

Facilitating informed choice by living donor candidates:

Estimating risk, acknowledging uncertainty, sharing in decisions

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DISCLOSURES

NONE

Objectives

- To distinguish between association, risk and direct causality
- To review risk factors for CKD/ESKD in the population and in living donors
- To learn that genetic traits may be enriched in select populations (e.g APOL1)
- To use APOL1 testing as an example for a pragmatic approach to risk factor assessment in living donors
- To concede that medical decision making should balance donor autonomy with provider paternalism

Case History #1

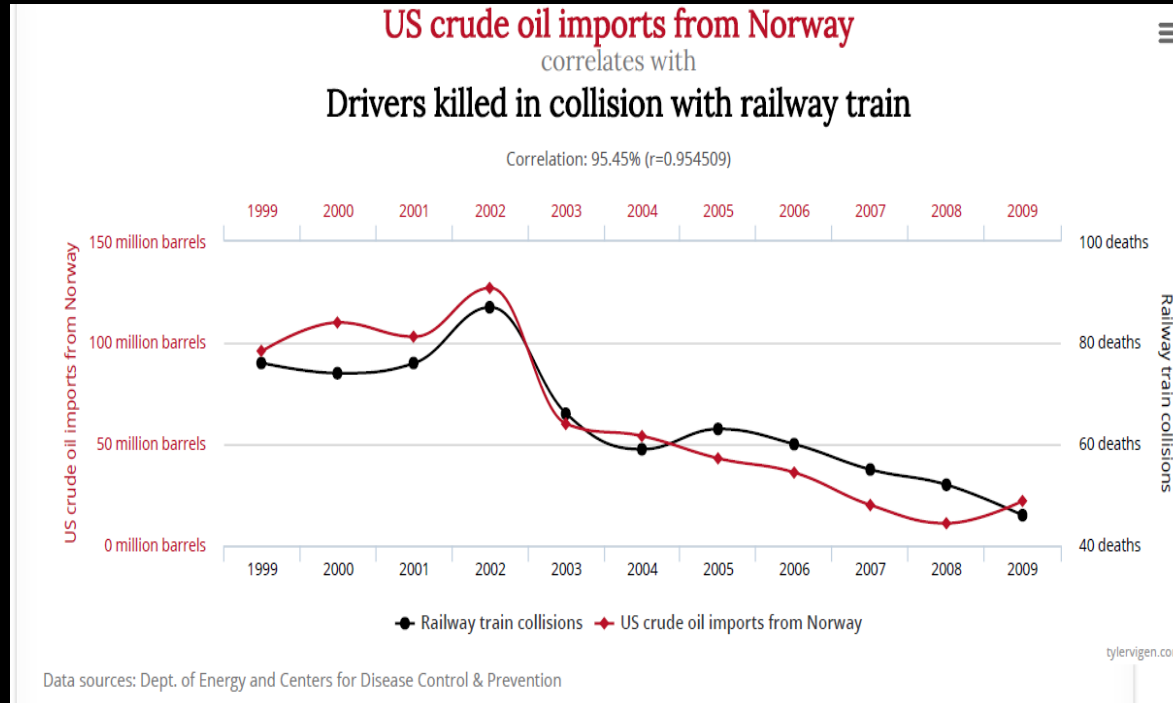
- 58 yo Black female wants to be a kidney donor to her brother with ESKD.
- Family history: one brother with DM, ESKD
- Donor evaluation:
 - BMI 28, BP 120/82, fasting glucose 104, A1C: 5.5 GTT 2 hr: 149
 - S. creatinine 0.9 (eGFR 82, with 'race' neutral formula 71); Measured Cr. clearance: 99
 - Blood type B (recipient O)
 - Remainder of testing normal

Should she be approved to donate?

Should she be counseled and tested for APOL1 risk alleles?

What do association studies tell us?

- Associations may be random or real (eg., moderate alcohol and reduced death)
- Associations are not the same as risk factors for the associated event



Norwegian oil does not increase driver deaths

Driver train collisions do not increase Norwegian oil imports

- Associations do not indicate which factor is influencing which
- Associations may be statistically significant but clinically trivial
- Associations are correlations and do not prove causality

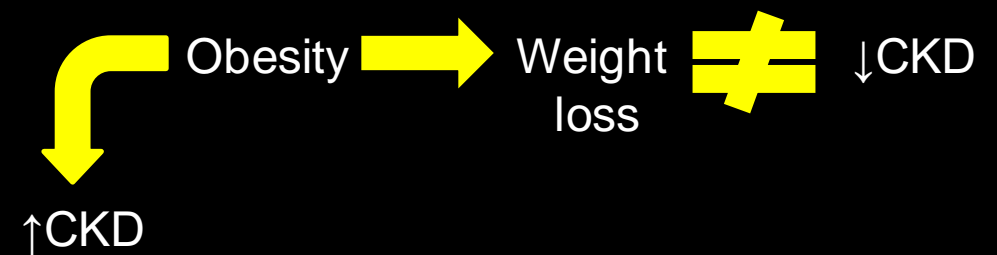
Risk factors and what they mean

1. Obesity – modifiable risk factor

- Fact: Obesity is a risk factor for HTN and for ESRD (aHR **1.65** to 4.39 at 25 yr*)
- Fact: Obesity is modifiable
- Fact: Losing weight improves HTN
- Thus, obesity causes or worsens HTN and reducing weight has a beneficial effect on HTN
- Not established: Obesity is a cause of CKD
- Not established: Reversing obesity will reduce risk of CKD
- Thus, advising weight loss to prevent CKD or reduce risk for it, has no data to support it

2. Genetic susceptibility – non modifiable risk factor

- Factor V Leiden increases risk of DVT
- Factor V Leiden does not cause DVT
- Baseline risk for DVT in 20-yr old: 1 in 10,000
- Risk with 1 copy of Factor V Leiden: 1 in 2,000



- ❖ Prevalence of Factor V Leiden with Northern European ancestry: **6%**
- ❖ Prevalence in African Americans: **< 1%**

Assessment of risk in living donor candidates

- Generally considered unacceptable risk factors
 - Inadequate kidney function/Established kidney disease
 - Hypertension on multiple drugs
 - Diabetes
 - Other major organ disease, untreated psychiatric disease, inability to give informed consent

