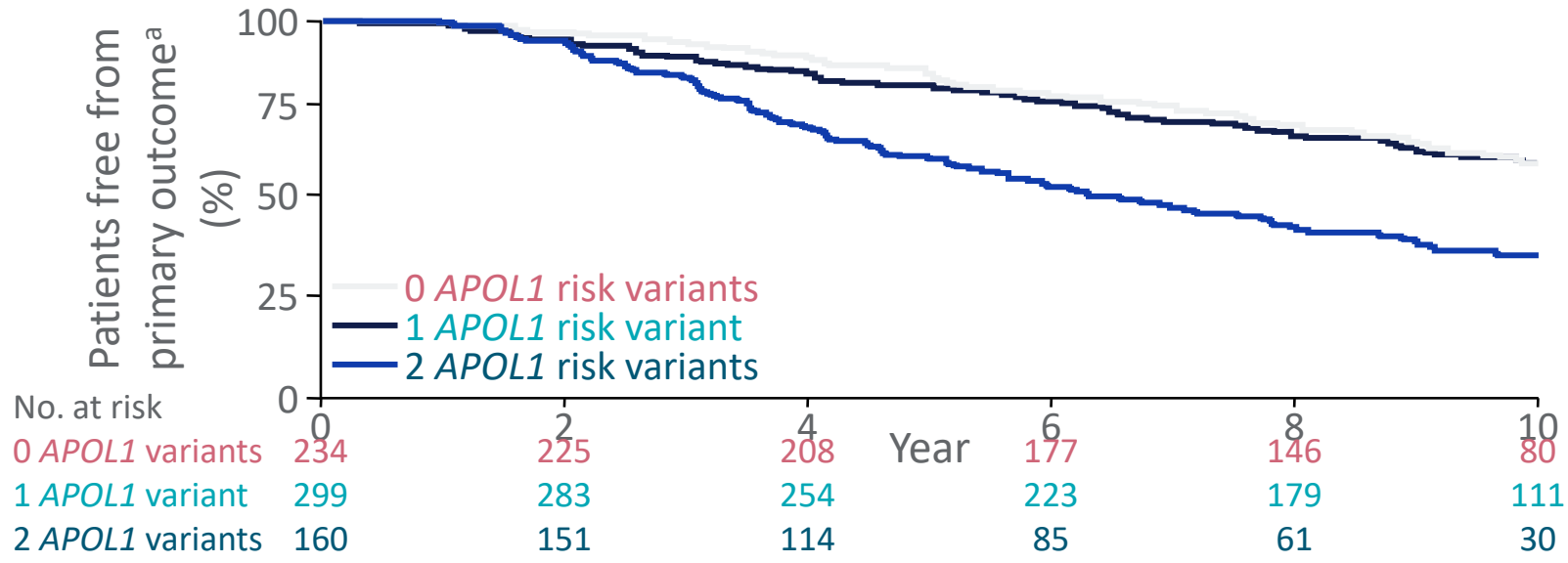
APOL1 et greffe rénale

Dr Aude Servais
Service de néphrologie adulte,
Inserm U1163, Institut Imagine
Centre de référence des maladies rénales héréditaires (MARHEA)
Hôpital Necker, Paris, France

ANJH 2024

Introduction

- Compared to other populations, individuals with *APOL1* HR genotype have markedly:
  - higher incidence rates of kidney failure
  - faster progression of chronic kidney disease

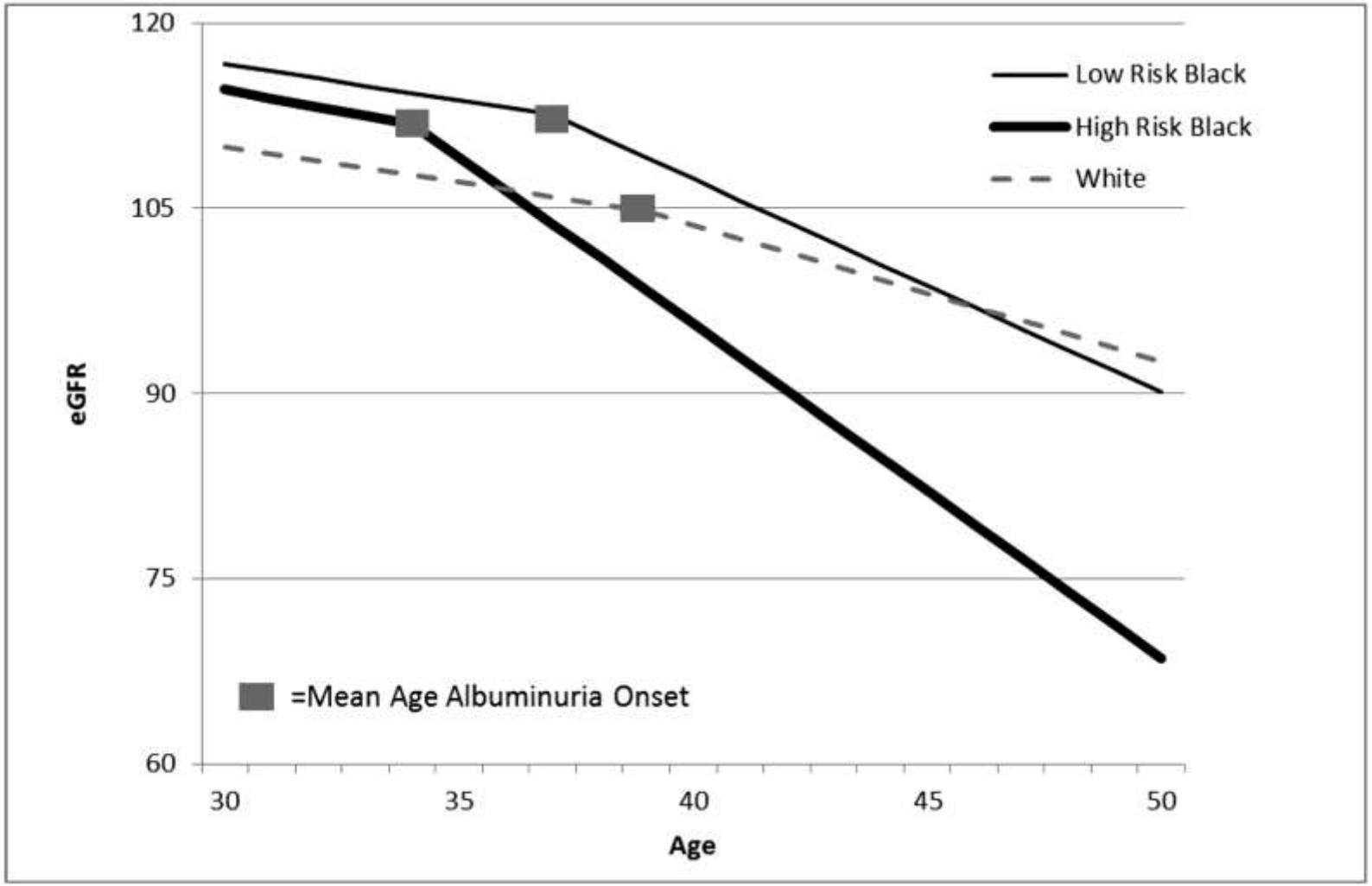


693 patients from AASK study (Hypertension-attributed CKD)

[a]Doubling of serum creatinine or ESKD

Parsa A, et al. *N Engl J Med*. 2013;369:2183-2196.

eGFR decline

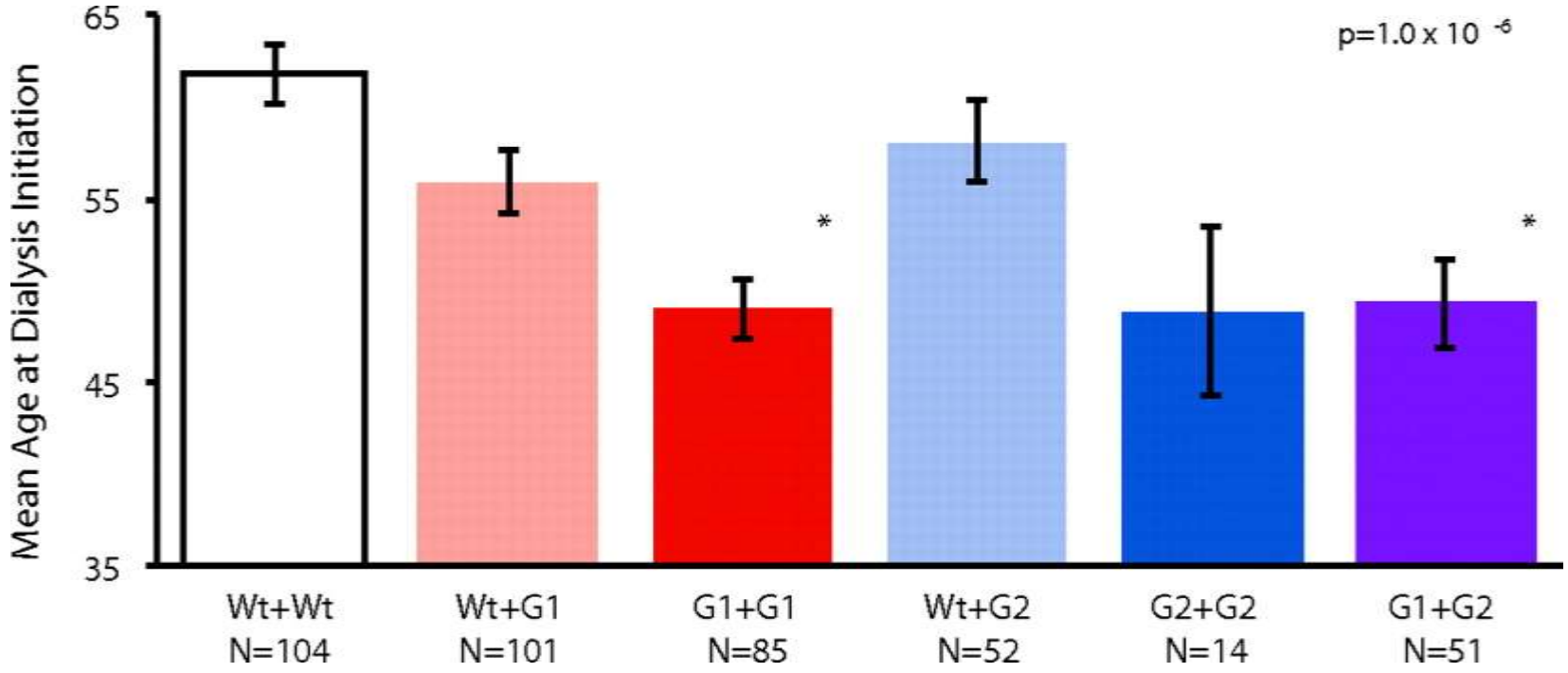


Mean age 35 years
13.2% of blacks had two *APOL1* HR alleles

3030 young adults (CARDIA study)

