

Live Kidney Donor Risk: Big Data and the New Calculators

Dorry Segev, MD, PhD
Professor of Surgery and Epidemiology
Associate Vice Chair, Department of Surgery
Director, Epidemiology Research Group in Organ Transplantation
Johns Hopkins University

"The only remaining problem was the ethical decision concerning the removal of a healthy organ from a normal person for the benefit of someone else. For the first time in medical history a normal healthy person was to be subjected to a major surgical operation not for his own benefit."

Joseph Murray, Nobel Lecture, 12/8/90

1965



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1965



2015



Questions We Want to Answer

- *Baseline risk*
(risk individual will have if doesn't donate)
- *Absolute risk*
(total risk individual faces if donates)
- *Attributable risk*
(extra risk individual faces if does donate)
- By race, age, sex, BMI, insurance, SES, etc?

Questions We Can Answer

- *Baseline risk*
Risk in “healthy non-donors”
- *Absolute risk*
Risk in donors
- *Attributable risk*
Difference between above two

Studying ESRD

- Rare event
 - Require thousands of donors to see one event
 - Require tens of thousands to estimate the risk with any degree of confidence, for any subgroups
 - Require a non-self-reported source
(Most centers lose touch with donors)
 - Require national representation
(Low-volume centers, various demographics)

Ibahim/Matas NEJM 2009

- 3698 living donors single center 1963-2007; 99% Caucasian
- ESRD ascertainment through donor followup
- 11 cases of ESRD (1.8 per 10,000 person-years); 3 were non-Caucasian
- All donors with ESRD were biologically related to recipient

Mjoen et al, Kidney Int 2014

- 1901 living kidney donors 1963-2007 (single center performing all donations in Norway)
- 368 marginal donors excluded (hypertension, BMI>30, eGFR<70, macroalbuminuria, age>70)
- Followup through 2010
- Controls: Norwegian cohort enrolled 1984-87; included only self-reported health as "good" or "excellent"; excluded obese, SBP>140, DM, cardiovascular disease

Mjoen et al, Kidney Int 2014

- Nine cases of ESRD in LD (3.0 per 10,000 py); all biologically related to recipient

Kidney donation	11.38 (4.37–29.63, $P < 0.001$)
Inclusion year	0.90 (0.82–0.99, $P = 0.03$)
Age, years	1.02 (0.99–1.05, $P = 0.13$)
Male	0.90 (0.43–1.88, $P = 0.77$)
Systolic BP	1.01 (1.00–1.06, $P = 0.03$)
Smoking	1.19 (0.51–2.76, $P = 0.68$)
BMI	1.13 (0.96–1.32, $P = 0.14$)



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OPTN Live Donor Registry

- Every single live donor in the US since 1988
- Currently N>112,000
- Advantages: massive, unbiased
- Disadvantages:
 - Incomplete, limited-term outcome capture
 - But... SSN captured since 1994 – linkage
- Medicare (CMS)
- Social Security (SSDMF)

NHANES-III

- Interviews, physical examination, and laboratory tests of 20,024 adults and 13,000 children administered by medical personnel
- Very detailed initial visits
- Can identify “healthy non-donors”
- Cross-sectional: no follow-up (except linkage)
- Medicare (CMS)
- Social Security (SSDMF)