- Variably accepted risk factors (some becoming more prevalent)
 - Obesity
 - Prediabetes
 - Hypertension on a single drug
 - Genetic traits (APOL1, Sickle cell trait)
 - Factor V Leiden
 - Kidney stones

General factors associated with ESKD

177,570 individuals from a Kaiser Permanente Cohort

Health checks between 1964-1973

ESRD ascertained through USRDS through 2000 (842 cases)

Multivariate analysis (aRR)

- Diabetes: **2.53**
- HTN: **1.72** (Pre-HTN) to 2.94 (Stage 2 HTN)
- Albuminuria: Dipstick positive **2.37** (trace) to **7.9** (3-4+)
- Male Sex: **1.22**
- Age: 1.91 (31-40 yr); 2.23 (41-50 yr); 1.51 (51-60 yr); **0.55** (> 60 yr)
- Higher BMI: **1.65** (overweight) to 4.39 (Class 2+ obesity)
- Ancestry: **1.83** (Asian); **3.02** (African)
- Positive family history of kidney disease: **1.40**
- No college vs college graduation: **1.55**
- Uric acid > 6 compared to < 4: **2.14**

Other risk factors for ESKD

- Sickle cell trait: aHR **2.03** (REGARDS study)
- APOL1 risk status: aHR **1.77** (REGARDS study)
- Low birth weight and SGA (Norwegian Birth Registry)
 - aHR **1.6** if LBW; aHR 1.51 if SGA compared to control
- Kidney stones: aHR **2.3 to 3.94** (Olmstead County, MN)
- Microscopic hematuria: aHR **18.5** (Israeli military recruits)
- Living kidney donation: 5-10-fold higher risk

Naik. R.P. et al, JASN 28: 2180-2187

Ruggajo, P et al., AJKD 2016, 67: 601-608

Dhondup T et al., Am J Kid Dis [2018, 72: 790-797](#)

Vivante, A et al, JAMA 2011, 306: 729-736

Known risk factors for ESKD in living donors

- Male (at age 40): aHR 1.88
- Black (at age 40): aHR 2.96
- Age per 10 years (non-Black): aHR 1.4
- BMI per 5 kg/m²: aHR 1.61
- 1st degree biological relatedness with recipient (family history +ve): aHR 1.70
- Post donation eGFR at 6 months (eGFR6): aHR 1.28

Unclear if any risk factor other than age, gender, ancestry, family history, eGFR6 and BMI impacts post donation ESRD

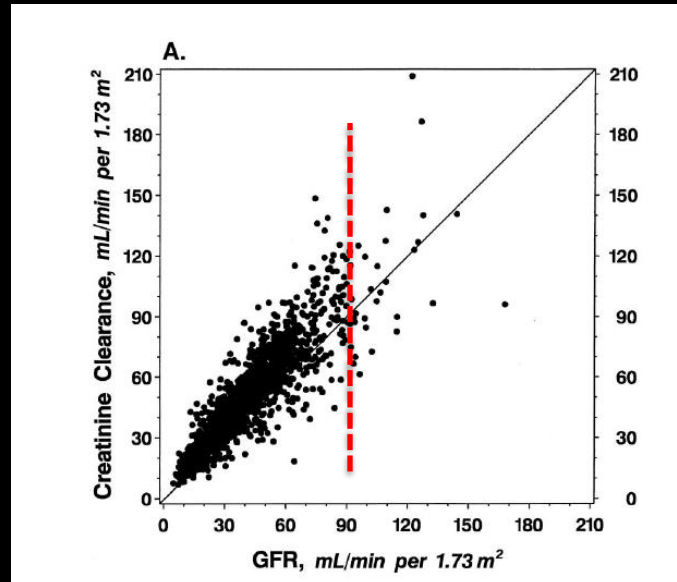
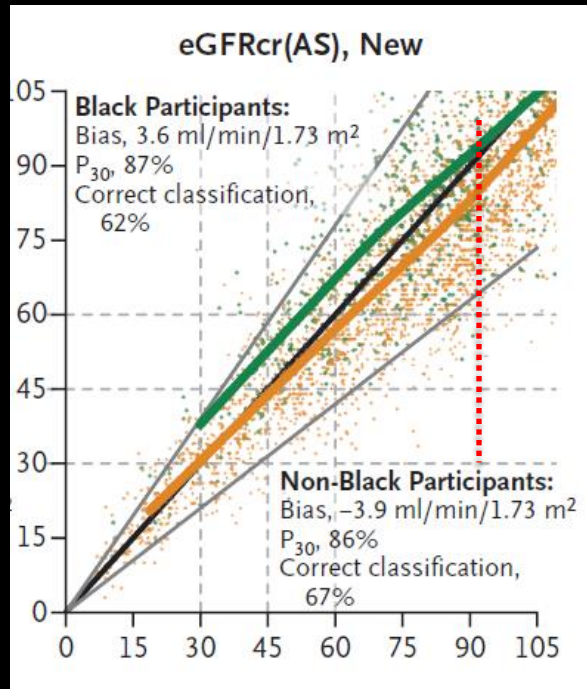
Massie et al., JASN [2017,28:2749-2755](#)

Massie et al., JAMA Surgery [2020.155:e195472](#)

Reduced eGFR

Test of kidney function

- General or overall measure: GFR or a proxy for GFR
 - S. Creatinine – eGFR: CKD-EPI 2009 (race inclusive); CKD-EPI 2021 (race neutral)
 - S. Cystatin C – eGFR (CKD-EPI 2012) ml/min/1.73m² [NKF eGFR calculator](#)
 - Measured creatinine clearance – needs 24 hr urine to derive ml/min or ml/min/1.73m²)
 - Measured GFR: Inulin clearance, iohexol clearance, Isotopic clearance: ¹²⁵I-iothalamate, ⁹⁹Tc-DTPA
- OPTN Policy 14.4.B
 - Measurement of GFR by isotopic methods or a creatinine clearance from a 24-hour urine collection



eGFR underestimates mGFR esp. in white women donors

Creatinine clearance overestimates mGFR in all donors

Inker LA et al., NEJM 2021 [DOI: 10.1056/NEJMoa2102953](https://doi.org/10.1056/NEJMoa2102953)

Levey AS et al., Ann Intern Med. 1999; [130:461-470.](#)