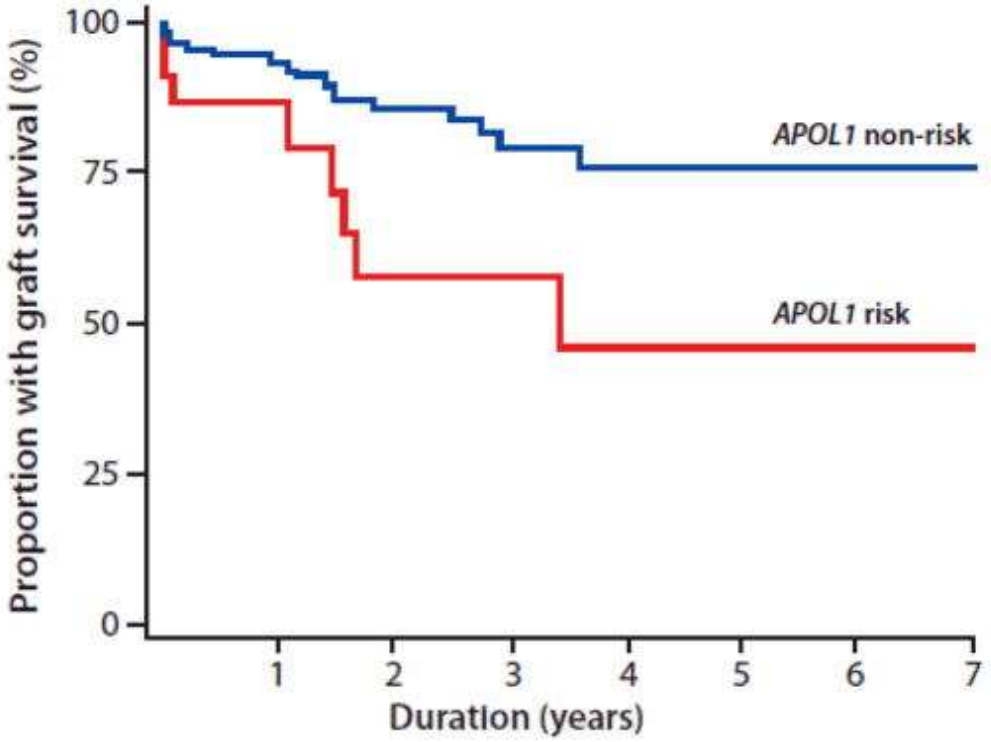
Peralta et al, JASN, 2016

Age at dialysis



Kanji et al, JASN, 2011

APOL1 and transplantation



***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

- 136 DDKT from 106 AA donors

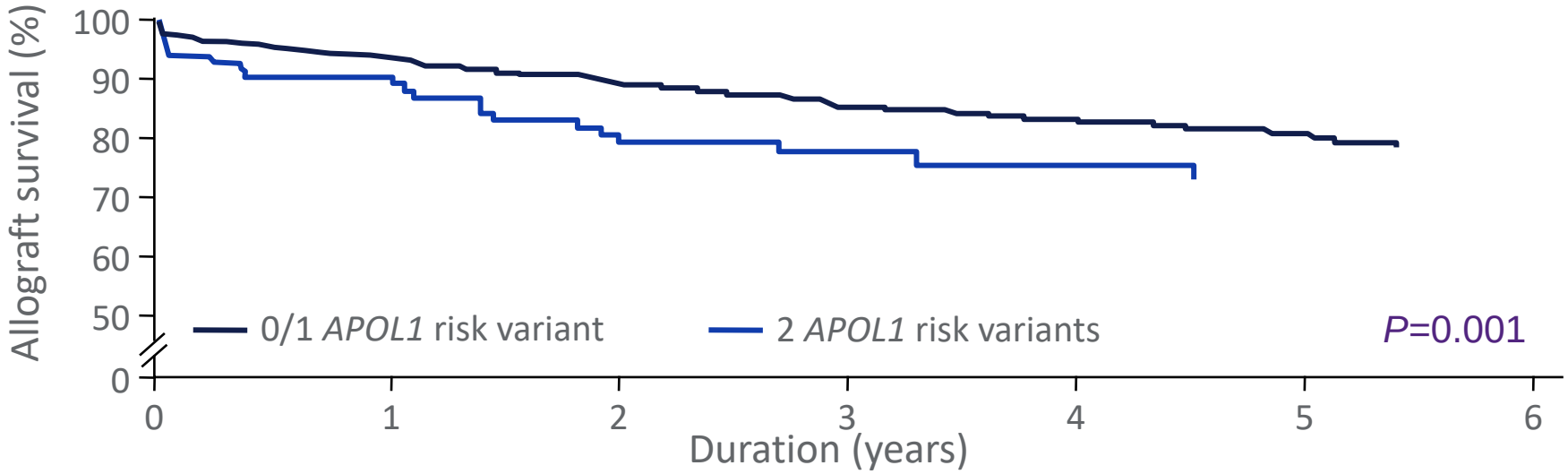
- Difference at 20 months
- *APOL1* HR alleles in donor kidneys independently predicted graft failure (HR 3.84, p=0.008)
- Donor *APOL1* genotypes, not donor ethnicity as in the Kidney Donor Risk Index (KDRI), contribute to more rapid graft failure

- Biopsy: 6/8 FSGS/arteriosclerosis

Reeves-Daniel et coll, AJT, 2O11

APOL1 and transplantation

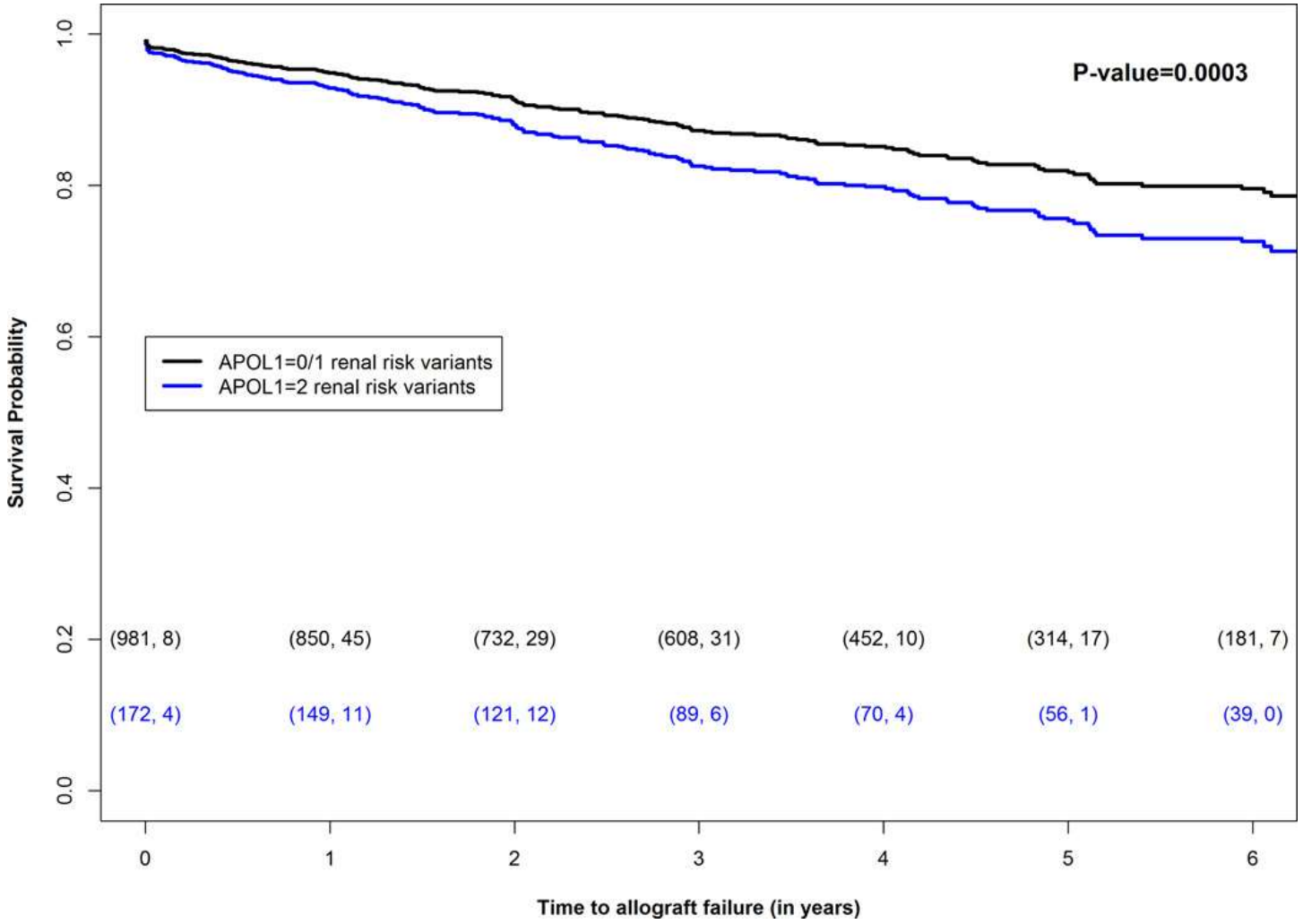
DNA samples from African American deceased donors of kidneys transplanted from 55 US centers



0 or 1 *APOL1* risk variant	No. at risk	575	486	387	306	213	151	101
	No. of graft losses	1	34	53	68	73	78	81
	Failure rate	0.2%	6.2%	10.6%	14.8%	16.7%	19.4%	21.7%
	No. censored	0	56	136	202	290	347	394
2 *APOL1* risk variants	No. at risk	99	86	63	45	35	29	29
	No. of graft losses	2	9	18	19	20	21	21
	Failure rate	2.0%	9.4%	20.6%	22.3%	24.5%	27.0%	27.0%
	No. censored	0	4	18	35	44	49	49

Freedman BI, et al. *Am J Transplant*. 2015;15:1615-1622.

APOL1 and transplantation

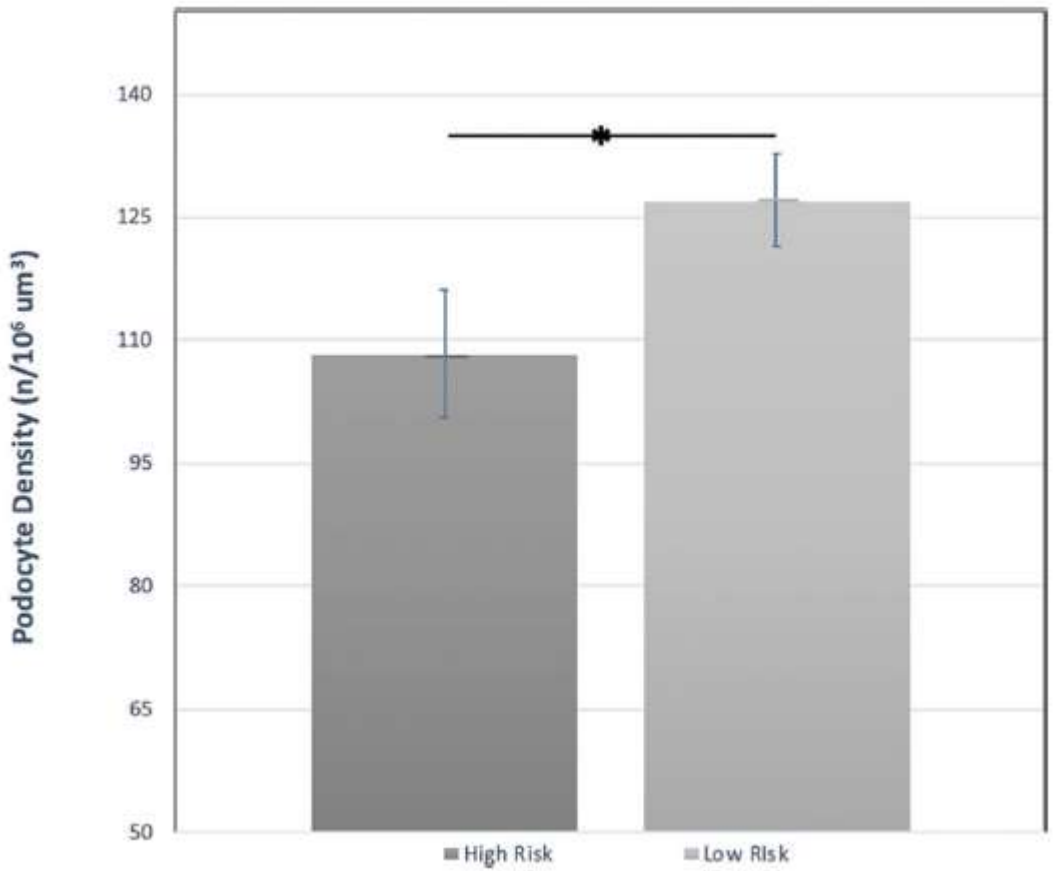


- Retrospective outcomes in 1153 kidney transplants from 624 unique African American donors
- Donor *APOL1* high-risk genotypes were associated with twice the risk of graft failure
- Time to renal allograft failure related to donor *APOL1*: HR 2.05 (P = 0.0003)

Freedman et al, Transplantation, 2016

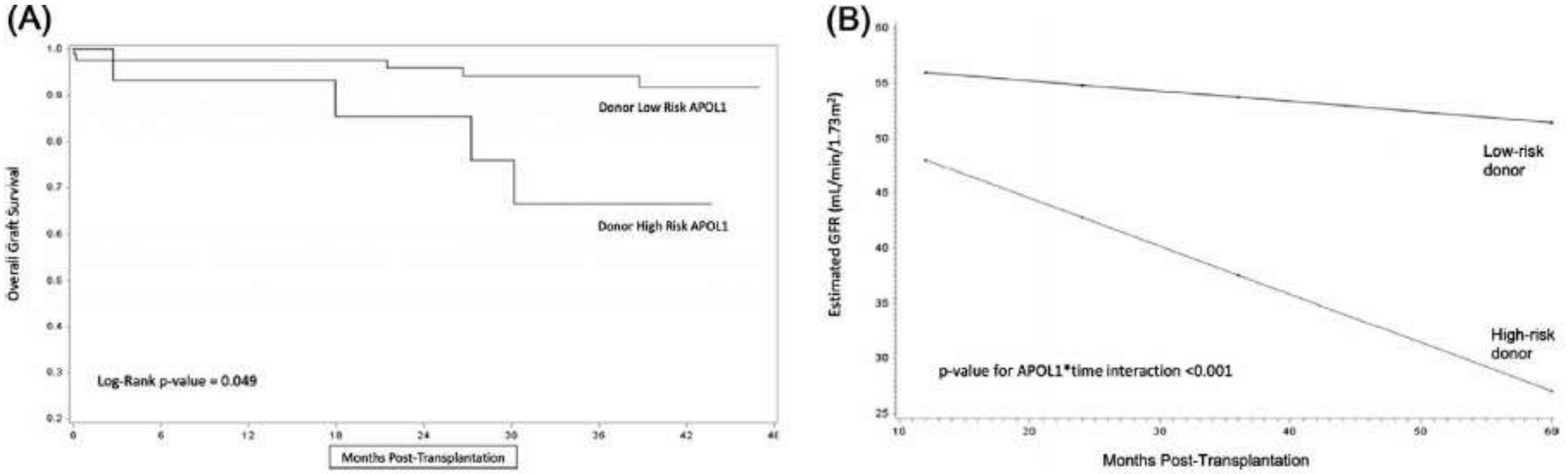
Podocyte density in kidney allografts

- Podocyte density is reduced in kidney allografts with high-risk *APOL1* genotypes at transplantation