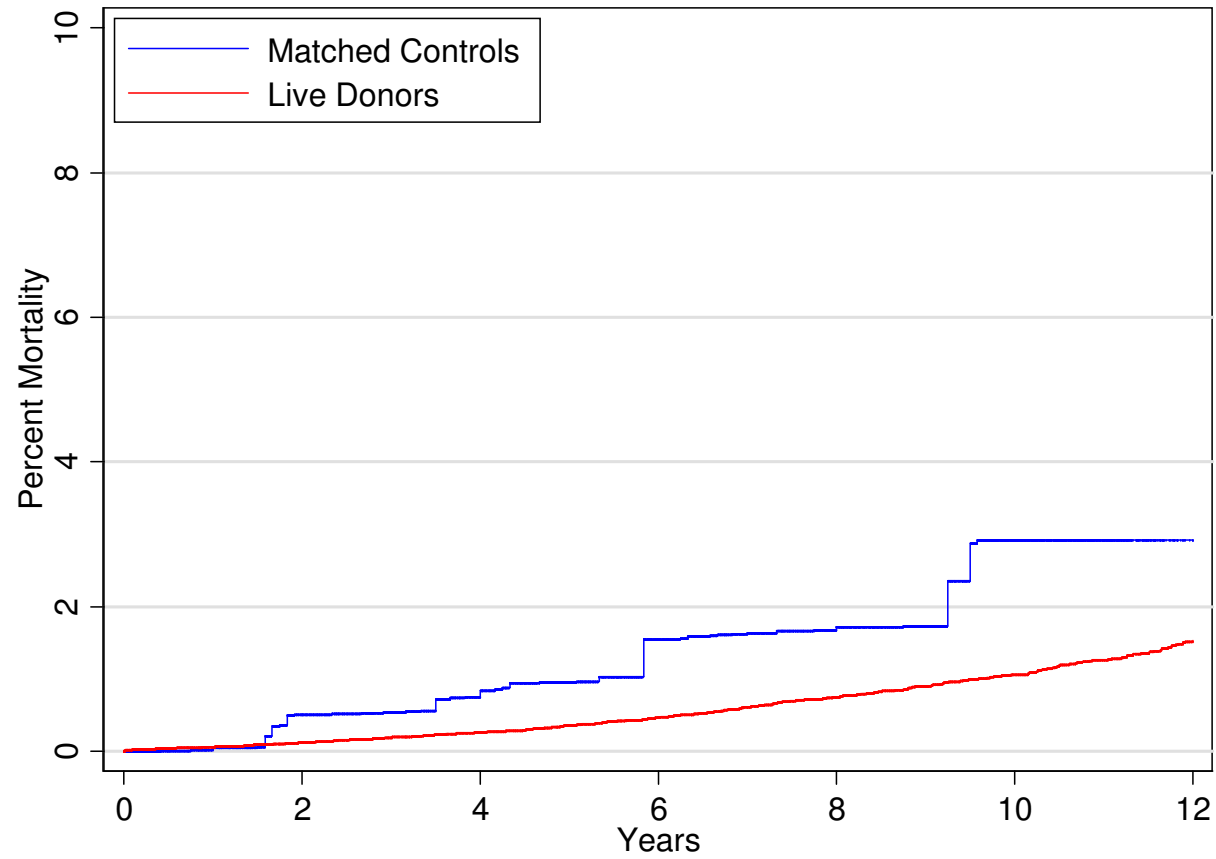
Live Kidney Donors: Mortality

- Size (N=80,347 -- previous study was 3700 donors: Ibrahim NEJM)
 - Powered for narrow confidence interval
 - Powered for subgroup estimates
- Generalizability (all U.S. centers represented, not just large-volume academic centers)
- Diversity (previous study was 98% Caucasian, national cohort was 27% non-Caucasian)

Segev, JAMA, 2010

Characteristic	Subgroup	90-day Mortality Rate	P-value
Overall		3.1 (2.0-4.6) per 10,000	
Age (years)	18-39	3.0 (1.6-5.3)	0.5
	40-49	3.7 (1.7-7.0)	
	50-59	1.5 (0.2-5.4)	
	>=60	6.6 (0.8-23.9)**	
Sex	Men	5.1 (3.0-8.2)	0.007
	Women	1.7 (0.7-3.4)	
Race/Ethnicity	Caucasian	2.6 (1.4-4.2)	0.04
	African American	7.6 (3.3-15.0)	
	Hispanic	2.0 (0.2-7.3)	
Hypertension	No	1.3 (0.4-3.4)	<0.001
	Yes	36.7 (4.4-132.6)**	

Segev, JAMA, 2010



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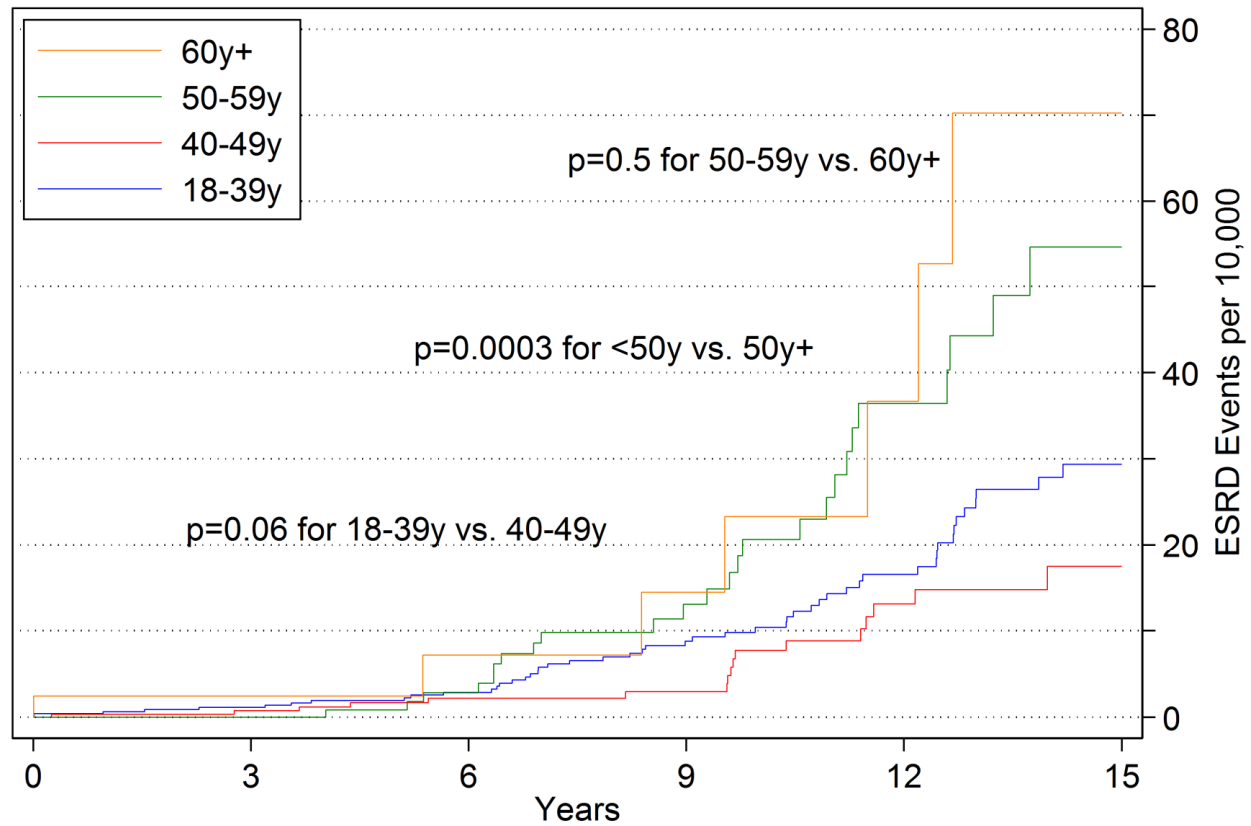
Segev, JAMA, 2010

Live Kidney Donors: ESRD

- Size (N=96,217)
 - Powered for narrow confidence interval
 - Powered for subgroup estimates
- Generalizability (all U.S. centers)
- Racial Diversity
- Proper comparison group
 - All previous studies had compared with “general population”