Case History #2

- 37 yr old white female donor candidate, no risk factors for kidney disease
 - Serum cystatin C 1.0
 - Serum creatinine 1.0
 - CKD-EPI 2021 Cr eGFR 74 ml/min/1.73 m²
 - CKD-EPI 2012 Cys C eGFR 79 ml/min/1.73 m²
 - CKD-EPI 2021 combined Cr-Cys C eGFR 78 ml/min/1.73 m²
- Question:
 - Is her kidney function normal? Should she donate?
 - What is her expected post donation eGFR? 50 ml/min/1.73 m² (CKD3?)
- What next?
 - Isotopic GFR (actual measured GFR) 104 ml/min/1.73 m²
 - Counsel donor about label of CKD post donation and permit donation**

Prediabetes

Prediabetes

- Fasting blood glucose: 100 – 125 mg/dl
- 2 hr post 75 gm glucose: 140-199 mg/dl
- HbA1C: 5.7-6.4% mg/dl

- Risk factors for diabetes: family history, ancestry, age, gender, prediabetes, gestational diabetes, BMI, BP, HDL

- Risk for developing diabetes:
 - <https://www.omnicalculator.com/health/risk-dm>
 - <https://qdiabetes.org/>

- Lowering risk of diabetes
 - Diet, exercise, weight loss

Concern with prediabetes: sequential risk for progression to diabetes and then to CKD/ESKD

May be appropriate for counseling and shared decision-making

Kidney stones

Kidney stones

- Asymptomatic – found incidentally on CT
- Symptomatic – risk of recurrence: [ROKS calculator](#)
- Risk of ESRD:
 - 3- 4-fold increased risk of ESRD even with asymptomatic stones*
- Modifying risk:
 - 24 hr urine (Litholink): to identify modifiable risk factors
- Options
 - Multiple stone episodes esp with other risk factors – advise against donation
 - Intervention to modify risk factors before permitting donation
 - Counseling if risk acceptable – shared decision making

*Shoag J et al., J Urology [2014, 192: 1440-5](#)

*Dhondup T et al., Am J Kid Dis [2018, 72: 790-797](#)

ESRD risk calculator

- <http://www.transplantmodels.com/esrdrisk/>

Pre-donation risk of ESRD at 15 years and in lifetime:

20-year-old white female nonsmoker, BMI 24, eGFR 100, Urine alb 6: **1 in 10,000 in 15 yr; 1 in 250 in lifetime**

20-year-old black male nonsmoker, BMI 24, eGFR 100, Urine alb 6: **1 in 1,000 in 15 yr; 1 in 50 in lifetime**

- <http://www.transplantmodels.com/donesrd/>

Post-donation risk of ESRD at 20 years:

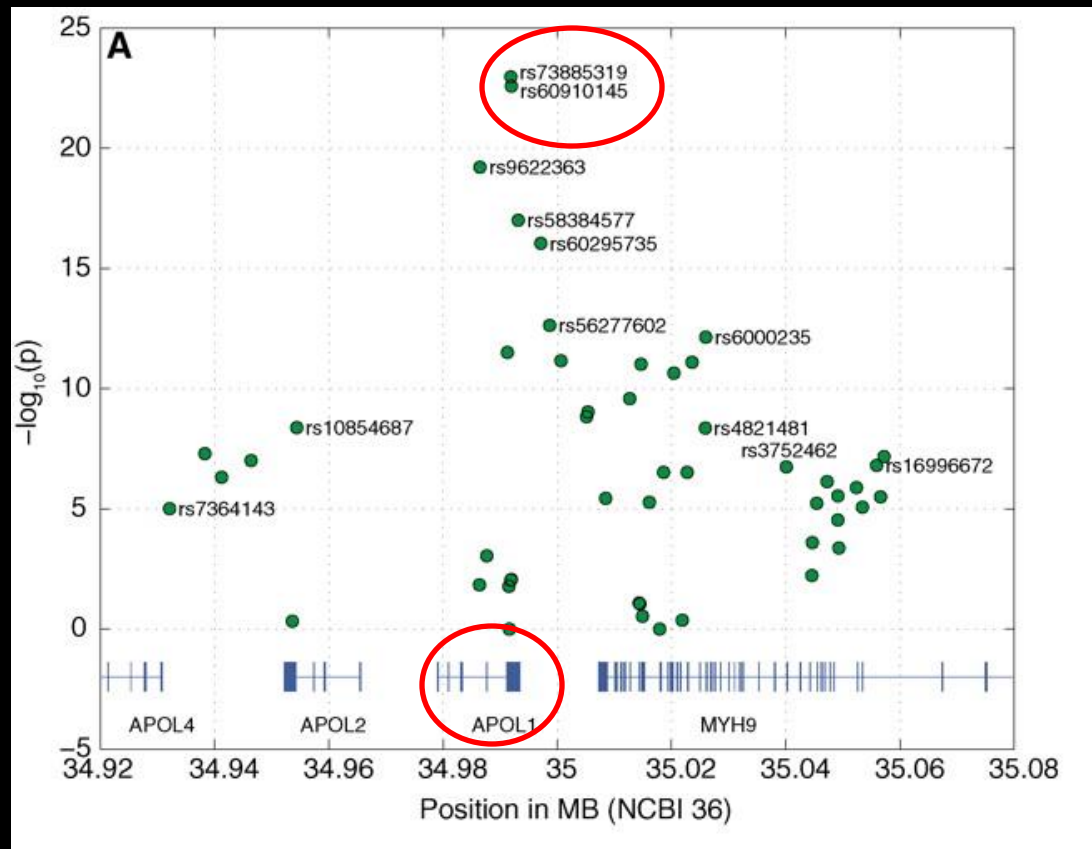
20-year-old white female BMI 24, unrelated to recipient: **1 in 1500 in 20 yr**

20-year-old black male BMI 30, related to recipient: **1 in 33 in 20 yr**

APOL1 and living donors

The discovery of APOL1 risk variants

- African Americans have higher risk of ESKD compared to those of European ancestry
- GWAS and other studies: genetic variation at locus on chr 22, later localized to gene APOL1



2 variants in APOL1 – G1 and G2 (vs G0)
2 copies of variants confer risk (G1/G1, G2/G2, G1/G2)