Chen et al, Clin Transplant, 2021

Graft survival

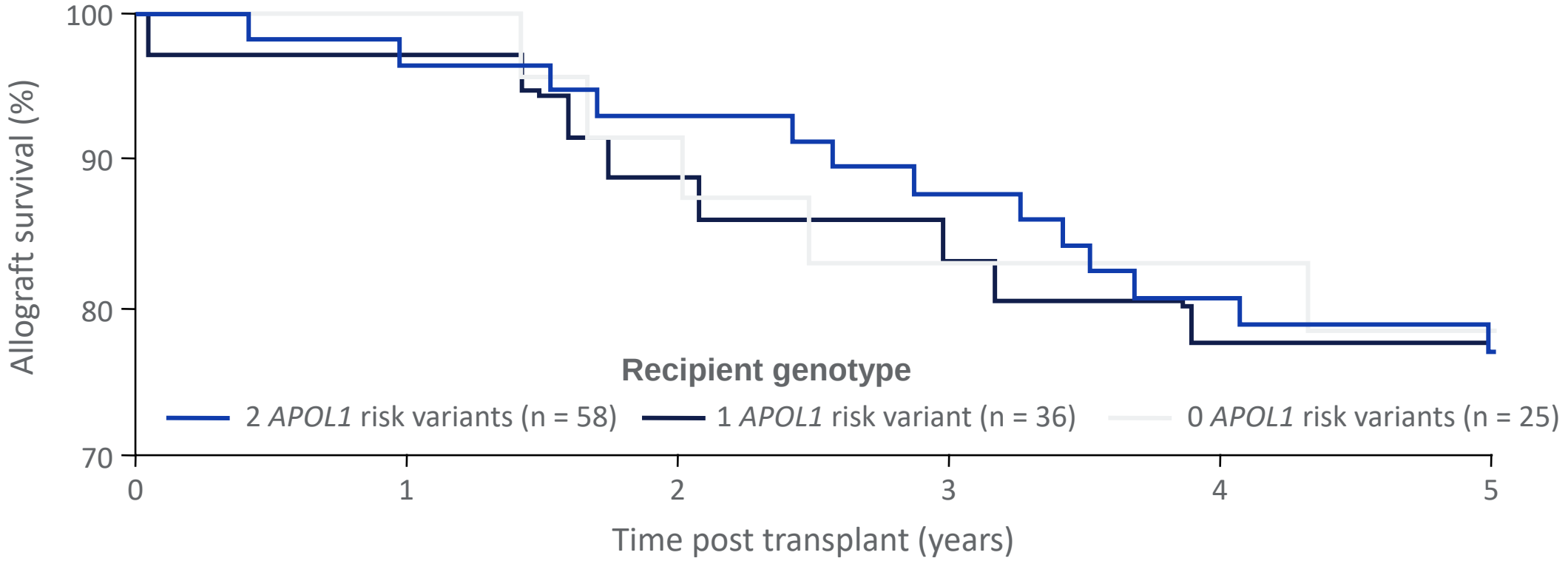


- Graft survival (high-risk 61% vs. low-risk 91%, p-value = 0.049): higher graft loss in recipients of *APOL1* high-risk allografts over 48 months
- More rapid eGFR decline (P < .001): at 60 months, eGFR was 27 vs. 51 mL/min/1.73 m²

Chen et al, Clin Transplant, 2021

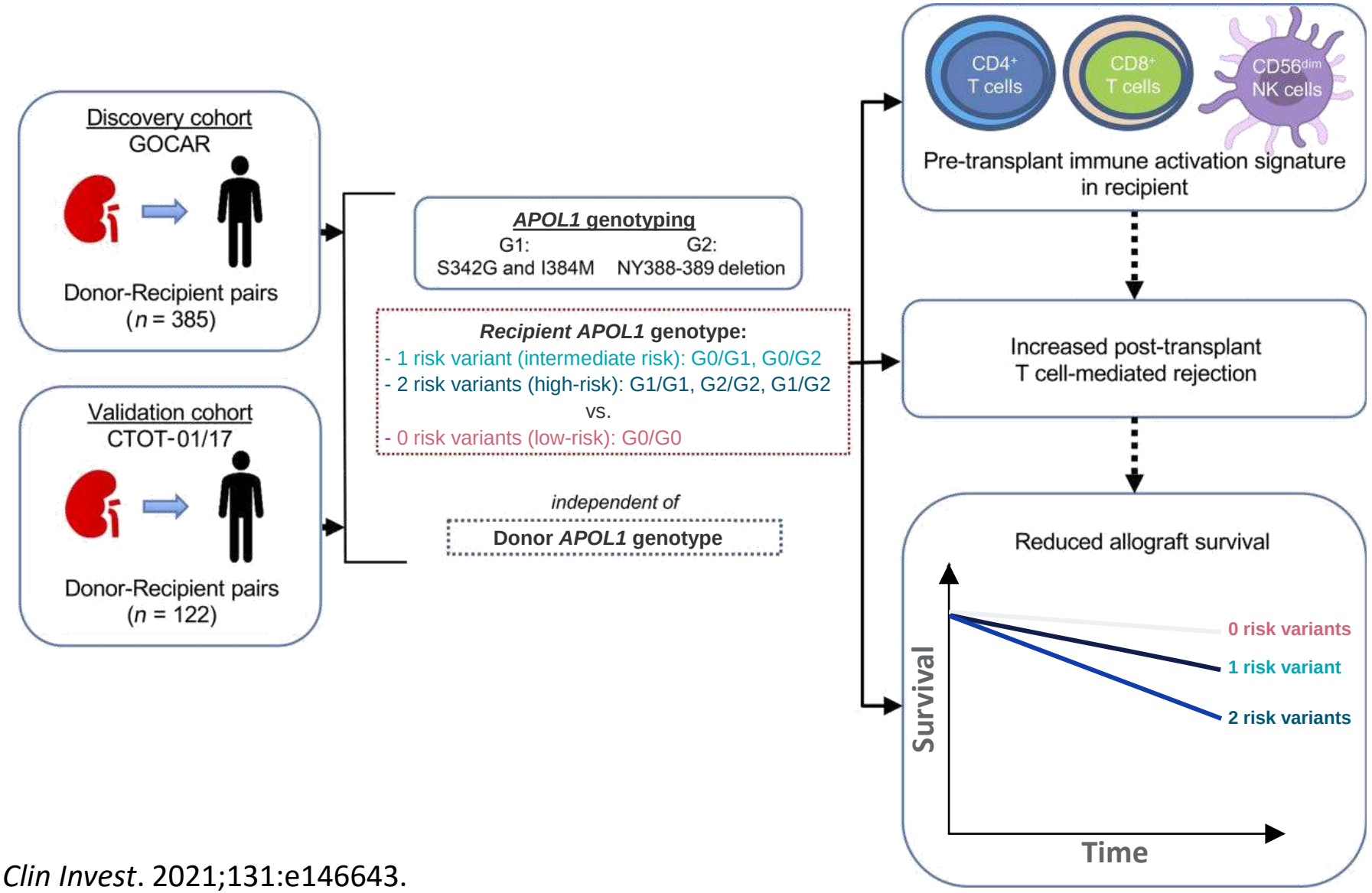
APOL1 and transplantation

Retrospective analysis of African American kidney transplant recipients (n = 119) between 1988 and 2002 from 2 US centers



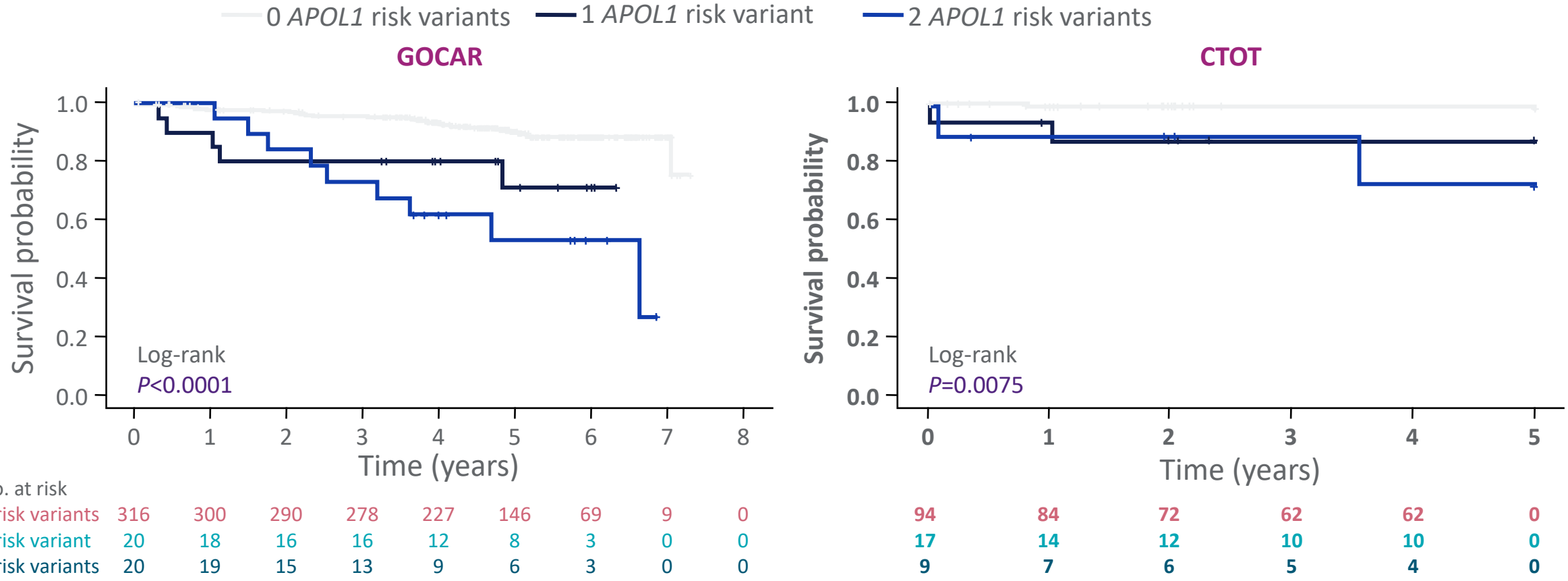
Lee BT, et al. *Am J Transplant*. 2012;12:1924-1928.

Recipient APOL1 and renal allograft survival



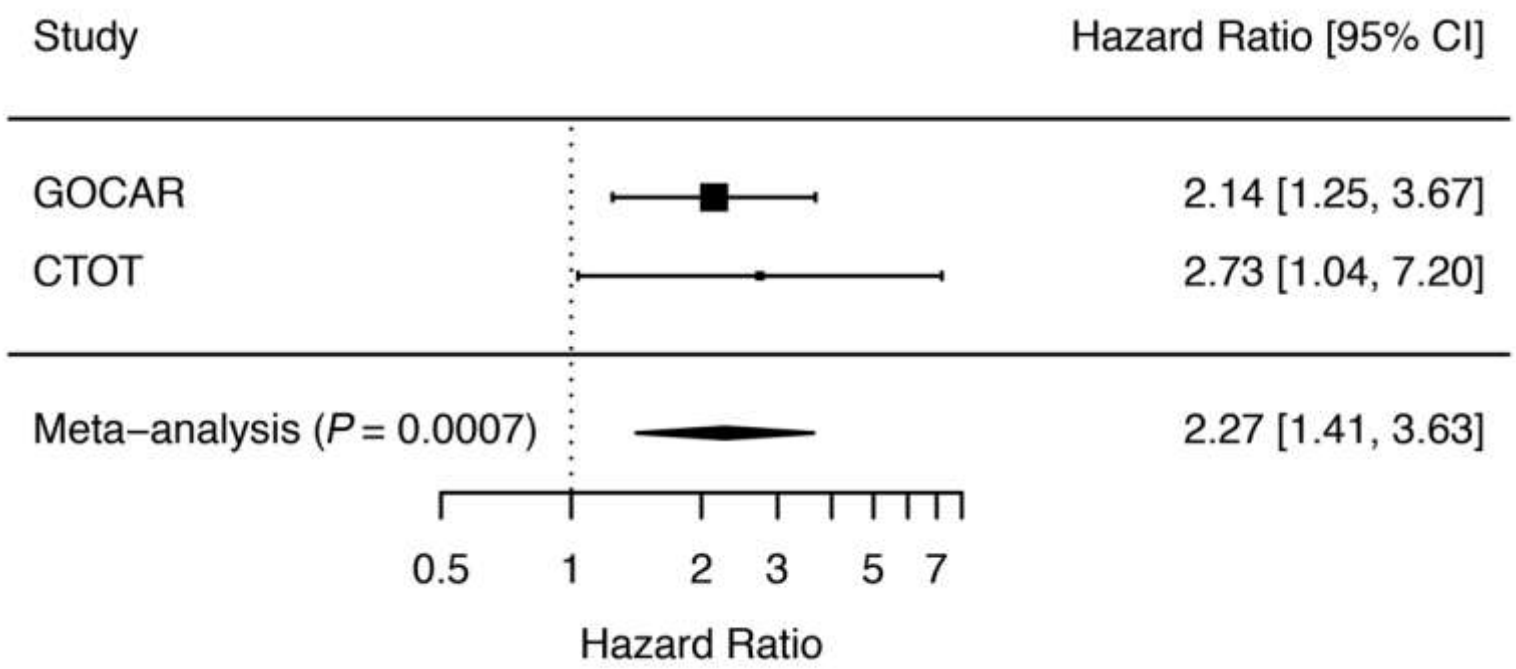
Zhang Z, et al. *J Clin Invest*. 2021;131:e146643.