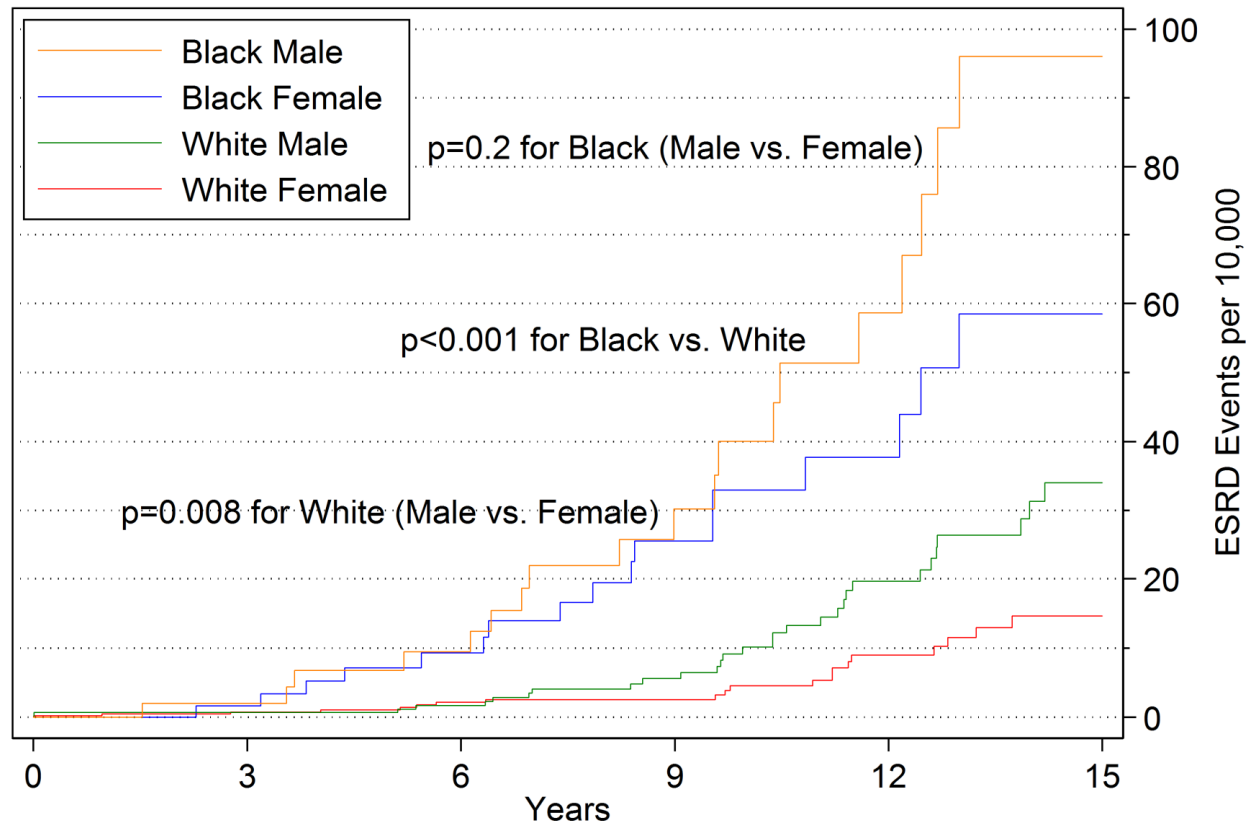
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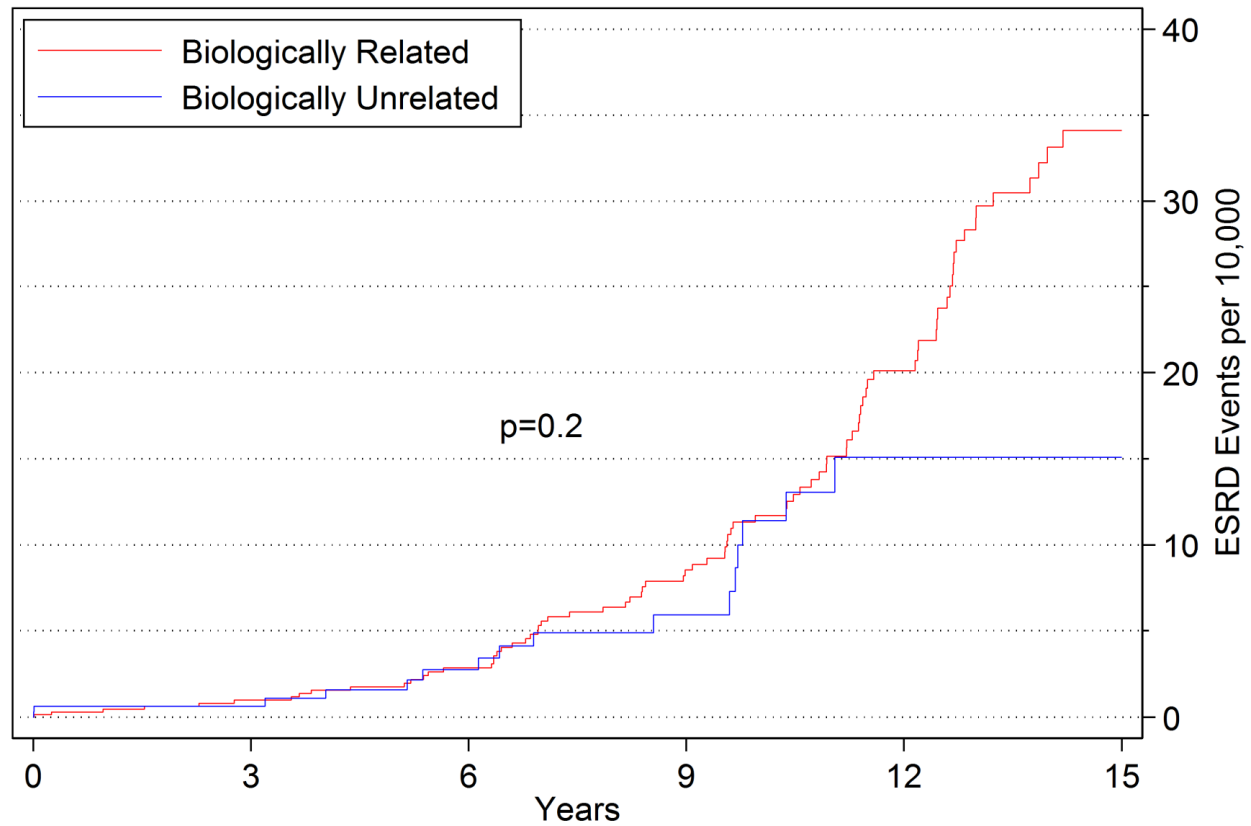
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