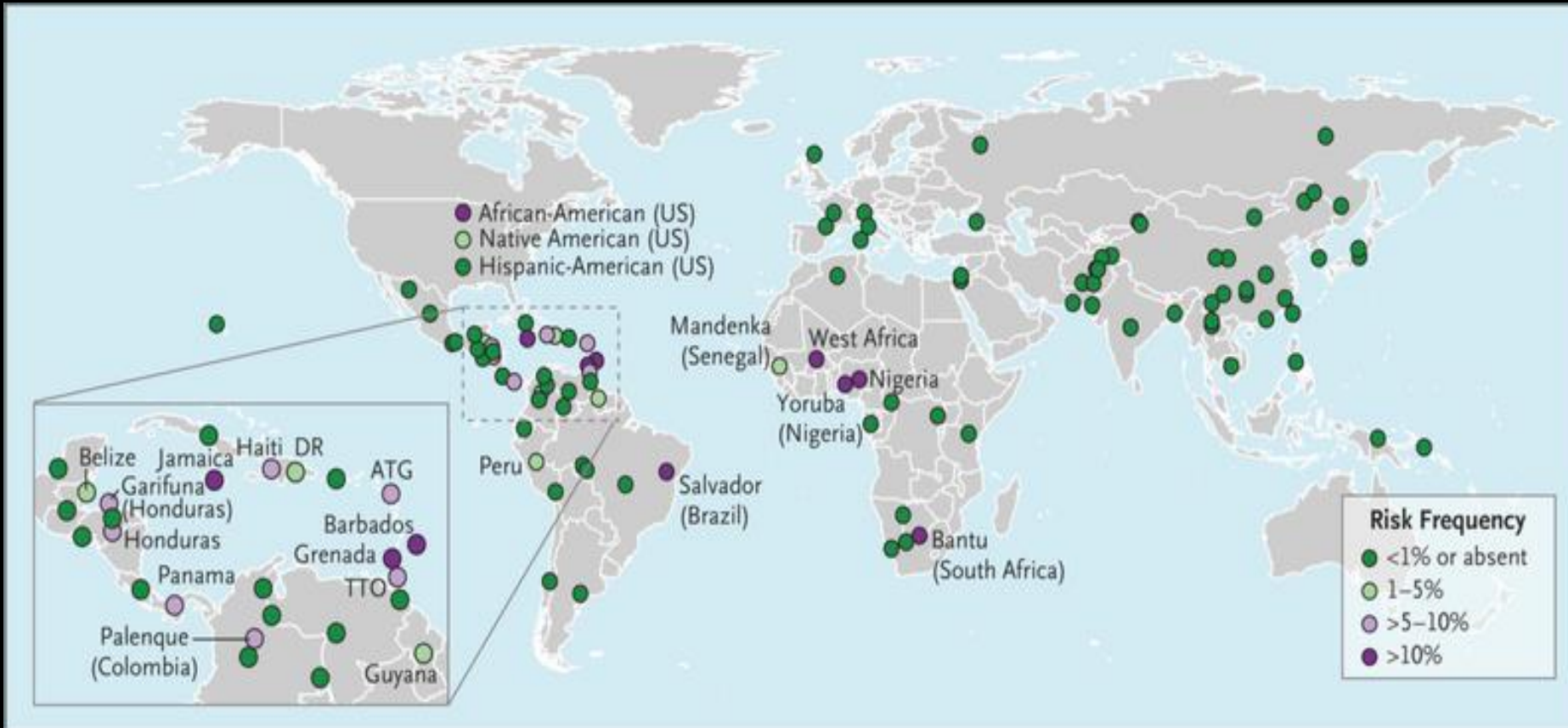
Evidence of positive selection - survival advantage

APOL1 G1 and G2 proteins lyse *Trypanosoma brucei rhodesiense* (African sleeping sickness)