Allograft survival



Zhang Z, et al. *J Clin Invest*. 2021;131:e146643.

Meta-analysis for the association of *APOL1* risk alleles with death-censored allograft survival across the GOCAR and CTOT studies



Zhang Z, et al. *J Clin Invest*. 2021;131:e146643.

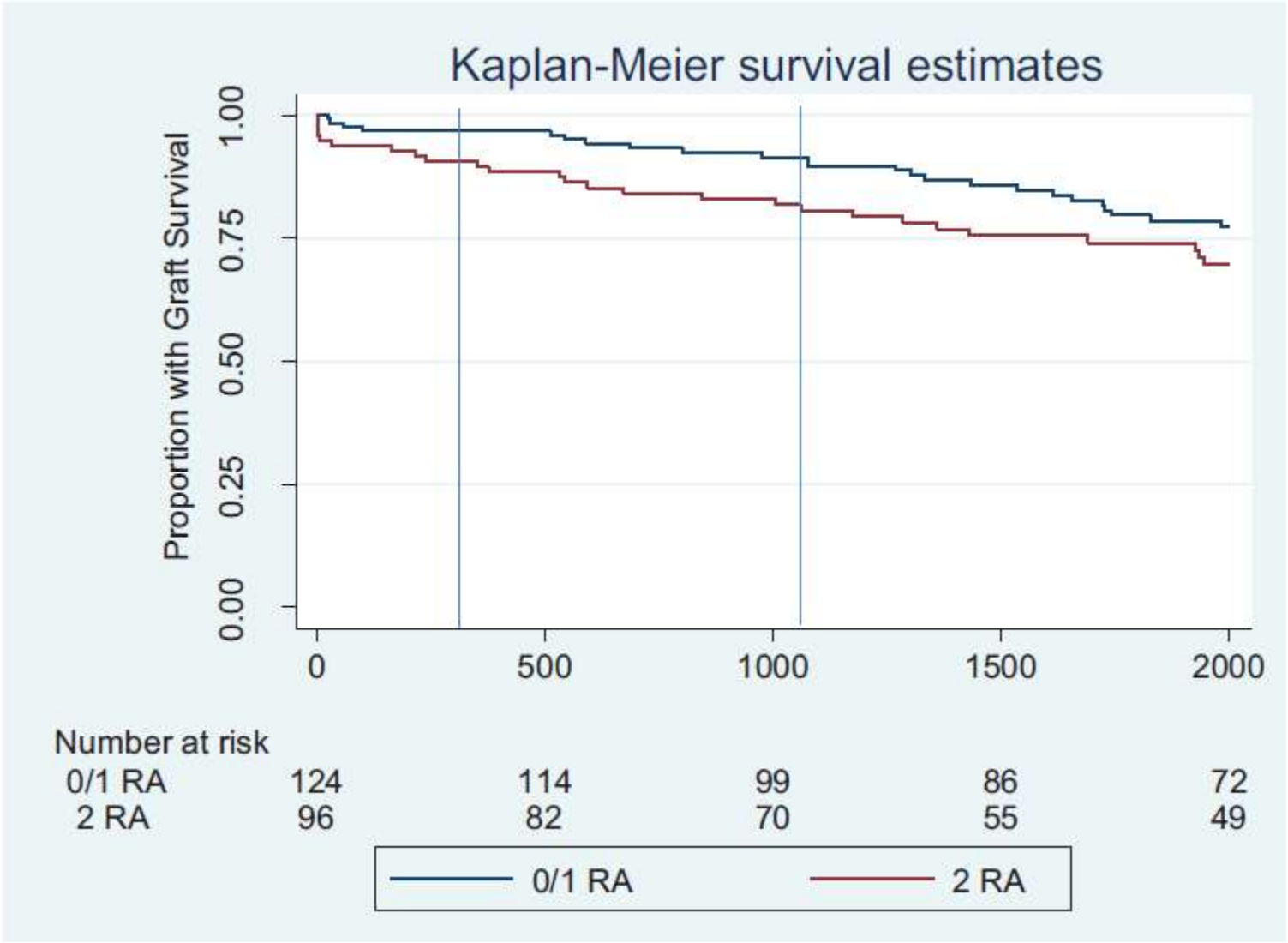
Recipient APOL1 G1/G2 alleles associate with clinical and subclinical rejection

- In GOCAR: 126 recipients (32.7%) had at least 1 episode of subclinical or clinical TCMR (with a Banff borderline score or greater)
- In CTOT, 15 recipients (12.3%) had at least 1 TCMR episode
- *APOL1* was significantly associated with any TCMR event in multivariable logistic regression models, independent of donor *APOL1* risk genotype
- Ex vivo studies of PMBCs revealed high expression levels of APOL1 in activated CD4+/CD8+ T cells and NK cells
- Enriched immune response gene pathways in risk allele carriers compared with noncarriers on the kidney transplant waitlist and among healthy controls

Zhang Z, et al. *J Clin Invest*. 2021;131:e146643.

Recipient *APOL1* Kidney Risk Alleles and Transplant Outcomes

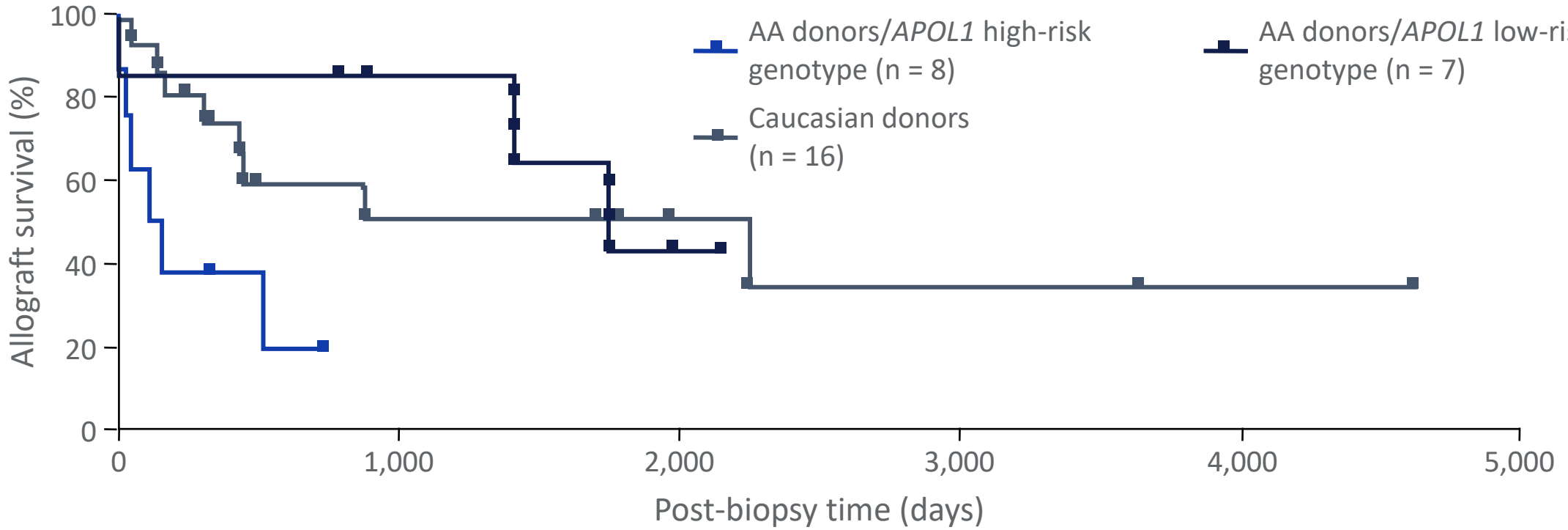
- Multicenter prospective study
- 221 incident African American kidney transplant recipients at 3 transplant centers
- Over 40% of kidney transplant recipients had the high risk *APOL1* genotype
- KTRs with 2 *APOL1* RA were transplanted at a significantly younger age
- The presence of a high-risk genotype in the recipient was associated with an increased risk of graft failure during the first posttransplant year
- However, no significant difference in overall survival or graft survival after 3 y posttransplantation.
- Donor APOL1 genotype status not available



Roy et al, Transplantation, 2023

De novo collapsing FSGS after transplantation

47% African American donors, including 53% *APOL1* high-risk genotype

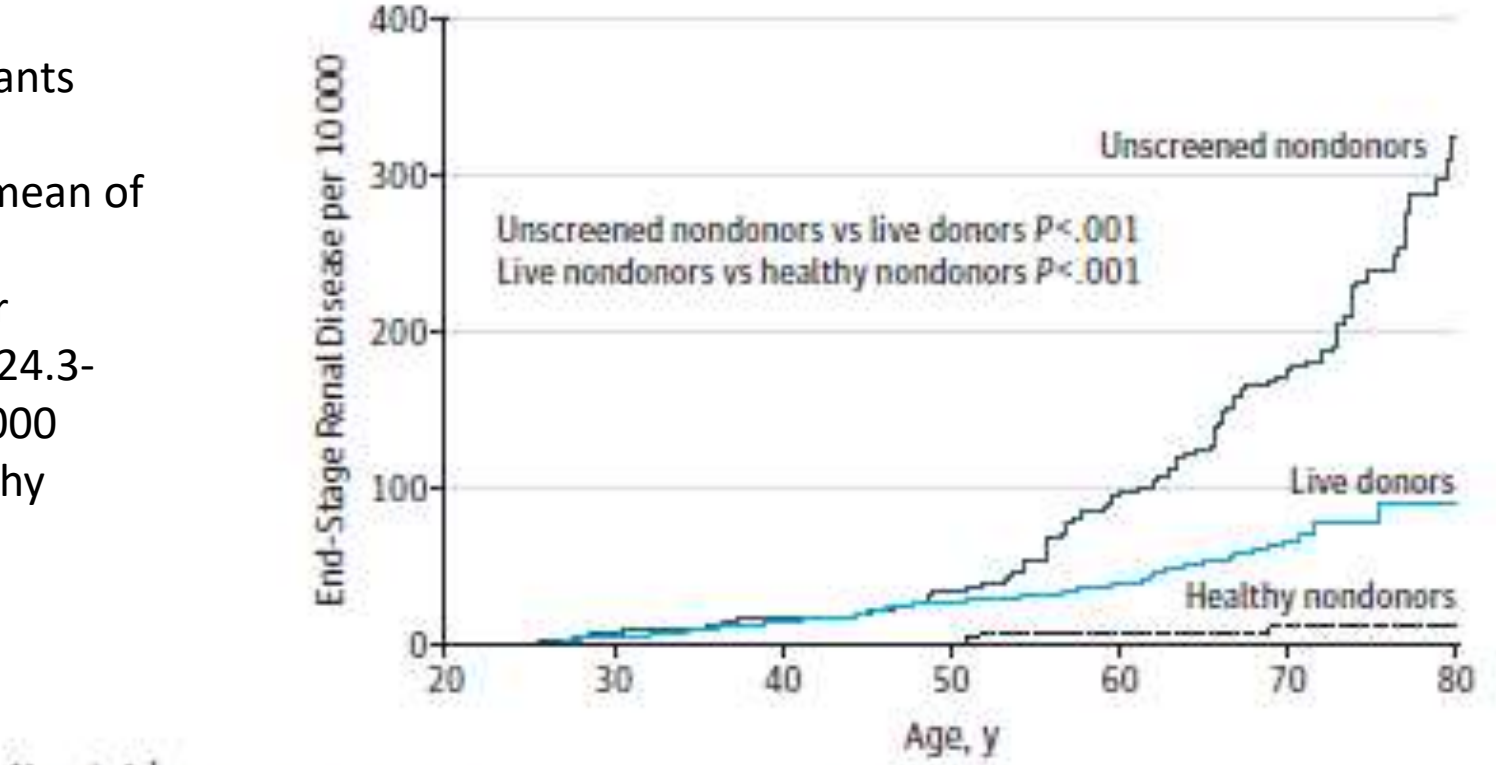


Grafts from kidney donors with *APOL1* high-risk genotype had worse survival than those from *APOL1* low-risk genotype donors

Santoriello D, et al. *Kidney Int*. 2018;94:1189-1198.