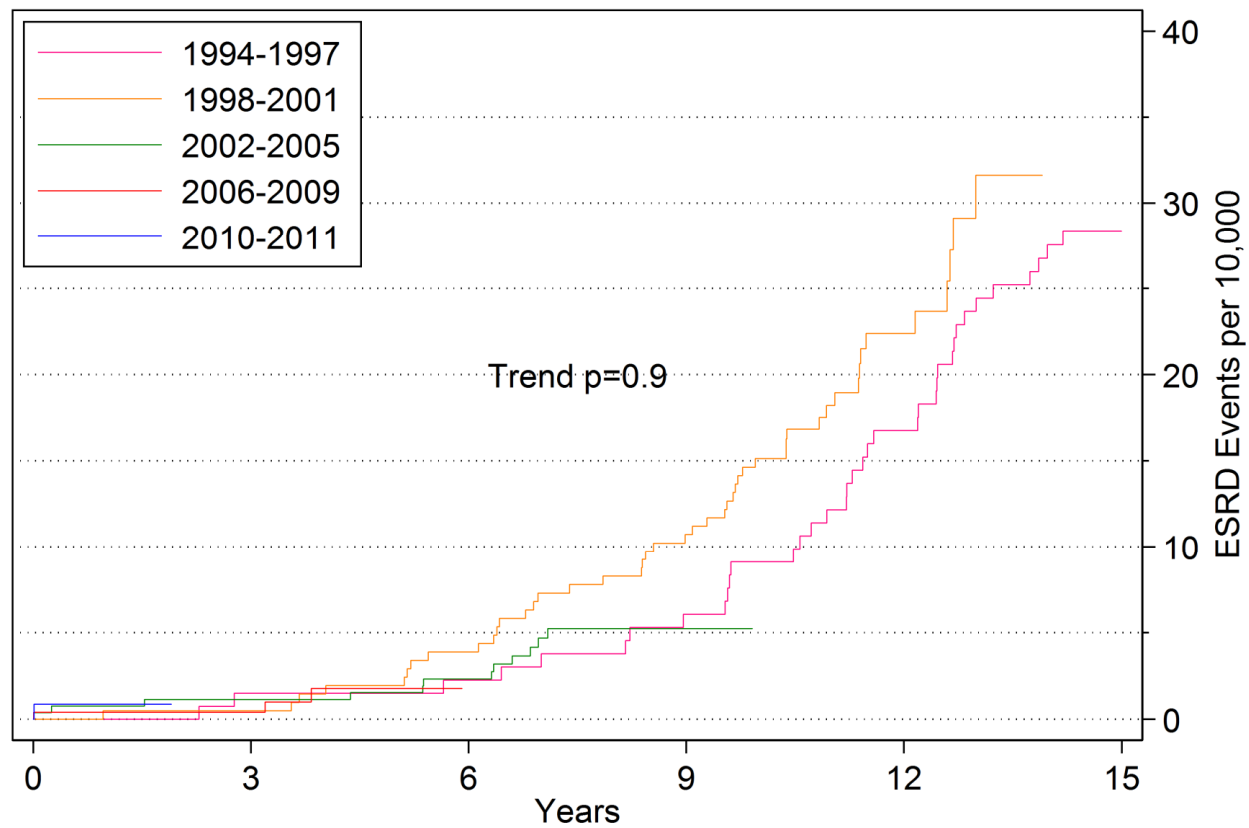
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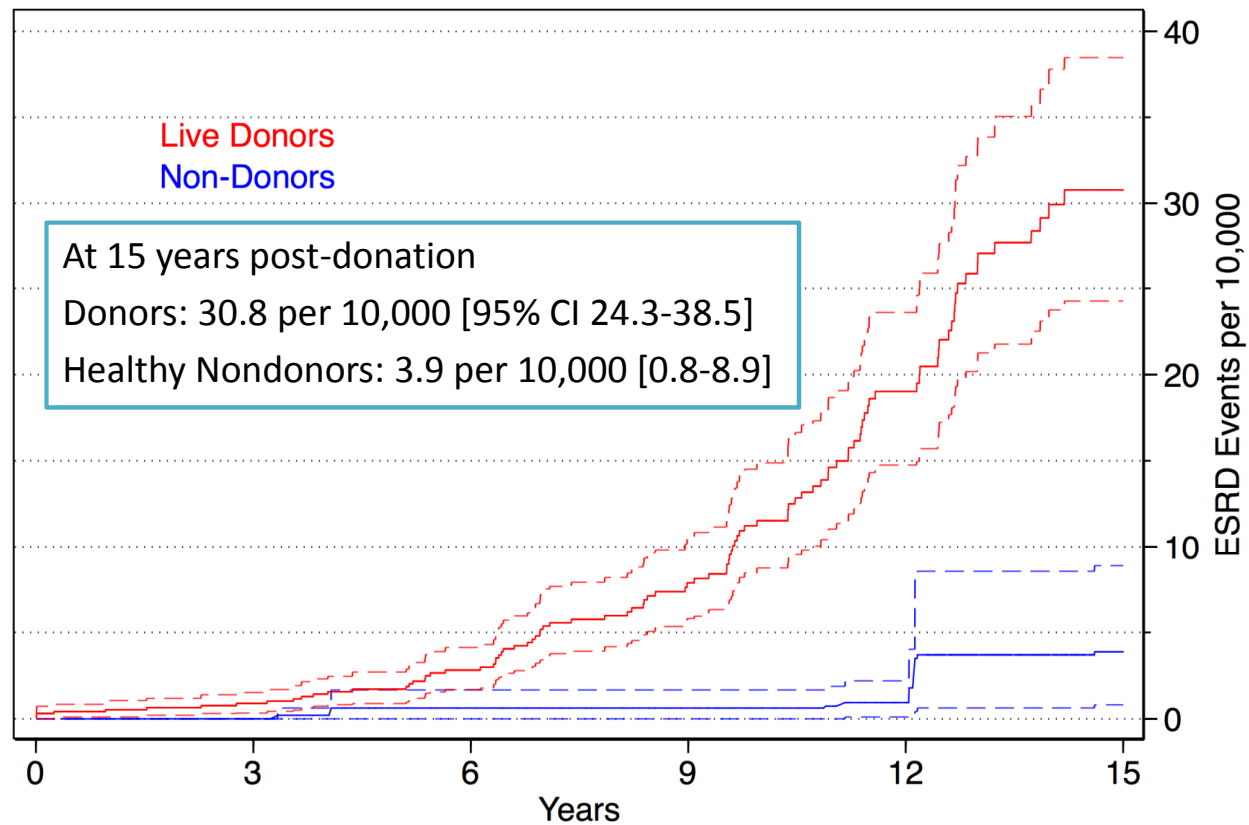