G1 and G2 rose 'recently' in Africa

G1 and G2 seen with sub-Saharan African ancestry

APOL1 risk allele prevalence

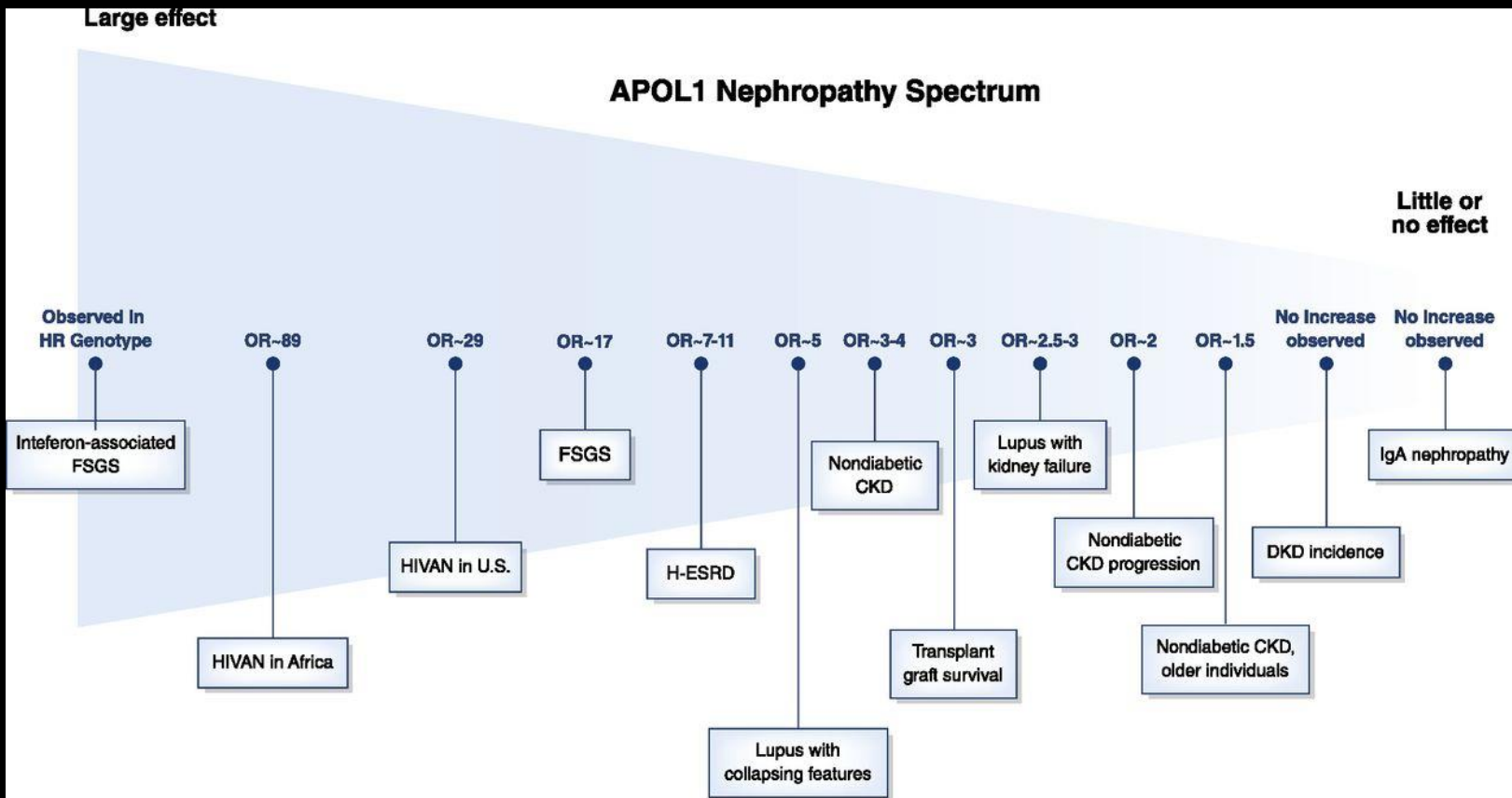


Allele prevalence

	G1	G2
African/AA	22.7%	13.6%
Latino	0.67%	1.4%
S. Asian	0.01%	0.02%

gnomAD v2.1.1

APOL1 related kidney disease (APOL1 nephropathy)



APOL1 RV

No impact

Variable impact on CKD development

Variable impact on CKD progression

Not all risk factors additive

Geographic: HIVAN S. Africa, US
(non-biologic factors)

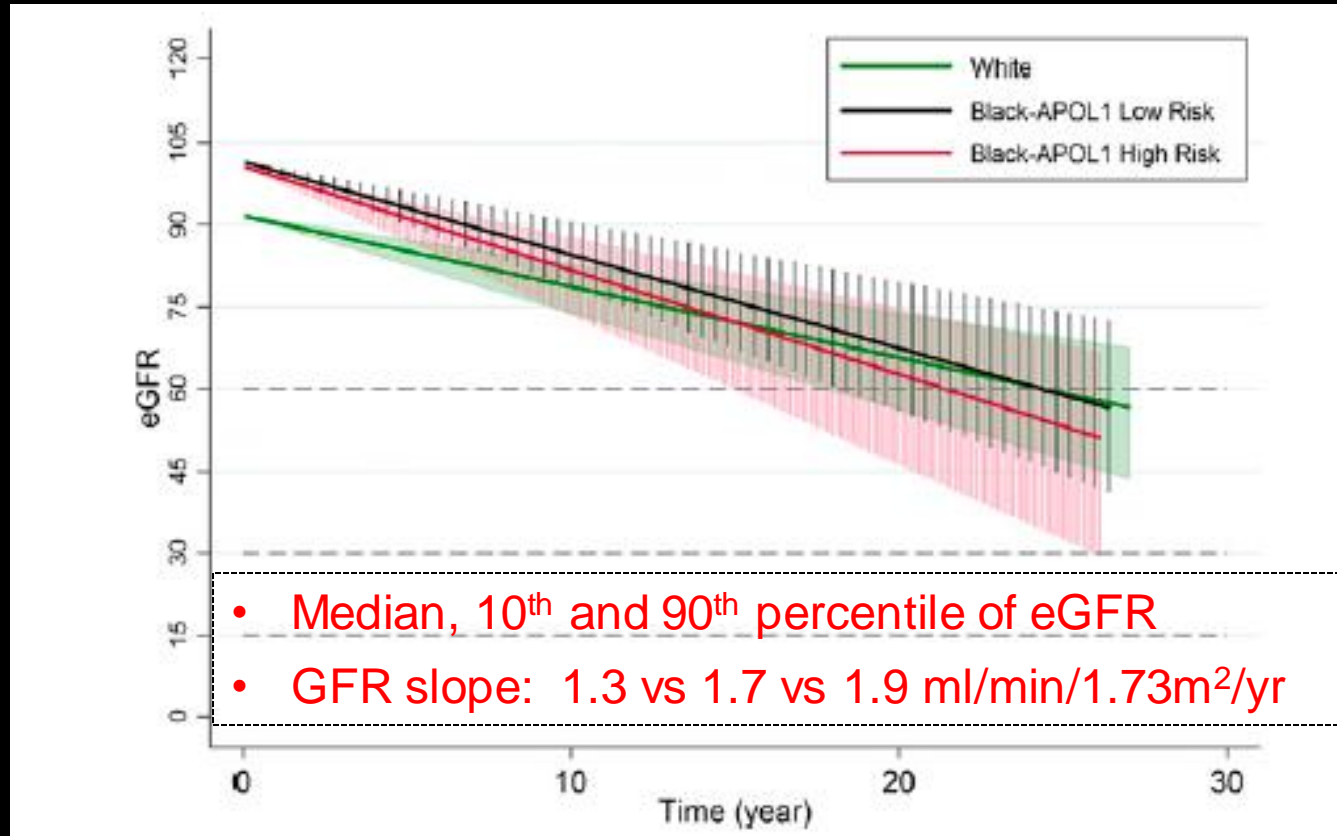
All these risk ratios come from **case control** studies

Newly recognized diseases in the APOL1 *spectrum*: Malarial glomerulopathy, COVID-associated glomerulopathy

From case control to population studies

APOL1 kidney disease – population studies - I

ARIC study – 20 yr follow up of community dwellers (45-64 without prior CKD): 15,140 participants



Blacks had higher incidence of HTN, DM and ESRD during 25-yr follow-up

Incident rate ratio for ESRD:

1.0 (White)

1.87 (Black low risk APOL1)

2.84 (Black high risk APOL1)