Living donors

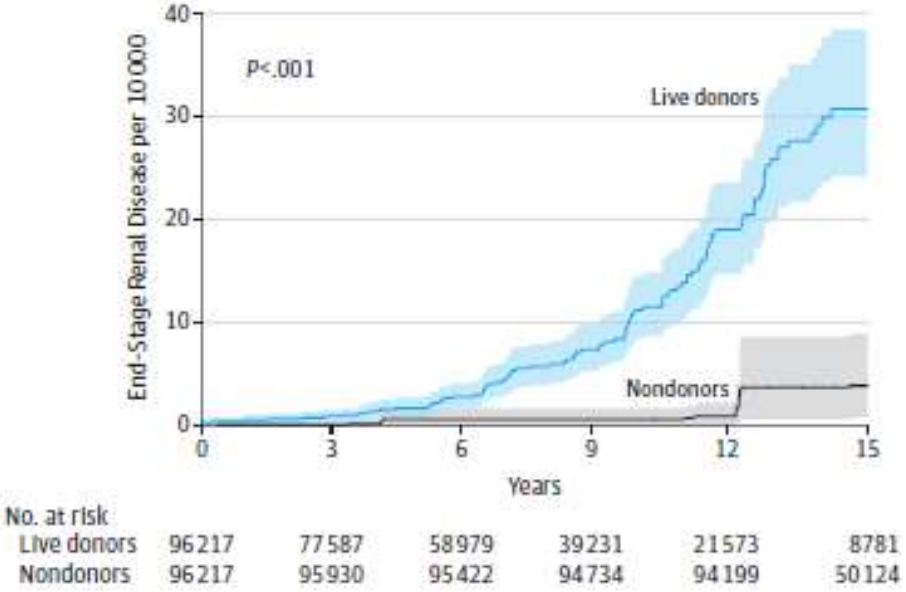
- 96 217 +20 024 kidney donors participants
- Median follow-up 7.6 years
- ESRD developed in 99 individuals in a mean of 8.6 (3.6) years after donation
- Estimated risk of ESRD at 15 years after donation was 30.8 per 10 000 (95%CI, 24.3-38.5) in kidney donors and 3.9 per 10 000 (95%CI, 0.8-8.9) in their matched healthy nondonor

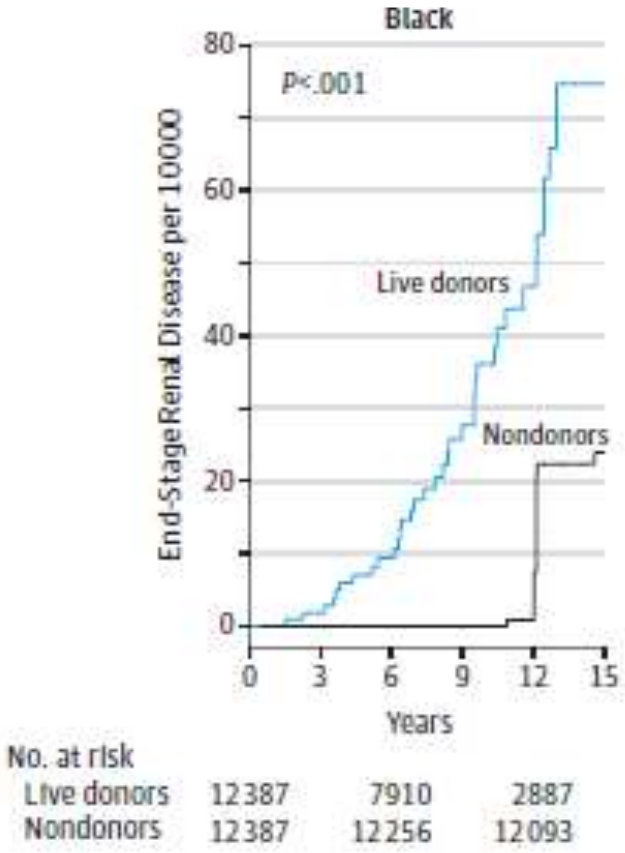


No. at risk							
Unscreened nondonor	1296	18436	36272	40863	26982	7990	647
Live donor	1143	13144	22647	22944	12151	2575	218
Healthy nondonor	1306	18487	36397	40961	28358	9011	870

Muzale et al, JAMA, 2014

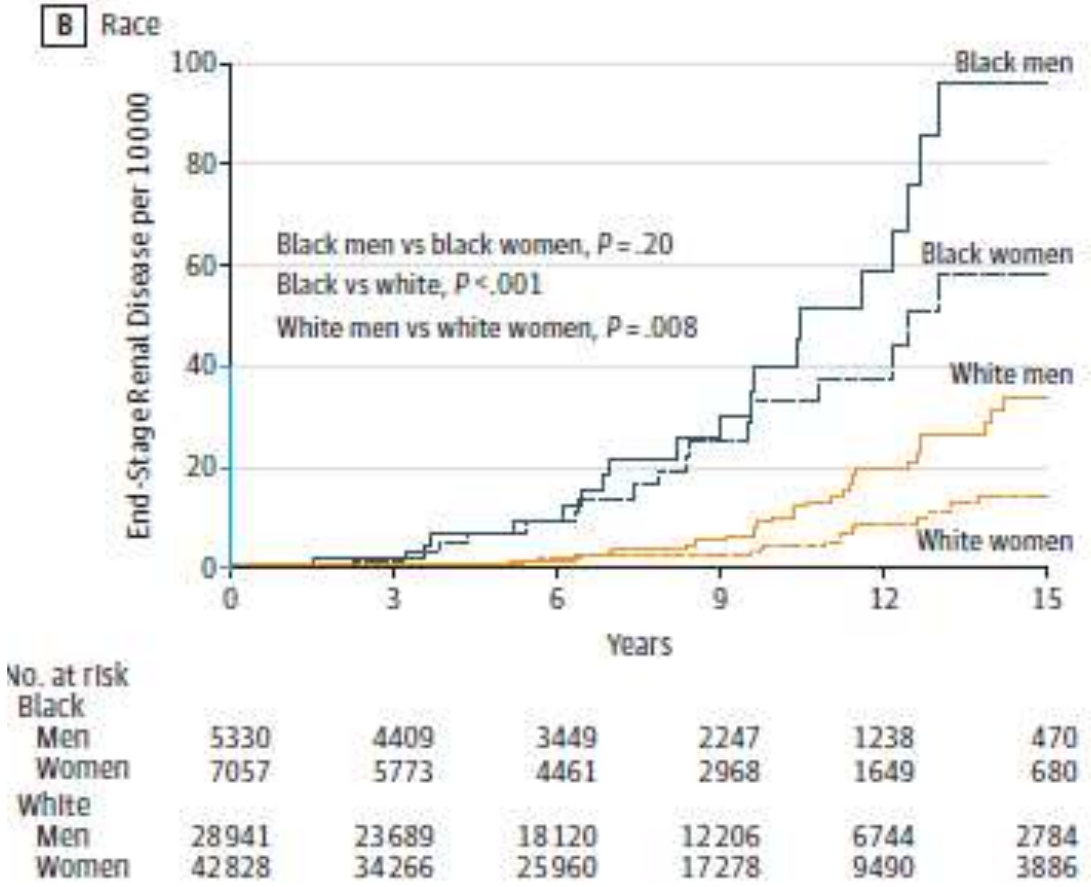
Cumulative incidence of ESRD





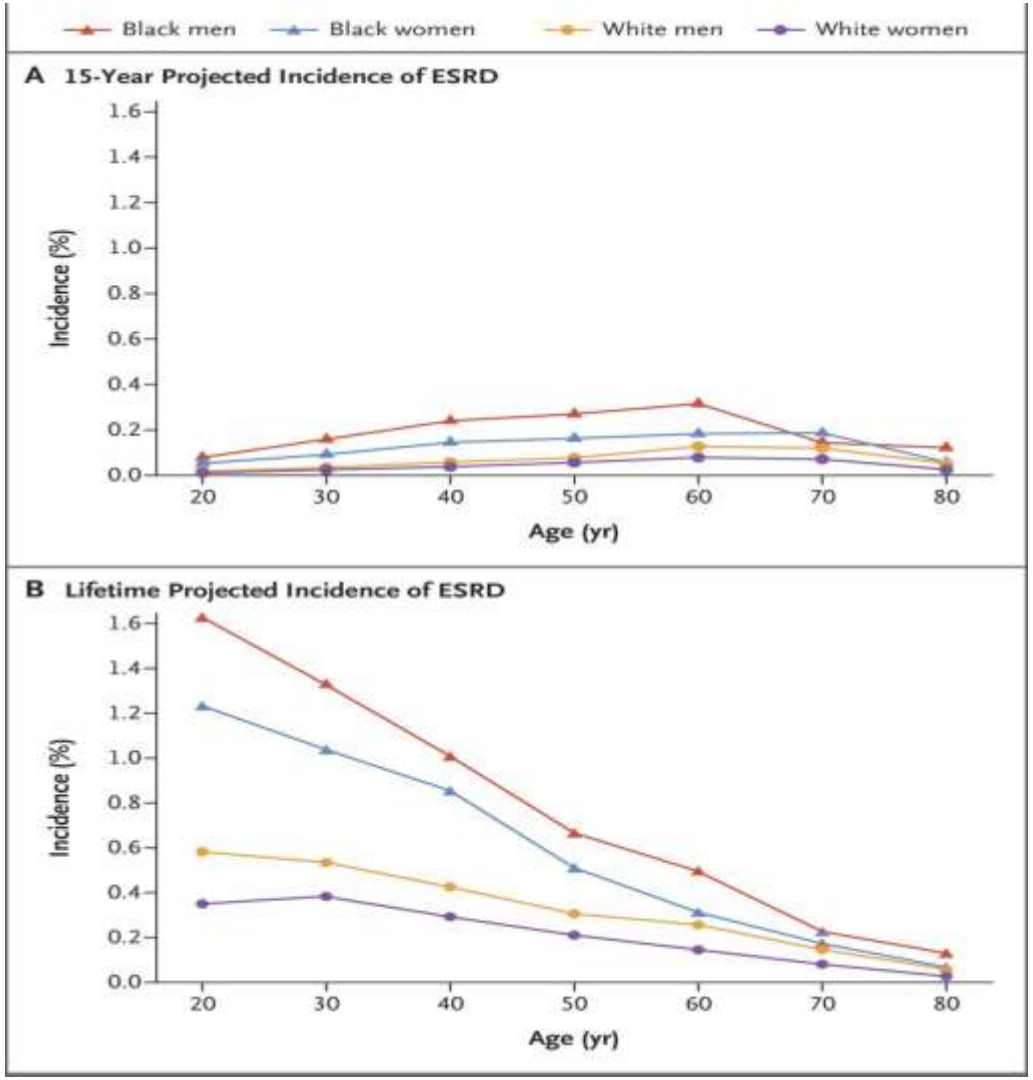
Muzale et coll, JAMA, 2014

Cumulative incidence of ESRD



Muzale et coll, JAMA, 2014

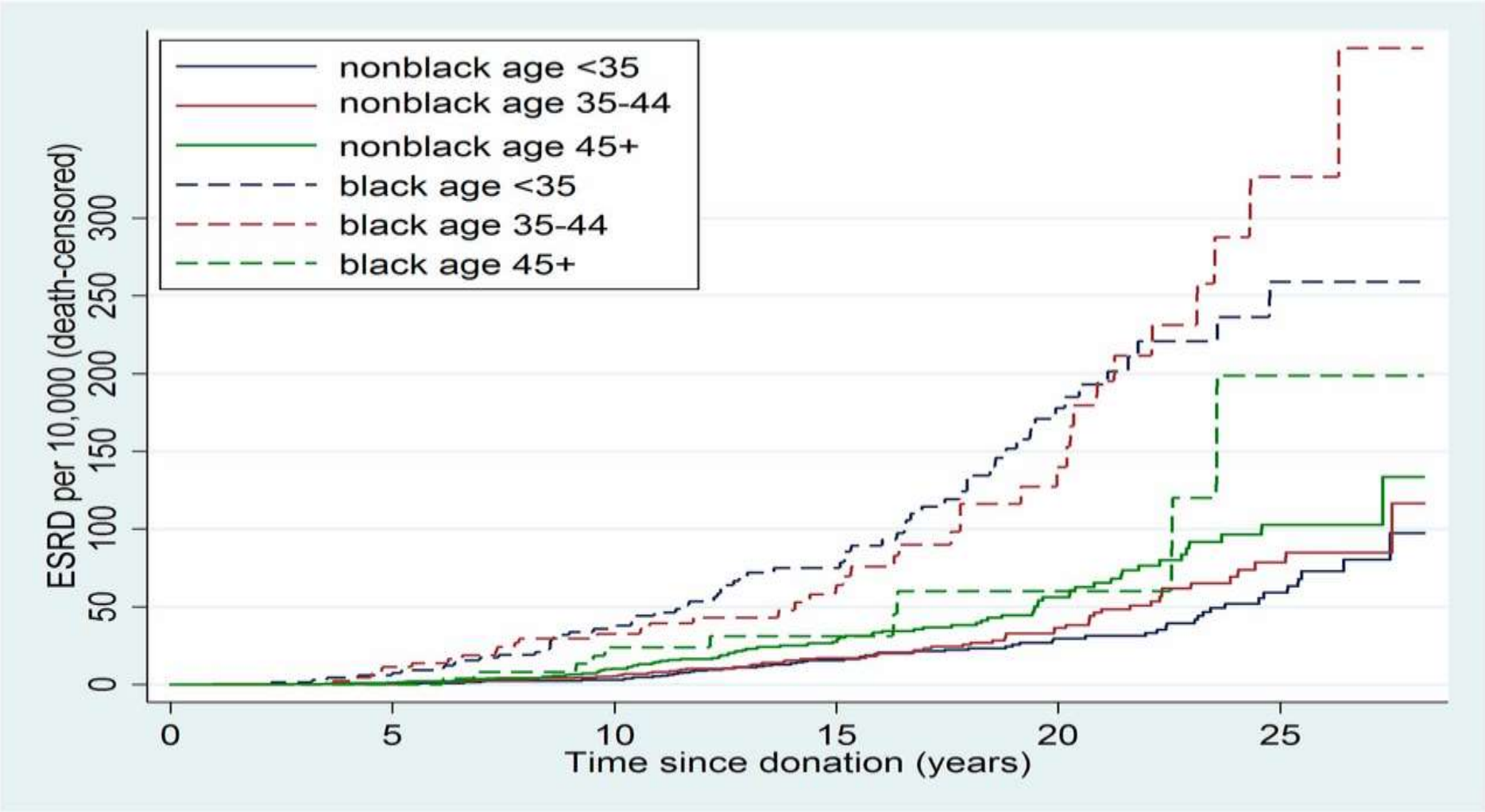
Kidney failure projection according to age, ethnicity and sex