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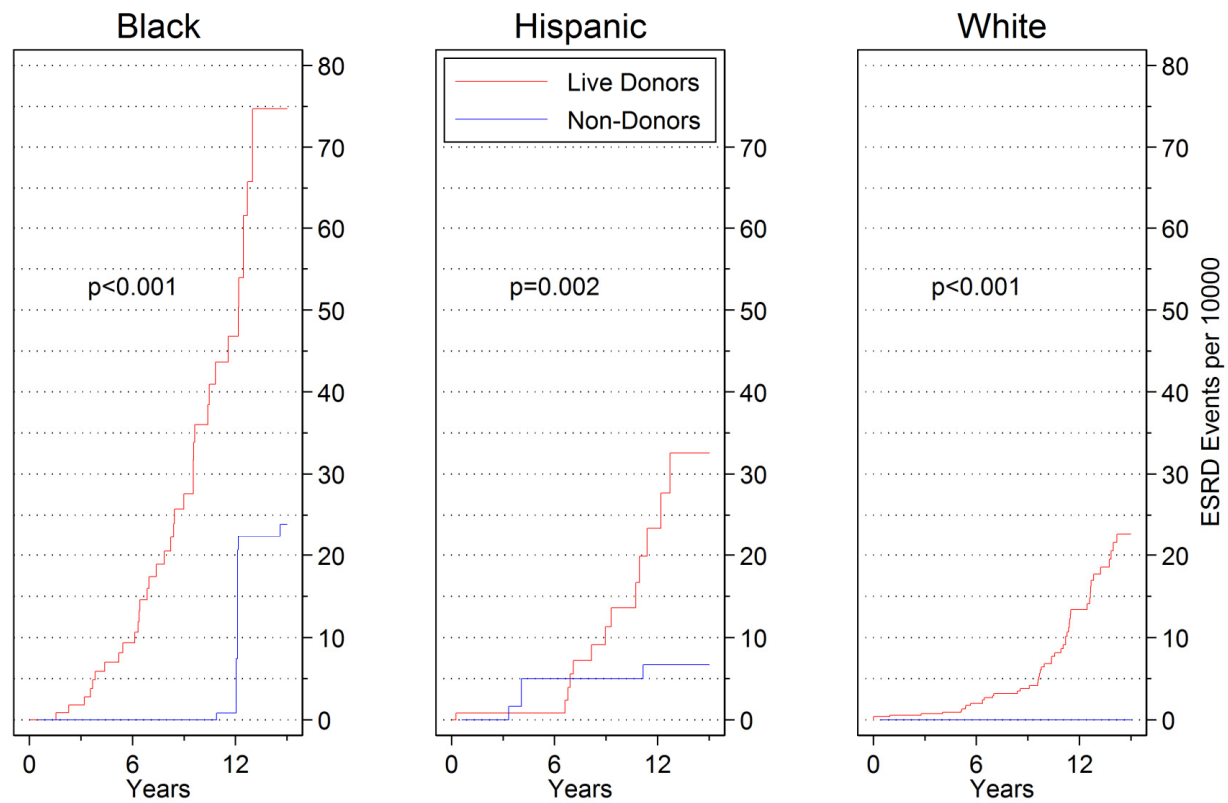
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Attributable Risk