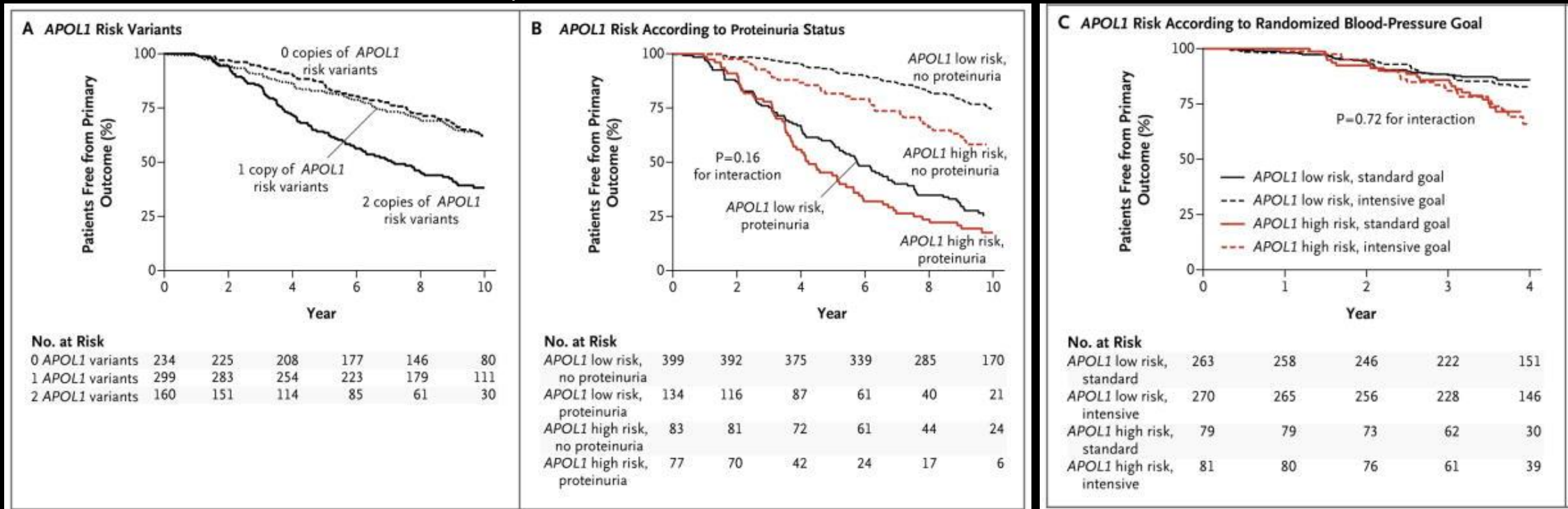
APOL1 kidney disease – population studies - II

REGARDS study – geographically diverse cohort: 30,239 individuals > 45 yr

- 9909 self reported Blacks - ~70% with HTN, 30% diabetes, 17% smokers
- Prevalence of CKD at baseline: Odds Ratio 1.28 for 2 risk variants compared to 0-1 variants
- Incidence of ESRD during follow-up (Mean 6.5 yr): 6.6 per 1000 patient years with 2 risk variants compared to 3.8 for 0-1 variants (HR **1.77**)

AASK study – African American Cohort with CKD attributed to HTN

- 1995-2007, intensive vs standard BP control
- 58.1 reached primary outcome (ESRD or 2 x serum creatinine) vs 36.6% - median follow-up 9 yr (HR **1.88**)
- No interaction between baseline proteinuria or BP control

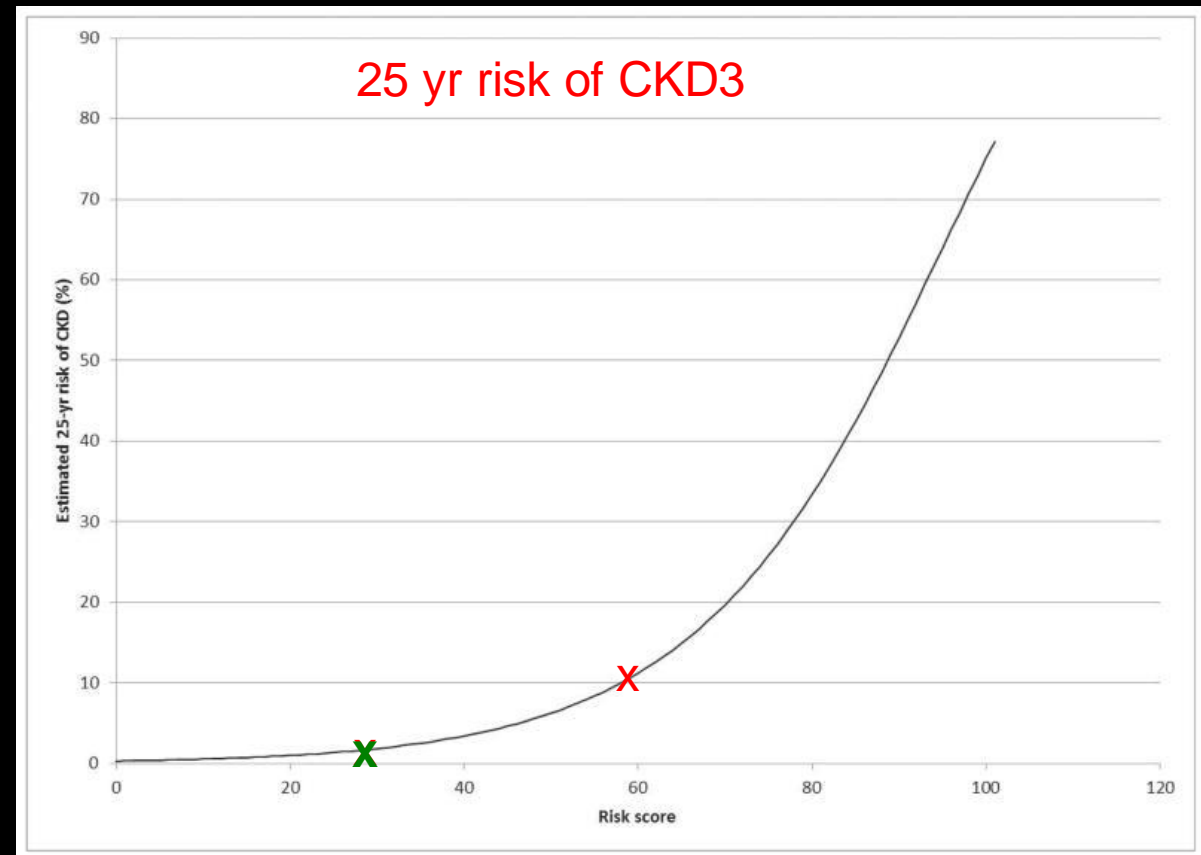


APOL1 in *potential* living donors

Coronary Artery Risk Development in Young Adults (CARDIA study)