- 15-year ESRD risk projections in the absence of donation varied by race and sex: 0.24%, 0.15%, 0.06%, and 0.04% in black men, black women, white men, and white women
- Increased risk of kidney failure in young patients, in particular if African origin

Grams et coll, N Engl J Med, 2016

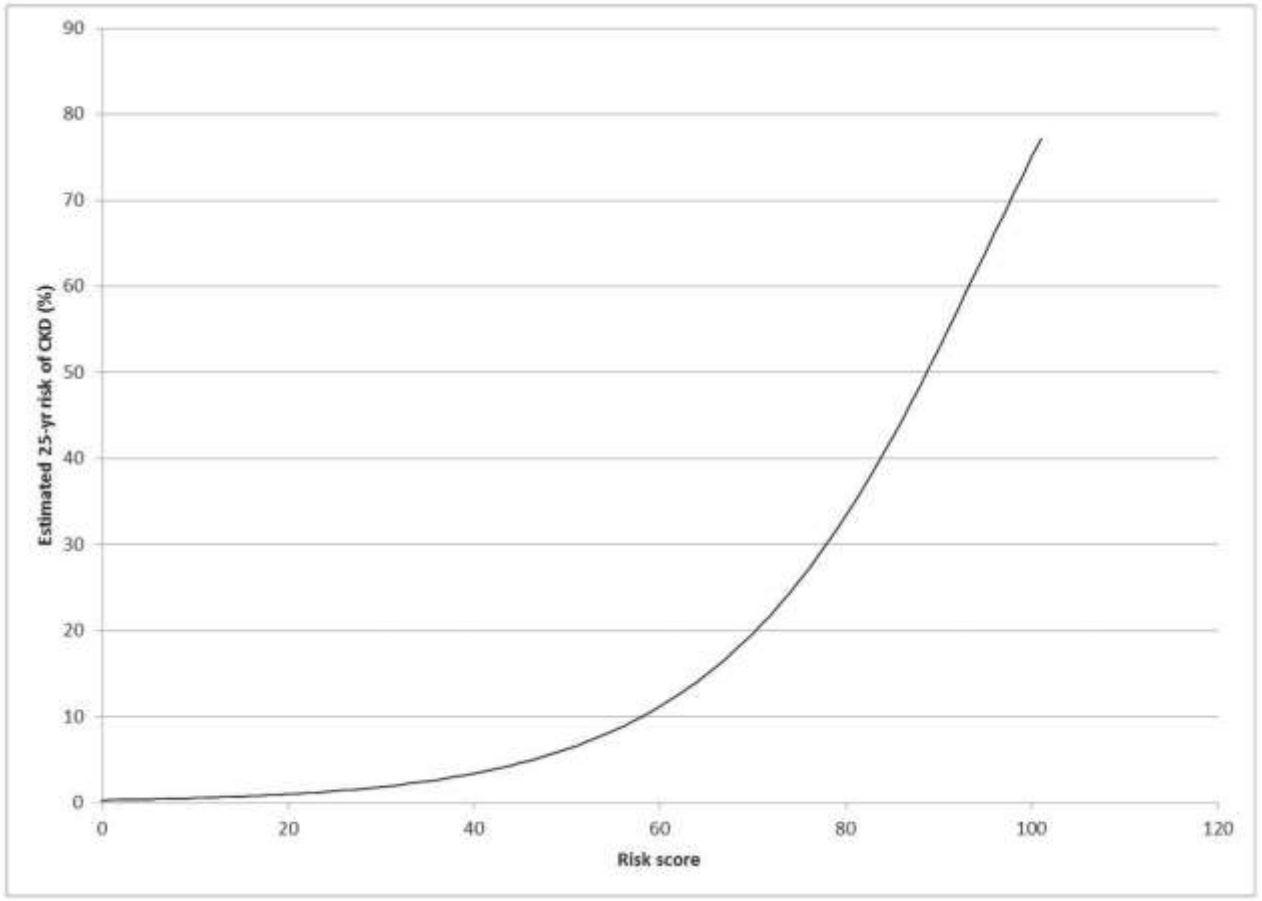
Living donation: risk factor of ESRD



Among nonblack donors, older age groups had higher cumulative incidence of ESRD, whereas among black donors, older age groups had lower risk of ESRD.

Massie et coll, JASN, 2017

Chronic Kidney Disease Risk in Young Potential Living Kidney Donors



- 3,438 healthy adults: mean age 24.8 years; 48.3% AA; median follow-up 24.9 years
- 25-year projected CKD risk varied by ethnicity and gender: risk was 0.30% for European American (EA) women, 0.52% for EA men, 0.52% for AA women, 0.90% for AA men
- Among 18-year-old AAs with *APOL1* HR variants without baseline abnormalities, 25-year risk significantly increased: 1.46% for women and 2.53% for men
- Among those with two *APOL1* renal-risk variants and baseline abnormalities, 25-year risk was higher: 2.53%–6.23% for women and 4.35%–10.58% for men

Locke et al, Ann Surg, 2018

Don vivant et HSF

- 2 cas donneurs vivants APOL1 HR développant une HSF et une IRT après don

Zwang et coll, AJT, 2016
Kofman et coll, AJKD, 2014

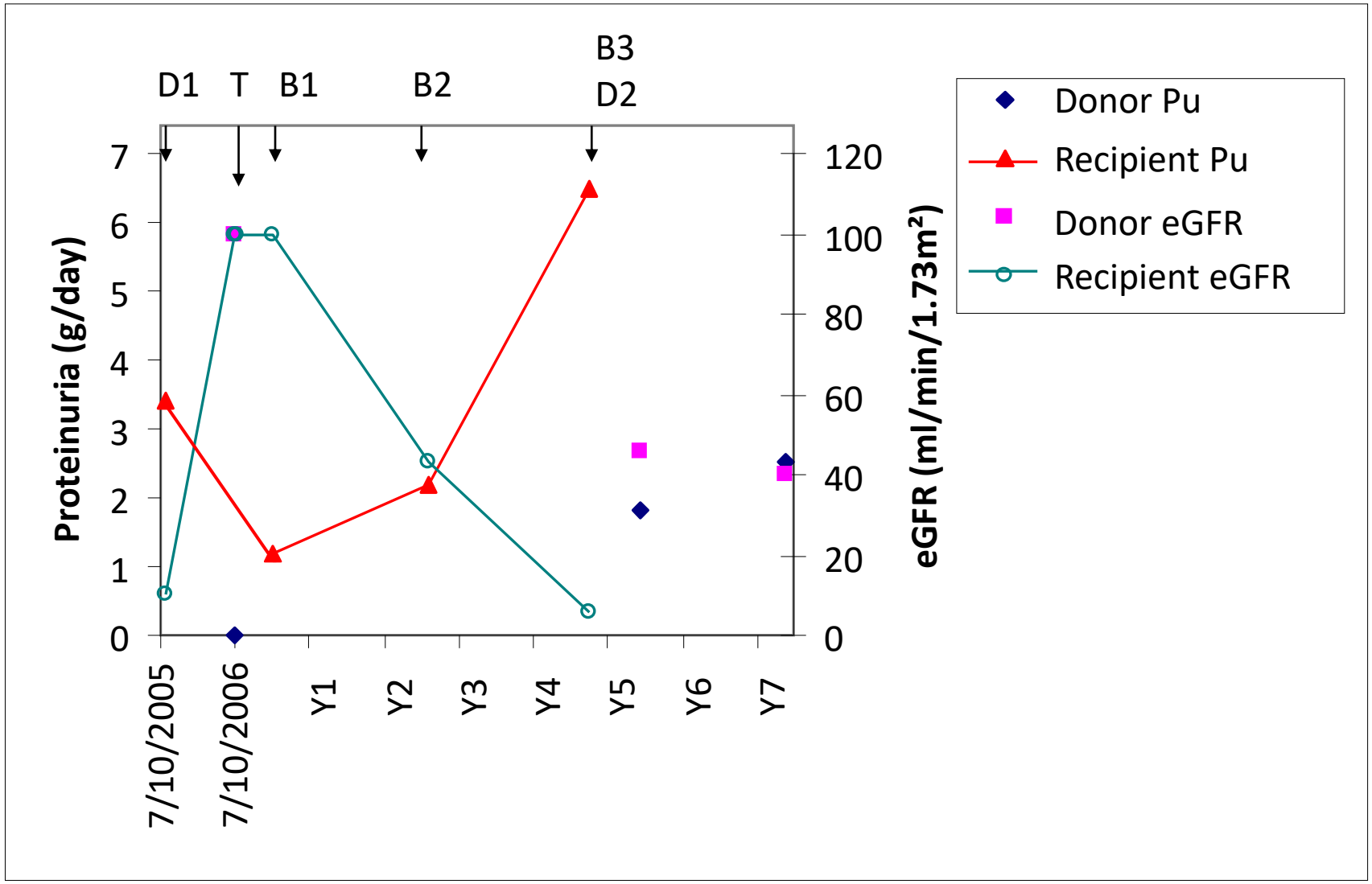
Don vivant, *APOL1* et HSF

1 donneuse 38 ans

ATCD diabète gestationnel, PU en cours de grossesse, BMI 31

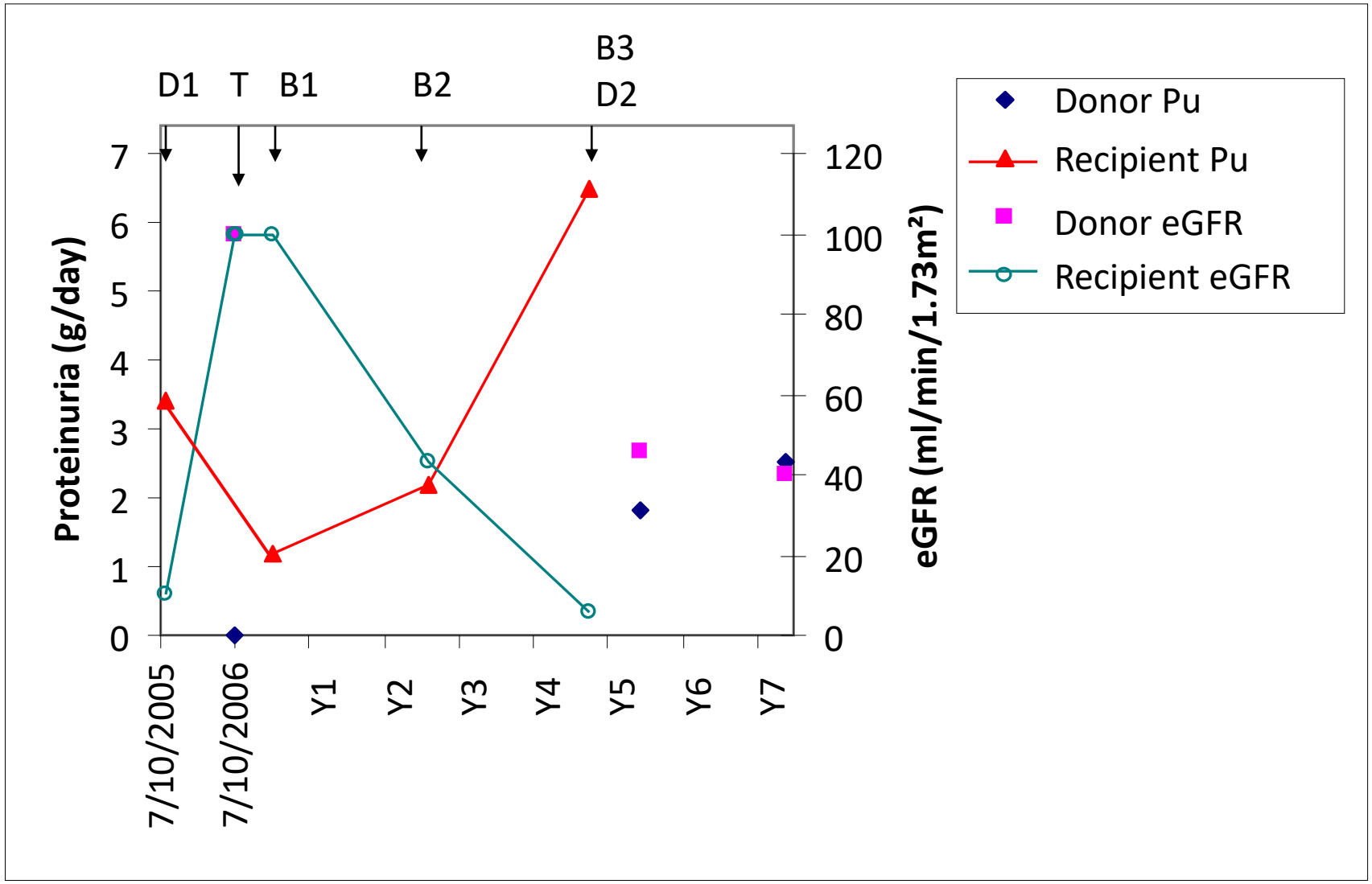
IRT, 7 ans après don

Zwang et coll, AJT, 2016



1 donneur développant une IRC et une PU 7 ans après don
Don à son frère jumeau: perte du greffon sur HSF 5 ans après