- “Extra risk” at 15y post-donation
 - Black:
 - $74.7 [47.8-105.8] - 23.9 [1.6-62.4] = 50.8$ per 10,000
 - Hispanic:
 - $32.6 [17.9-59.1] - 6.7 [0.0-15.0] = 25.9$ per 10,000
 - White:
 - $22.7 [15.6-30.1]$

Muzaale/Segev, JAMA, 2014

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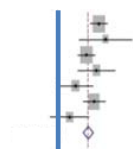
The NEW ENGLAND JOURNAL *of* MEDICINE

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FEBRUARY 4, 2016

VOL. 374 NO. 5

Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate



CKD Prognosis
Consortium



Grams et al, NEJM, 2016

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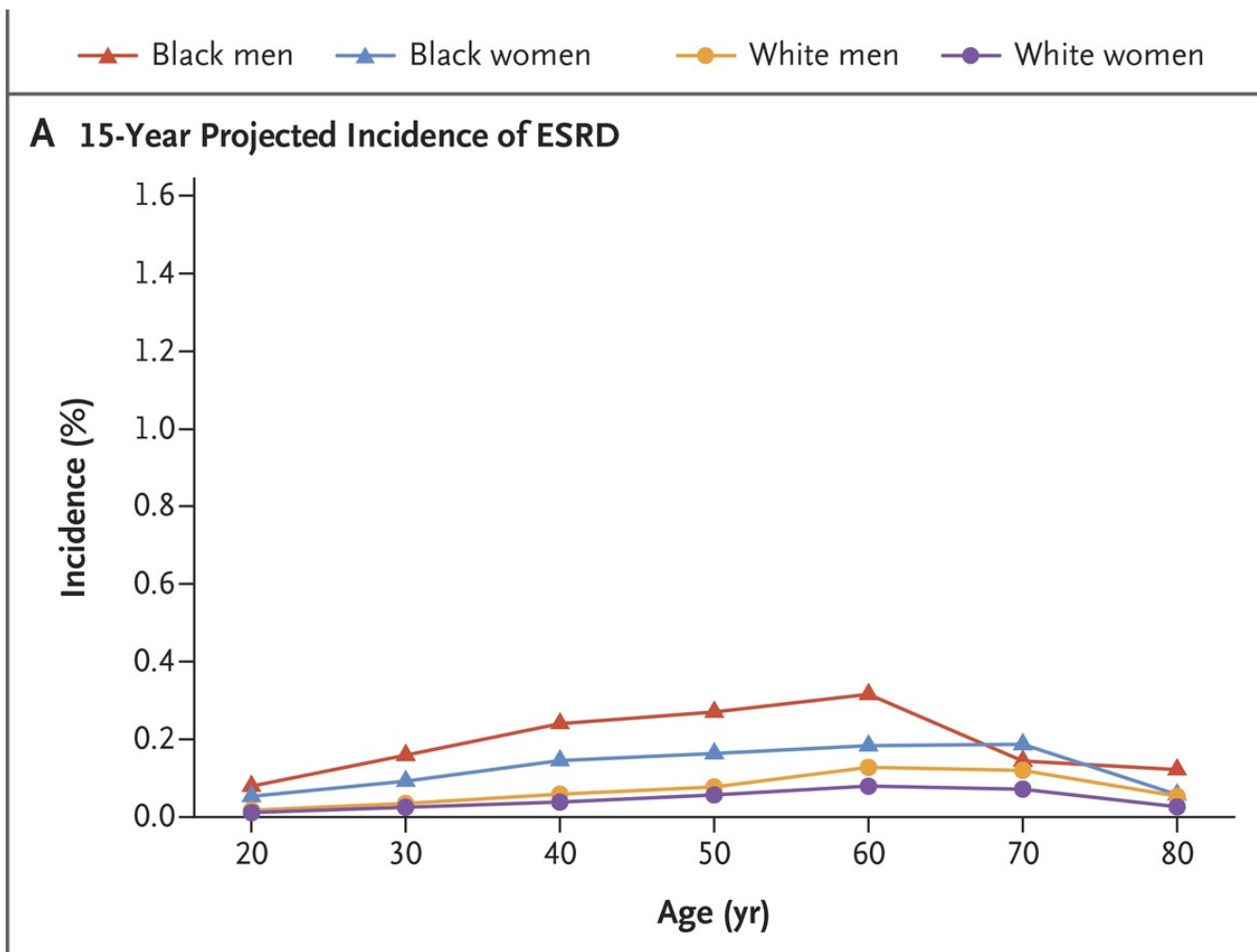
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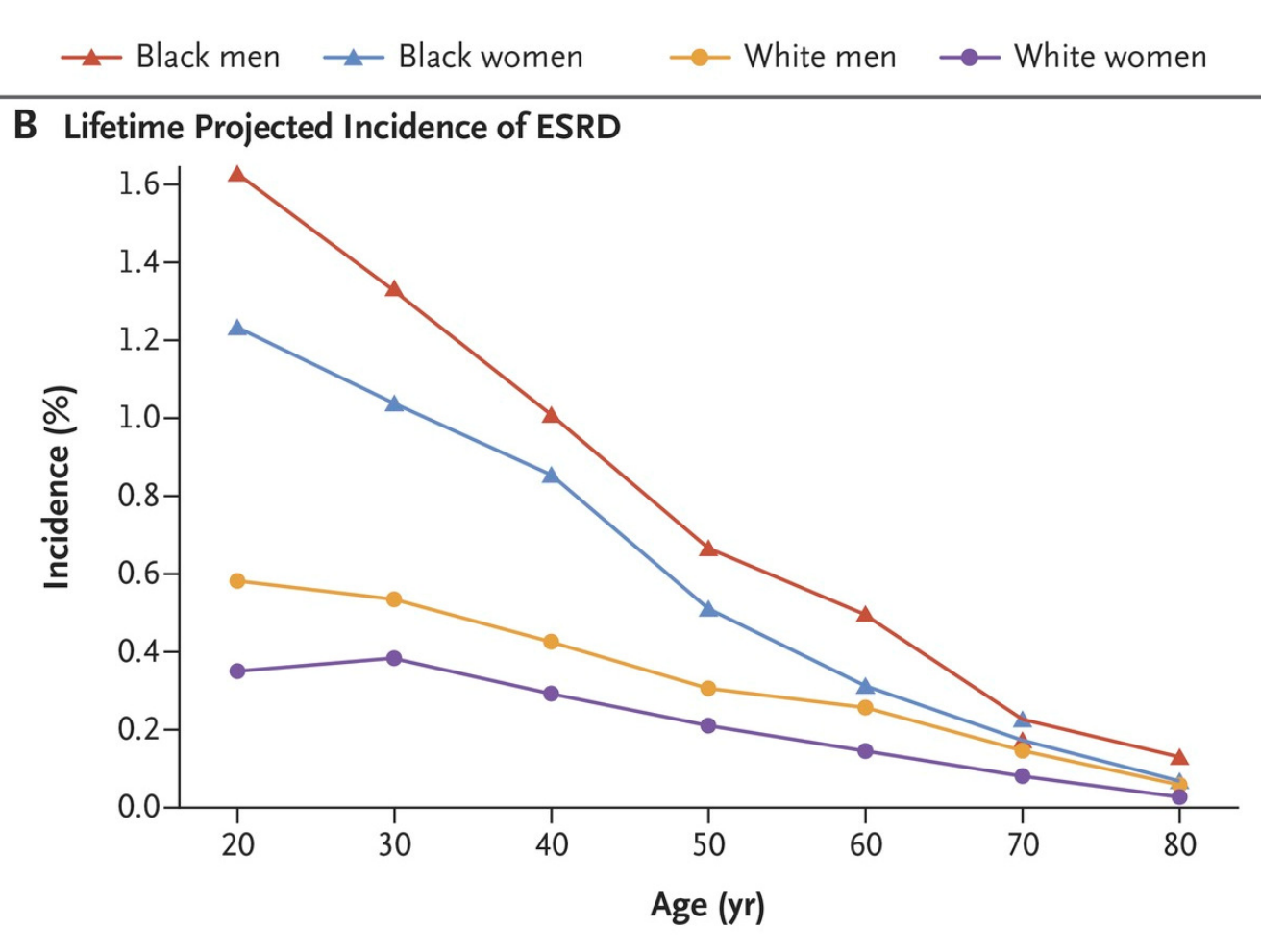
FEBRUARY 4, 2016