- longitudinal multicenter study of young adults (18-30) from 4 urban areas – 50% AA
- Applied exclusion criteria to identify potential donors based on known characteristics (3438 people included)
- 55 candidates developed CKD3 (Median time 20.3 yr)
- Baseline risk factors for CKD3 after 25 yr followup:

Risk factor		aHR	Points
Age	Per 1 yr > 18	1.06	1/yr
Male		1.73	9
BMI	> 30	2.05	12
IFG		3.00	18
eGFR	90-99	3.11	18
Smoking		1.79	9
FH HTN	1° relative	1.92	11
FH DM	1° relative	2.25	13
APOL1	AA + 0 risk	1.75	9
	AA + 1 risk	2.26	13
	AA + 2 risk	4.94	26



Options to approach APOL1 in living donors

- Test no one:
don't inform, don't ask, don't test since
“we do not know what to do with it”
- Test all:
don't ask, test all, exclude if positive since
“we think we know what it all means”
- Test with conditions:
Inform, ask permission to test, test, share test results, individualize decisions

A proposed path forward

Information:

- All donor candidates of appropriate ancestry should be informed about APOL1 and CKD
- All should be counseled about the pros and cons of testing

Testing:

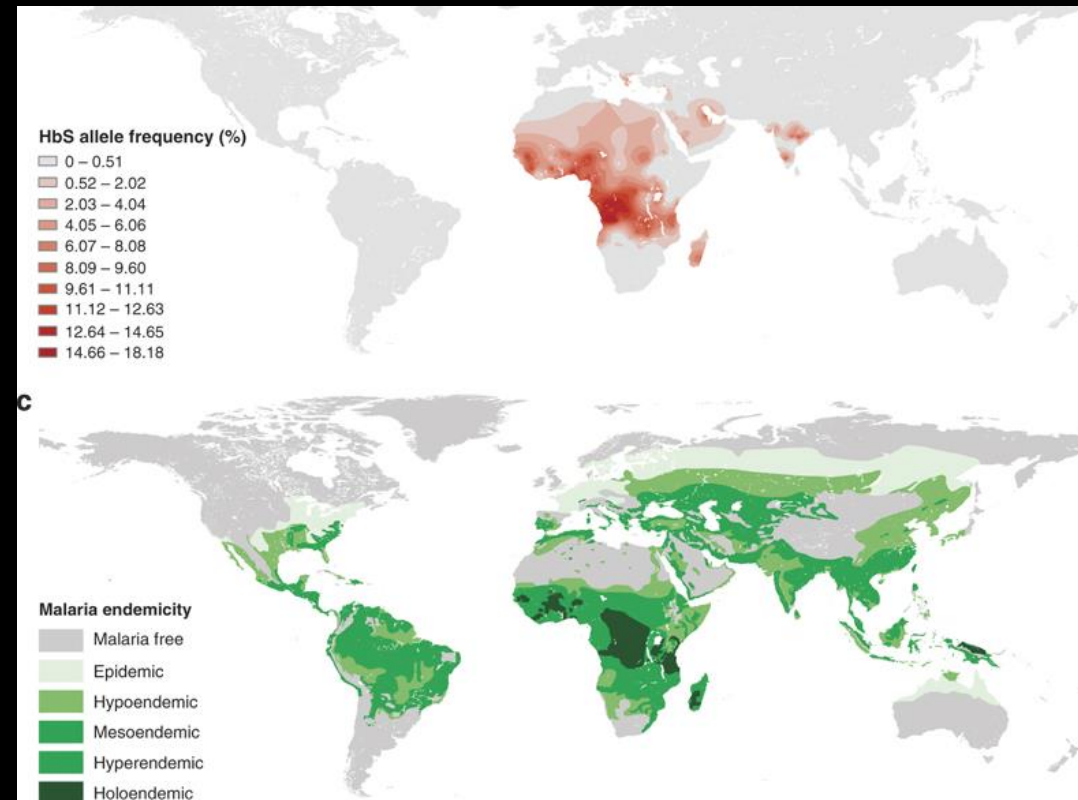
- All donor candidates who are otherwise acceptable should be offered testing
- Testing offered only to those who pass preliminary medical and psychosocial evaluation

Test results:

- Should be shared with donor candidate
- Positive test results, as with other single risk factors, should not exclude donation
- If threshold of risk acceptable to transplant center, the donor should share in decision making
- Should not be shared with the waitlist candidate (intended recipient)

Sickle cell trait

- Sickle hemoglobin (HbS) is a variant hemoglobin from a single amino acid change in β -globin (β glu \rightarrow val)
- Ancestral genetic variant enriched in people of African ancestry but also the Mediterranean region, the Arabian peninsula and India.
- Preserved and expanded because it confers protection against malaria
- Sickle cell disease: 2 copies of HbS
- Sickle cell trait: 1 copy of HbS
- Newborn screening in the US:
 - 8% of Blacks carry the sickle cell trait



Sickle cell trait (SCT) and ESKD

REGARDS study:

- ~9000 blacks: 7.5% SCT; SCT increased risk of prevalent CKD (OR 1.89)
 - (adjusting for age, sex, smoking, HTN, DM, APOL1 high risk status)
- SCT increased risk of incident ESRD: 8.5 per 1000 patient yr vs 4 per 1000 for non-carriers
 - Adjusted HR for SCT 2.03
 - Significant interaction between SCT and HTN (but not DM or APOL1) for prevalent CKD
- Risk of progression to ESRD similar for SCT and APOL1 high risk alleles (aHR 2.03 vs 1.77)

Should living donors be tested for sickle cell trait?

Should positive living donors be excluded from transplant?

Back to Case #1

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- Family history: one brother with DM, ESKD
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 - S. creatinine 0.9 (eGFR 82, with 'race' neutral formula 71); Measured Cr. clearance: 99
 - Blood type B (recipient O)

Should she be approved to donate?