Kofman et coll, AJKD, 2014

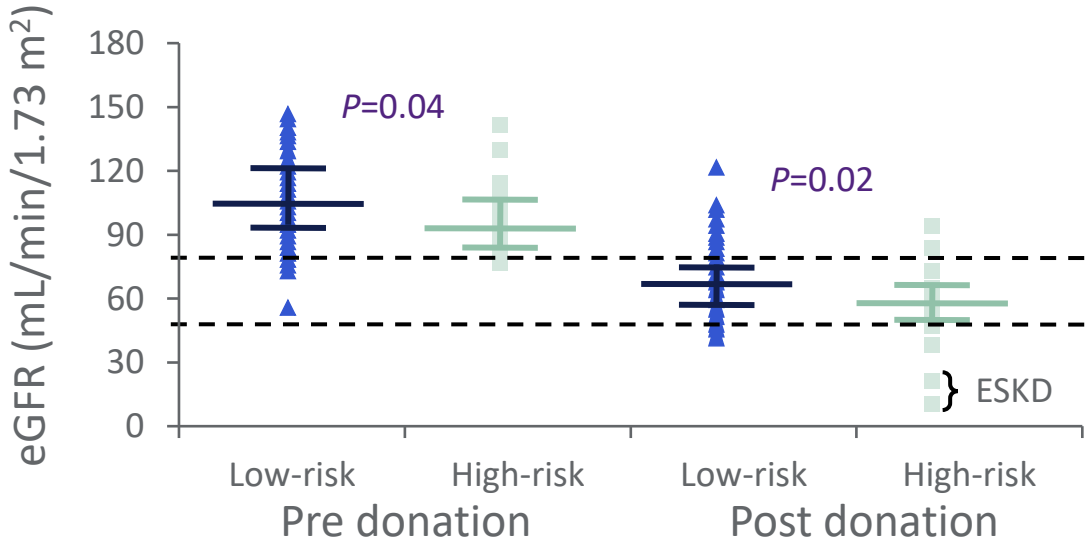


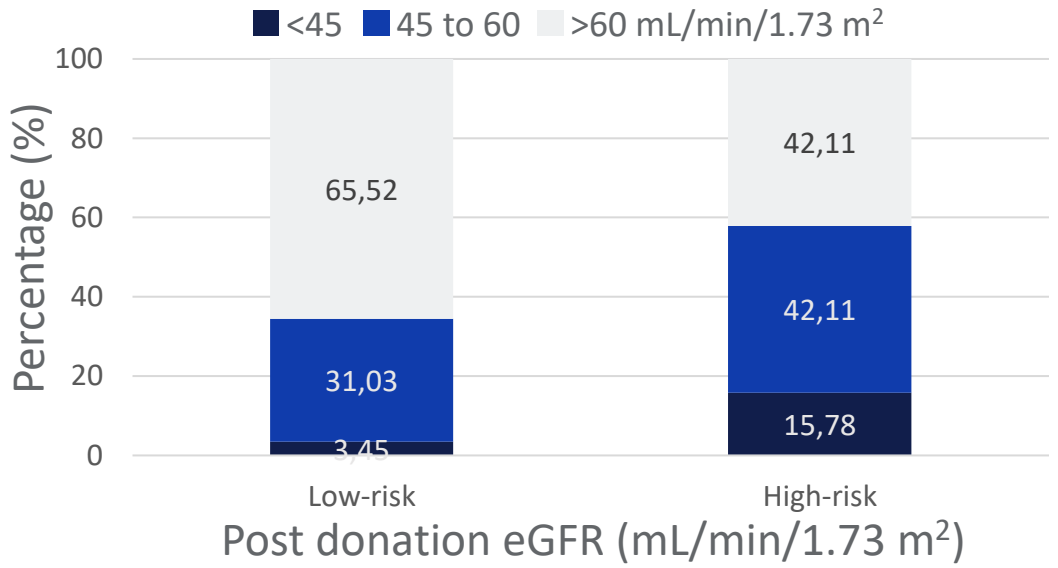
1 donneur développant une IRC et une PU 7 ans après don
Don à son frère jumeau: perte du greffon sur HSF 5 ans après

Kofman et coll, AJKD, 2014

APOL1 and kidney donation

- Observational cohort study of donors who donated a kidney between 1993-2010 at two US transplant centers:
  - 136 Black living donors with median follow-up 12 years and 78% first-degree relatives
  - 14% had 2 *APOL1* risk variants



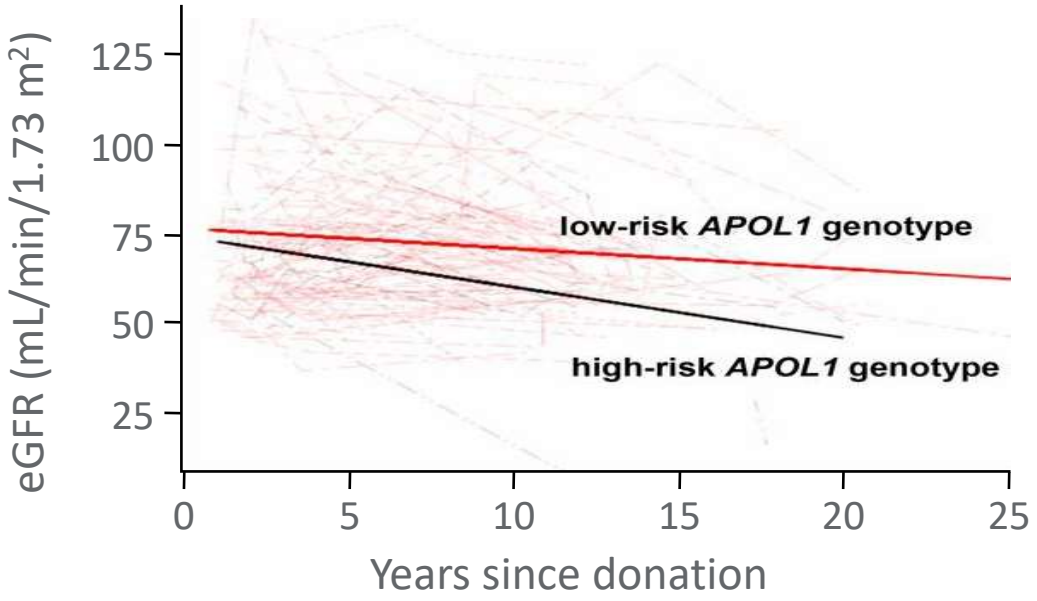


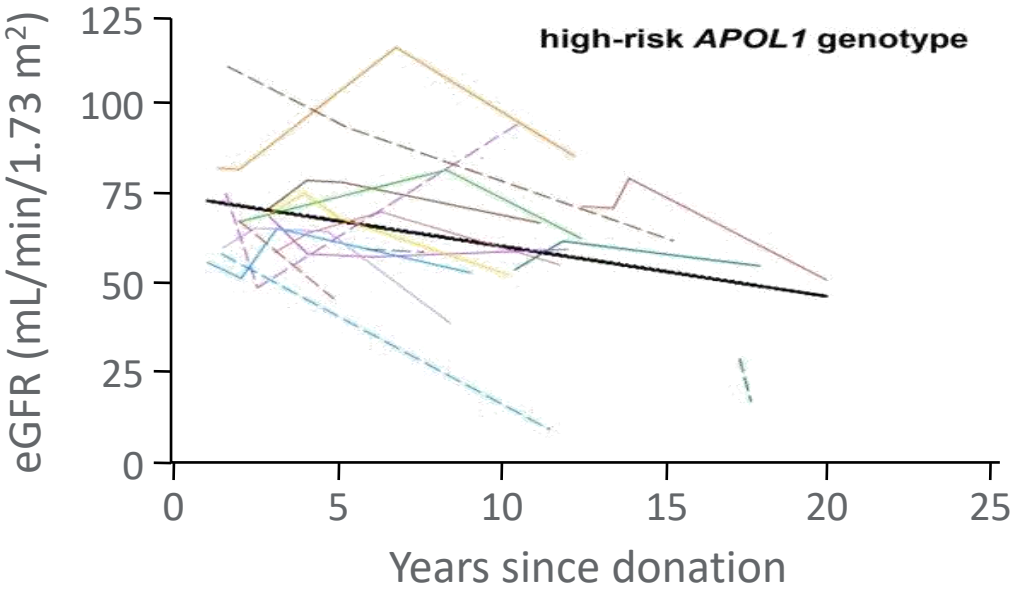
eGFR in donors with *APOL1* high-risk genotype was **10 mL/min lower pre and post donation** vs those with *APOL1* low-risk genotype

2 ESKD (10, 18 years) among 19 patients with *APOL1* high-risk genotype

Doshi MD, et al. *J Am Soc Nephrol*. 2018;29:1309-1316.

APOL1 and kidney donation

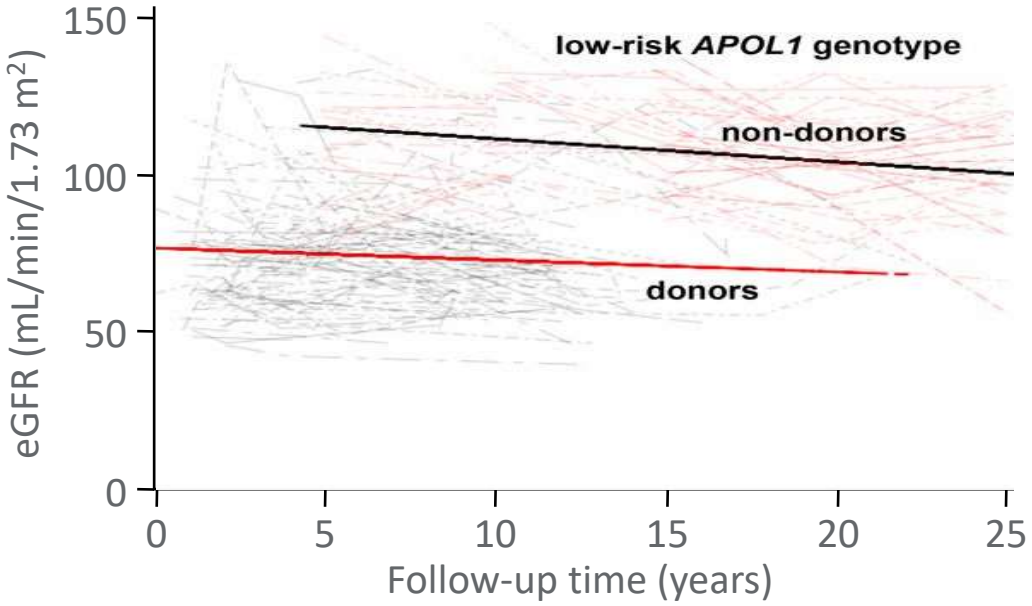


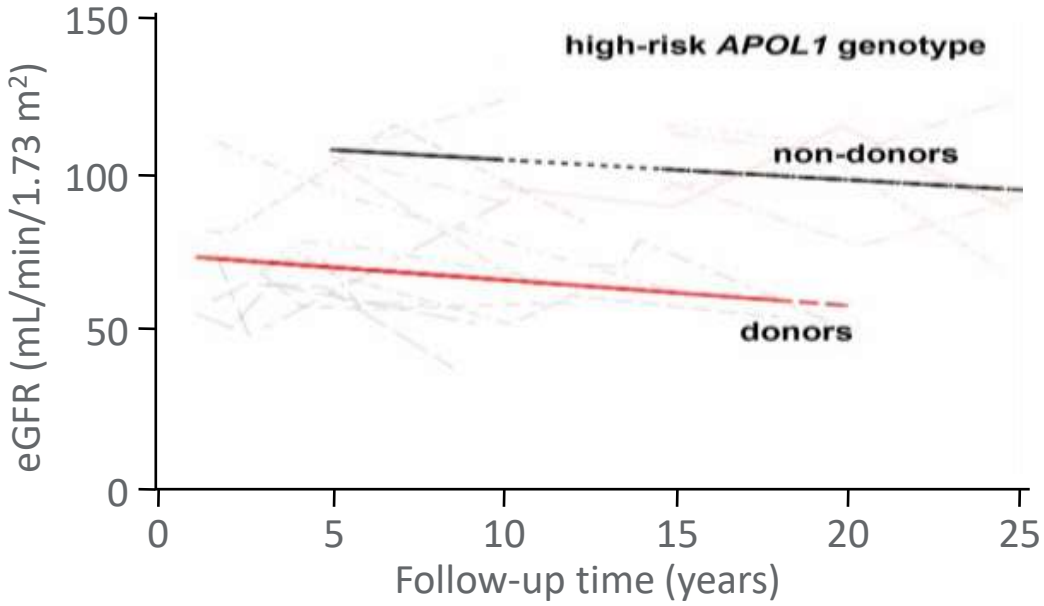


Rate of decline in post-donation eGFR is greater among donors with *APOL1* high-risk genotype versus *APOL1* low-risk genotype

Doshi MD, et al. *J Am Soc Nephrol*. 2018;29:1309-1316.