VOL. 374 NO. 5

- ACR 4 mg/g
- SBP 120 mmHg
- No diabetes
- No hypertension meds
- Non-smoker
- BMI 26

Age	Base-case eGFR
20	114
30	106
40	98
50	90
60	82
70	74
80	66





Base Case

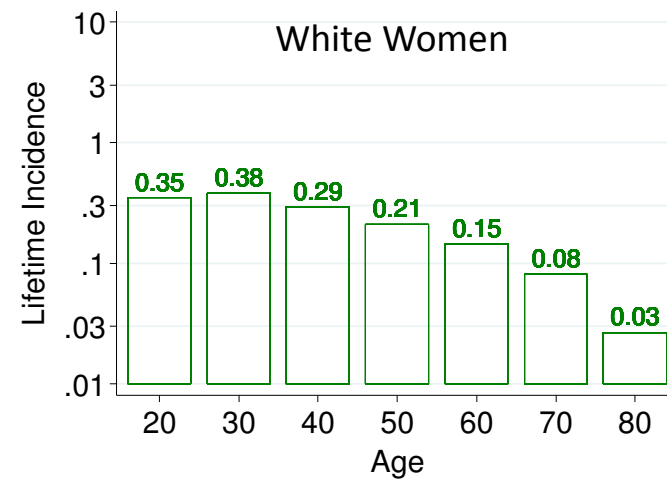
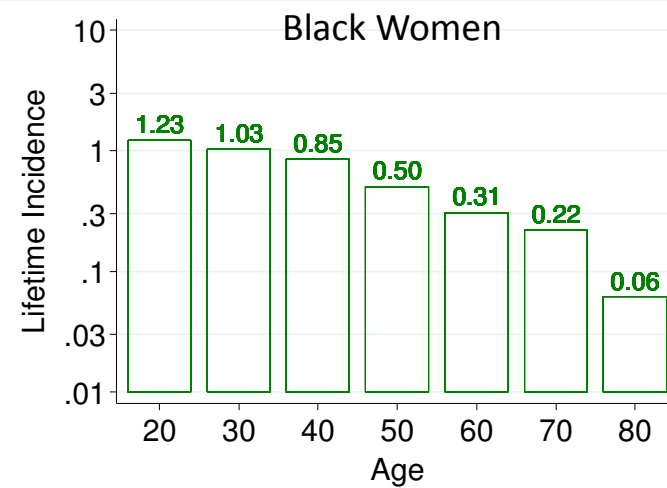
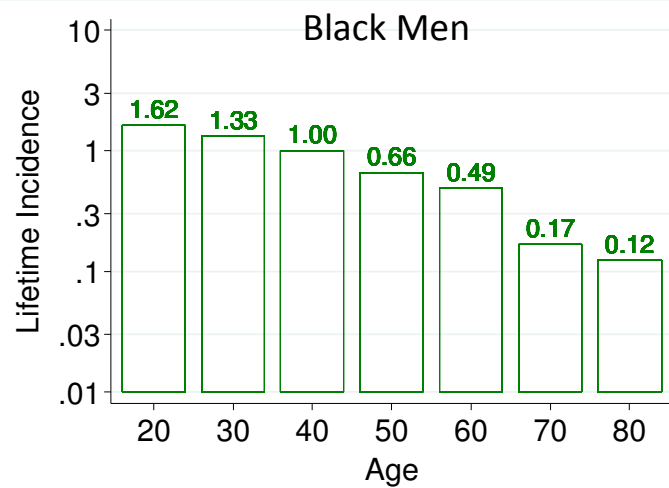
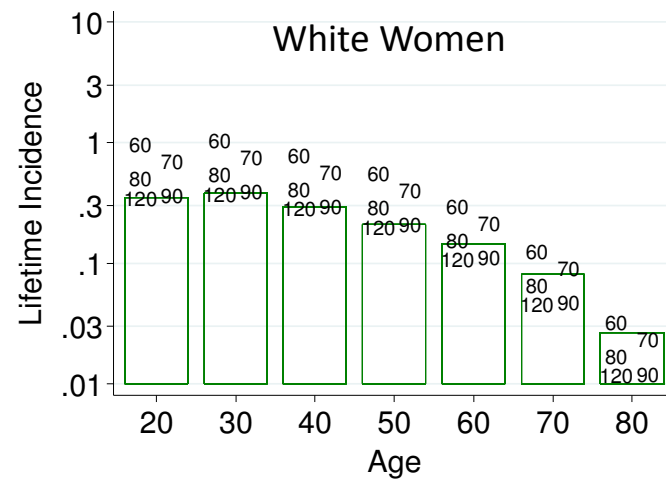
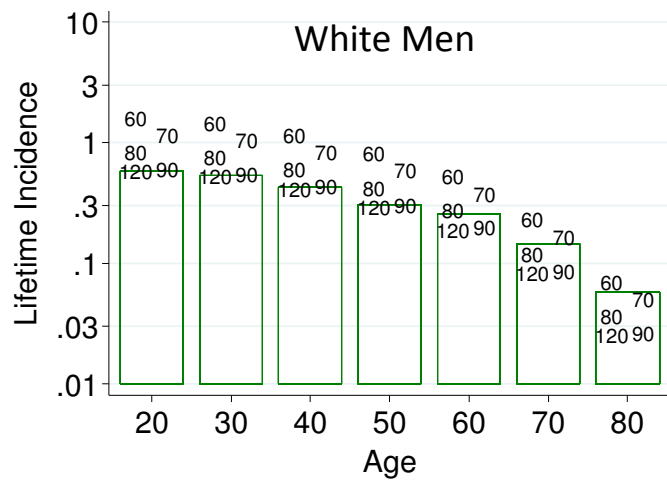
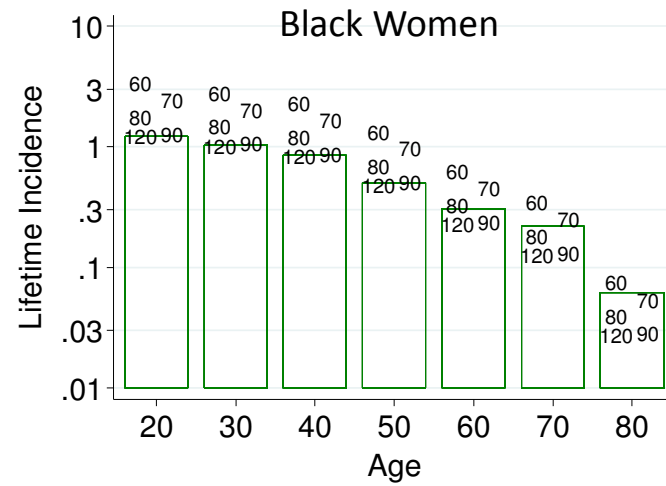
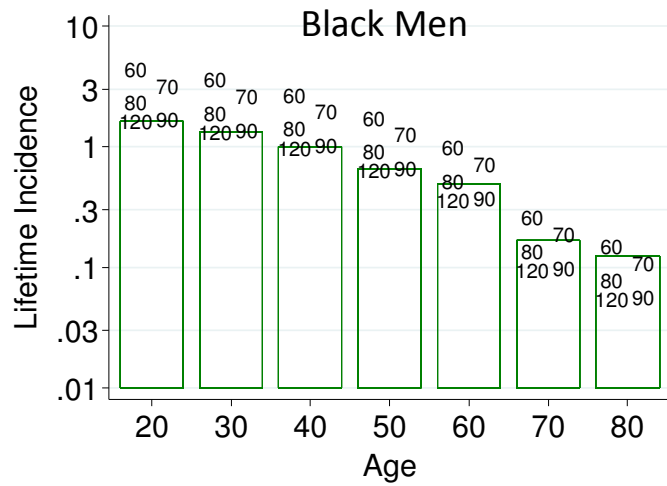