Should she be counseled and tested for APOL1 risk alleles?

- She was counseled about APOL1 risk alleles and ESKD
 - She got tested: APOL1 G1/G1
 - She accepted risk and elected to donate
- She was advised that disclosure of APOL1 status may result in non acceptance in paired exchange
 - She donated 3 years ago and is well

Summary and Conclusions

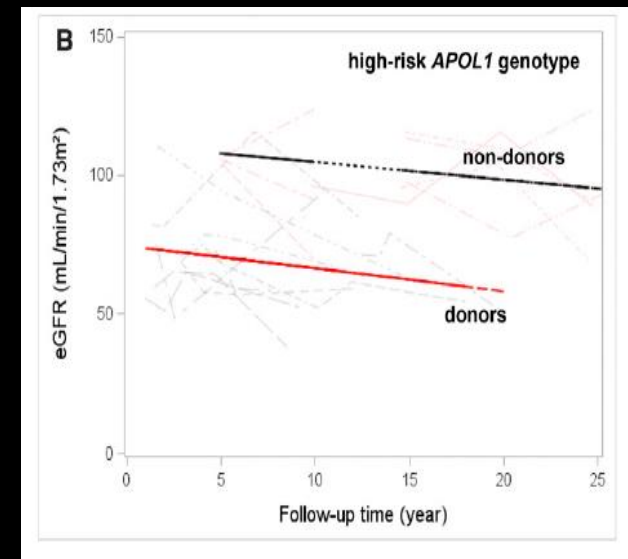
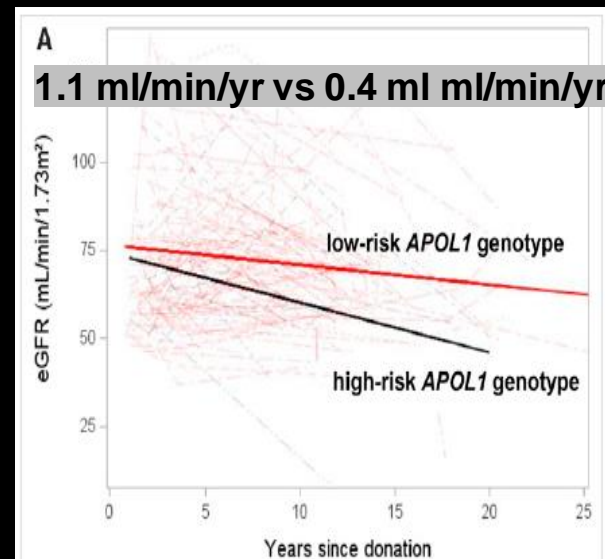
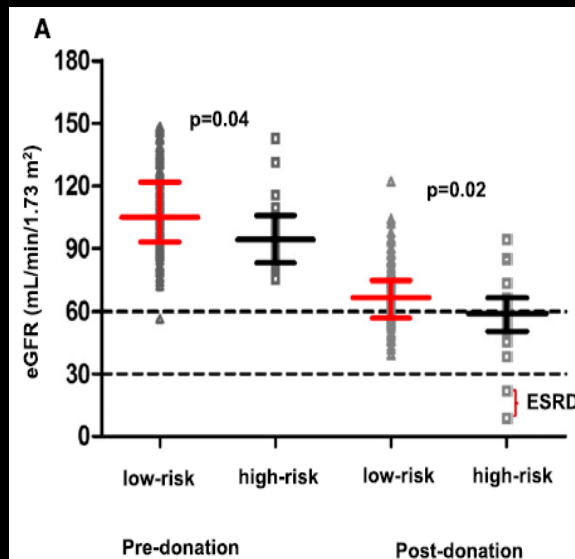
- There are several risk factors for ESKD in the general population and it is likely that these apply to living donors as well
- The magnitude of risk, the directionality of risk and the presence of other risk factors for ESKD must be a consideration when evaluating risk factors
- Some risk factors such as gender and ancestry are not modifiable and different thresholds of acceptable risk should be considered for different demographic criteria
- APOL1 variants (G1, G2) are a **risk** factor for CKD/ESKD but not a **cause** of kidney disease
 - Most with 2 risk alleles do not get disease
 - The magnitude of risk with 2 APOL1 variants is equivalent to other 'accepted' risks (e.g., eGFR 90-99)
- In the absence of data, we owe donor candidates the best knowledge with minimal bias
- When there is clinical equipoise, we must balance provider paternalism with donor autonomy and acknowledge that donor candidates have a share in decision making



Questions?

APOL1 in living donors

- Two center retrospective study: 249 AA live kidney donors invited:- 136 studied; FH positive for HTN (72%), ESRD (78%)
- High risk genotype 19, low risk 117 genotypes
- 77% of donors were 1st degree relatives
- Follow-up median 12 years



- 2 of 19 high risk donors developed ESRD: 10 and 18 years post donation
- No difference in post donation HTN between high and low risk groups

Limitations:

Small sample size. Limited study recruitment

What is the current practice

Survey among ASTS, AST or ASN members – surveyed were surgeon and nephrologist

- 5177 eligible: 383 completed
- Testing practice – 4% routinely, 14% sometimes, 16% didn't know
- Experience with test results – 13%
- Plan for future: 63% plan to use, 21% do not, 16% do not know
- Hypothetical case: If 2 risk variants – 50% would recommend against donation; 40% shared decision
- 69% believed all AA donors should be given option of testing as it helps donors make donation decisions

What is the African American Perspective?

Sampling of former AA living donors at 1 center – semi-structured interviews

- 45 donors contacted, 62% participated
 - 96% thought that routine testing should be offered
 - 87% willing to undergo testing before donating
 - 61% would have donated even with 2 risk alleles
 - Participants were apprehensive about future risk of kidney disease, insurance coverage and discrimination

Community deliberations on the topic at 3 sites:

Jackson, MS; Nashville, TN and Seattle, WA

- Strong support for APOL1 testing in kidney transplant settings
 - Unanimous support for testing deceased donor kidneys
 - Significant support for testing living donors (73%) but vigorous opposition to required (vs optional) testing
 - Most (90%) oppose prohibiting donation based on positive test results

Session Survey

Christie P. Thomas, MD | April 20th 1:30 PM-2:15 PM



14th Annual Living Donation Conference
Presented by the American Foundation for Donation and Transplantation