APOL1 and kidney donation





Given the mean age at donation was 37 years, 67% of these donors can be expected to have stage 3 or higher CKD by the age of 49 years, and more will progress to ESKD in middle age

Doshi MD, et al. *J Am Soc Nephrol*. 2018;29:1309-1316.

Etude donneurs vivants d'origine africaine en France

- Etude monocentrique rétrospective à Necker entre 2009 et 2016
- Doneurs de rein d'origine africaine
- Mesure DFG
- Mesure volume rénal par scanner
- Scintigraphie rénale
- Suivi 1 an post don
- Polymorphisme *APOL1*

Gaillard et al, Transplantation, 2018

Caractéristiques des donneurs

	White donors	African origin donors	P value
N	197	43	-
Female (%)	121 (61.4%)	22 (70.9%)	-
Age (years)	50.8 (11.0)	40.4 (13.3)	<0.0001
BSA (m^2)	1.79 (0.21)	1.89 (0.2)	0.01
BMI (kg/m^2)	24.6 (4.2)	27.5 (4.5)	0.0007
Baseline mGFR ($mL/min/1.73m^2$)	95.5 (14.3)	99.4 (11.3)	0.29
Baseline eGFR ($mL/min/1.73m^2$)	92.0 (13.4)	98.0 (16.0)	0.16

Gaillard et al, Transplantation, 2018

Rôle de *APOL1*

	APOL1 HR African origin donors	*APOL1* LR African origin donors	P Value
Number	7	31	
Female (%)	7 (100%)	22 (70.9%)	
Age (years)	47.2 (9.9)	40.4 (13.3)	0.15
BSA (m^2)	1.83 (0.25)	1.89 (0.2)	0.57
BMI (kg/m^2)	27.9 (5.9)	27.5 (4.5)	0.88
Baseline mGFR	90.5 (11.6)	99.4 (11.3)	0.09
Baseline eGFR	88.2 (20.9)	98.0 (16.0)	0.28
1 year eGFR	57.7 (11.5)	62.4	0.35

Gaillard et al, Transplantation, 2018

Donneurs *APOL1* bas risque

	White donors	*APOL1* LR African origin donors	P
Number	62	31	-
Female (%)	21 (61.4%)	22 (70.9%)	-
Age (years)	43.3 (12.2)	40.4 (13.3)	0.32
BMI (kg/m^2)	26.8 (4.5)	27.5 (4.5)	0.51
Baseline mGFR	97.4 (11.8)	99.4 (11.3)	0.45
Baseline eGFR	96.5 (14.4)	98.0 (16.0)	0.67

Gaillard et al, Transplantation, 2018

Analyse du gain fonctionnel rénal

	White donors	*APOL1* LR African origin donors	P value
1 year eGFR (mL/min/1.73m^2)	66.1 (14.1)	62.4 (12.9)	0.22
Relative eGFR loss (%)	31.5 (9.6)	35.9 (10.2)	0.04
Relative FG (%)	39 (23)	29 (24)	0.05
Absolute FG (mL/min/1.73m^2)	18.3 (11.2)	13.2 (10.9)	0.03

Gain fonctionnel (FG): eGFR 1 an post don – eGFR pré don du rein restant

Gaillard et al, Transplantation, 2018

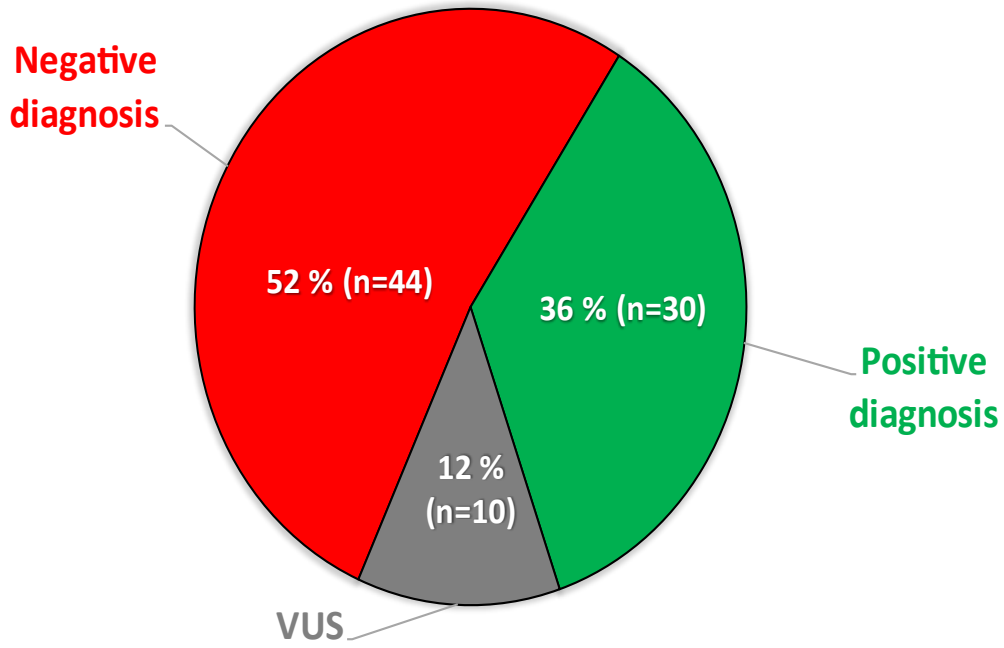
Volume rénal

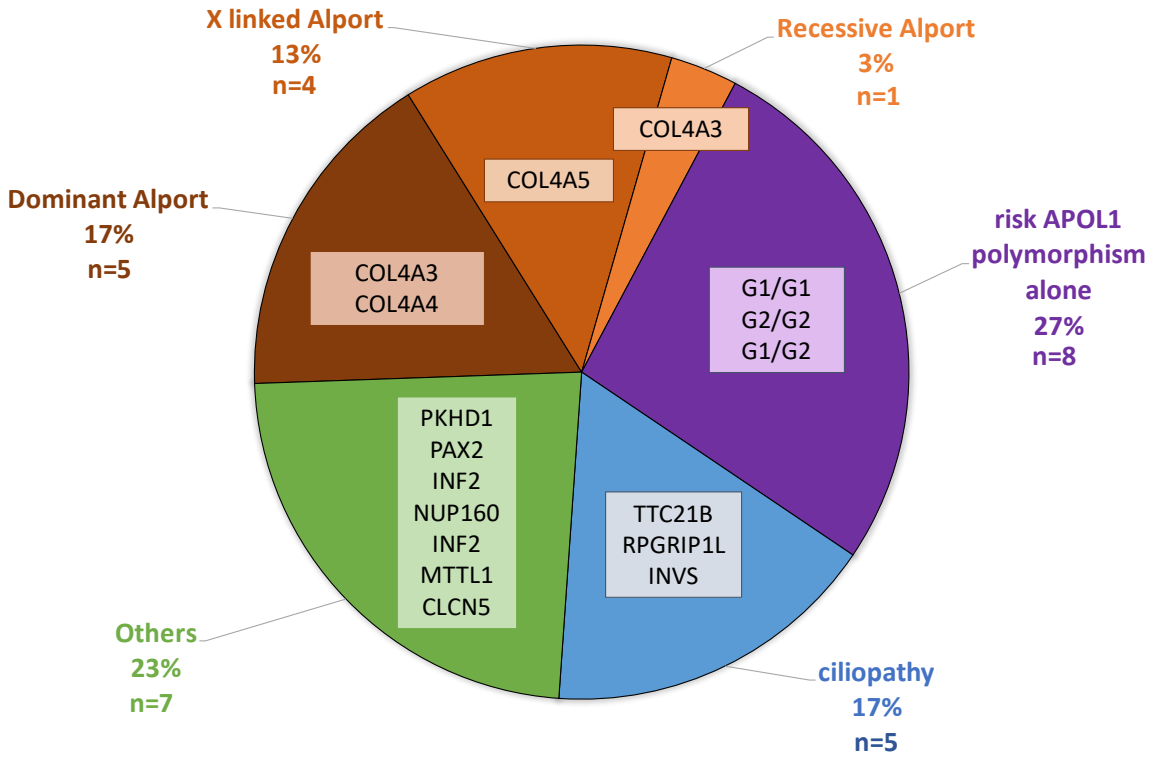
	White donors	*APOL1* LR African origin donors	P value
Left kidney volume (mL/1.73m²)	136.0 (23.9)	123.0 (24.3)	0.01
Right kidney volume (mL/1.73m²)	128.1 (19.4)	121.8 (19.9)	0.05
Total renal volume (mL/1.73m²)	264.2 (38.8)	245.3 (37.0)	0.02
Remaining kidney volume (mL/1.73m²)	130.3 (18.8)	122.4 (20.1)	0.04
mGFR/Vol	0.38 (0.06)	0.42 (0.1)	0.03

Gaillard et al, Transplantation, 2018

APOL1 in French recipients

84 patients referred to a pre transplantation nephro-genetic outpatients clinic and with molecular investigation at Necker Hospital between 2019 and 2023
Absence of initial diagnostic orientation, kidney failure <50 years and/or extra renal involvement and/or family history of CKD





Lemoal et al, manuscript in preparation

Apolipoprotein L1 Opinions of African American Living Kidney Donors, Kidney Transplant Patients, and Nonpatients

- 331 AA potential and former living kidney donors (LKDs), kidney transplant candidates and recipients, and nonpatients at 3 United States transplant programs about ApoL1 testing
- 72% felt that transplant programs should offer ApoL1 testing to AA potential LKDs
- 58% would undergo ApoL1 testing
- 81% of former LKDs would take the test now if offered
- Most transplant candidates expressed a low likelihood of accepting a kidney from a LKD (79%) or a deceased donor (67%) with the high-risk genotype.
- Strong support among LKDs and transplant patients for ApoL1 testing when evaluating potential kidney donors of African ancestry

Harris et al, J Surg Res, 2022

Impact of education on APOL1 testing attitudes

- 102 participants with self-reported African ancestry and positive family history of kidney disease
- Assessed views on *APOL1* testing before and after presentation of a set of potential benefits and drawbacks of testing and quantified the self-reported level of influence individual benefits and drawbacks had on participants' desire for testing in the proposed context of living donation
- 92% were aware of organ donation and more than half (56%) had considered living donation
- No significant change in response following presentation of the potential benefits and the drawbacks of APOL1 testing
- Across all participants, "becoming aware of the potential risk of kidney disease among your immediate family" was the benefit with the highest mean influence (3.3±1.4)
- The drawback with the highest mean influence (2.9±1.5) was "some transplant centers may not allow you to donate to a loved one"
- Importance of providing culturally-sensitive, comprehensive pre-test education to all individuals who are offered genetic testing

Nestor et al, Clin Transplant, 2022

APOL1 genotyping in kidney transplantation: to do or not to do, that is the question?

- Contra: screening all African Americans for HR APOL1 alleles may result in the exclusion of many potential donors (13% of African Americans), and unwittingly exacerbate known disparities among a vulnerable population who is already less likely to achieve transplantation, particularly live donor kidney transplantation
- Pro: physicians often order genetic testing to evaluate live kidney donor candidates whose relatives have Mendelian disorders. They exclude potential donors with causative variants. The only difference between these scenarios and *APOL1* is that KRVs are limited to African-derived populations and possessing a high-risk genotype translates into an approximate 20% likelihood of CKD. It is the obligation of transplant physicians to protect potential donors from serious outcomes.

Kumar et al, KI 2021; Freedman et al, KI, 2021

Considerations for genetic testing

- Evaluating ApoL1 Genetic Testing Policy Options for Transplant Centers: A Delphi Consensus Panel Project with Stakeholders:
  - Ask potential donors about African ancestry
  - make testing decisions only after discussion with donors
  - encourage disclosure of test results to relatives and organ recipients but do not require it
  - use test results to inform decision making, but never for unilateral decisions by transplant programs

- Autonomy in testing
- Education of patients
- Return of results
- Shared decision making

McIntosh et al, CJASN, 2024

APOL1 screening and ethical issues: French recommendations and KDIGO 2024

- KDIGO 2024:
  - Informed consent
  - Appropriate counselling support: informed decision making
  - Member of a population with known/suspected high prevalence
  - Kidney disease OR living donation OR relative with HR genotype
  - Only if APOL1 test results do not present significant risk of harm (benefits/risks)

- French recommendations: if donor<60 years, recommend not to donate

Conclusions

- Deacreased graft survival if *APOL1* HR donor
- More controverse about recipient *APOL1* genotype
- Increased risk of renal failure after kidney donation in *APOL1* HR genotype living donors
- *APOL1* genetic testing should be proposed with living kidney donors
- The National Institutes of Health (NIH) sponsored 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

Acknowledgments:

Genetic laboratory
U1163, Imagine Institute
Corinne Antignac
Olivier Gribouval
Olivia Boyer
Guillaume Dorval

Laurence Heidet

Adult and Pediatric Nephrology Departments,
Hôpital Necker

All French nephrologists

aude.servais@aphp.fr