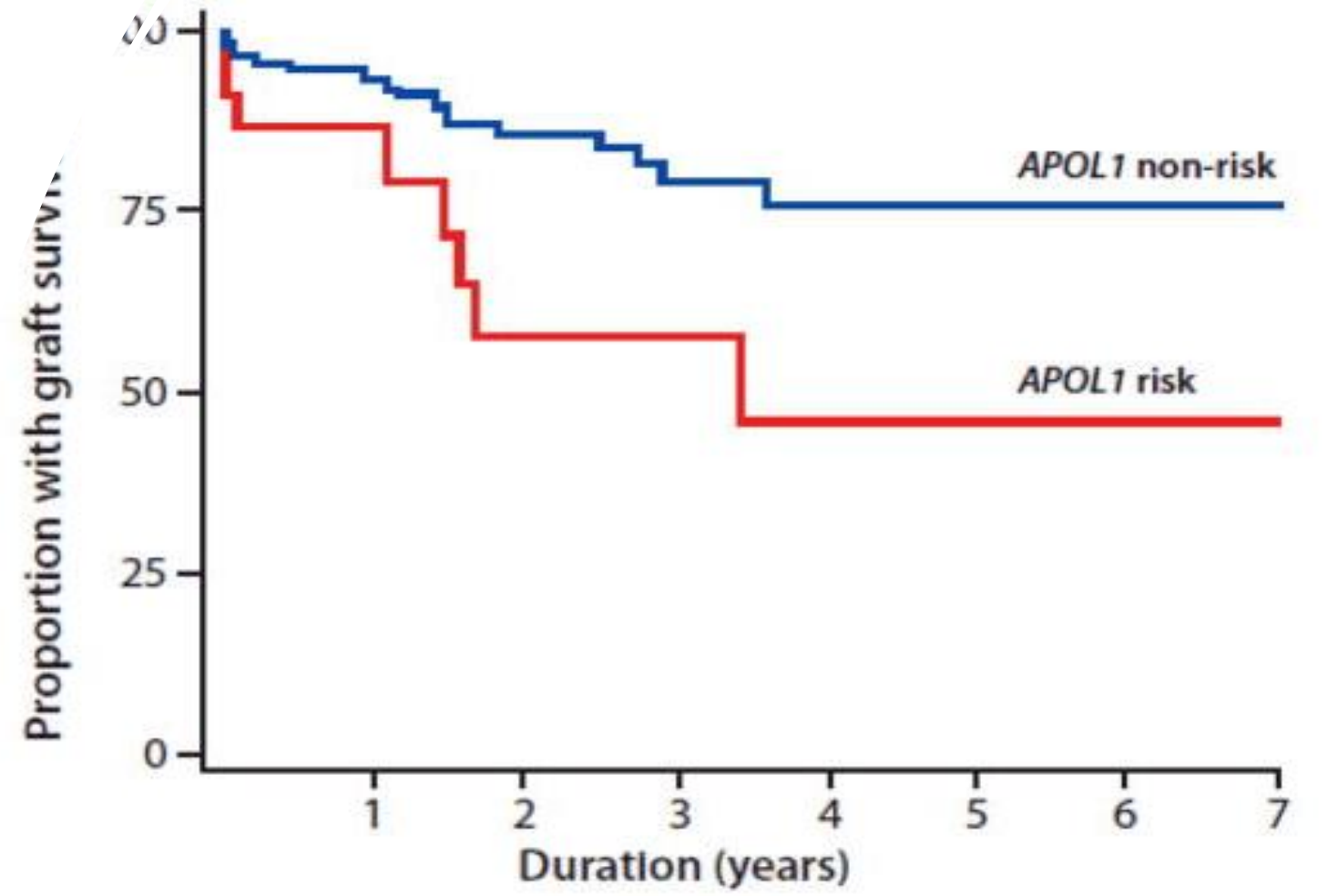
Kaplan-Meier survival estimates of graft survival stratified by *APOL1* RA status throughout follow-up

RA risk allele

Transplantation. 2023 Aug 1;107(12):2575–2580. doi: 10.1097/TP.0000000000004742



Kaplan-Meier renal allograft survival curve for recipients of donor kidneys with (red line) and without (blue line) two *APOL1* risk variant alleles



isk								
	114	82	52	35	18	7	6	3
oss (%)	–	7 (6%)	13(11%)	16 (14%)	17 (15%)	17 (15%)	17 (15%)	17 (15%)
	–	25	49	63	79	90	91	94
	22	12	8	5	2	1	1	0
%)	–	3 (14%)	7 (32%)	7 (32%)	8 (36%)	8 (36%)	8 (36%)	8 (36%)
	–	7	7	10	12	13	13	14

Am J Transplant. 2011 Apr 12;11(5):1025–1030. doi: 10.1111/j.1600-6143.2011.03513.x

Implications:

- What does this mean for
  - Donor?
  - Recipient?

- Should we exclude donors and recipients with high-risk APOL1 risk alleles
- Leading to unnecessary exclusion of donors and recipients?
- Will these patients survive longer on dialysis compared to transplantation?

Conclusion:

- ✓ *Frequency of high-risk APLO1 variants is high among people of African descent*
- ✓ *People with high-risk alleles progress faster to kidney failure*
- ✓ *Screening for early detection may be useful*
- ✓ *Has the potential to influence policy*
- ✓ *A potential target for genetic therapy that will aid in the prevention of CKD or delay the progression of CKD*
- ✓ *There is a need to screen potential kidney donors and recipients for high-risk APOL1 alleles*

MERCI