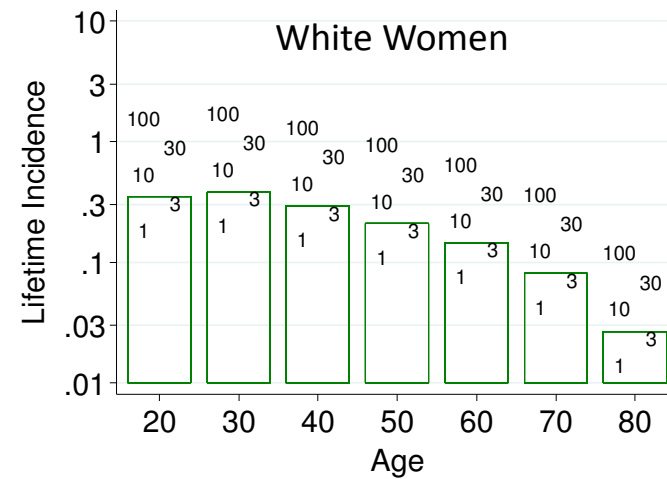
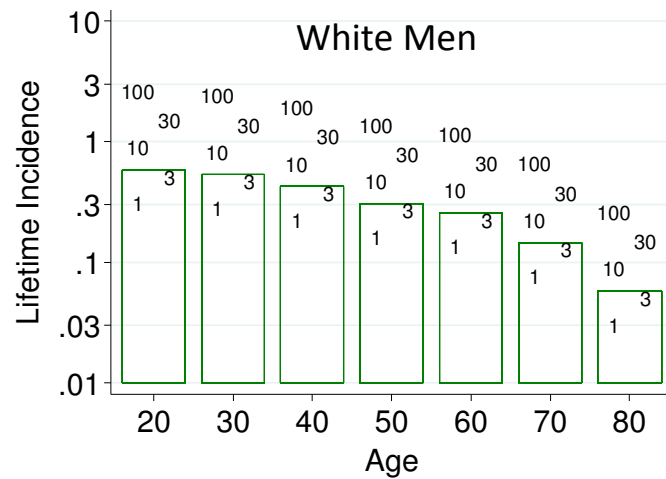
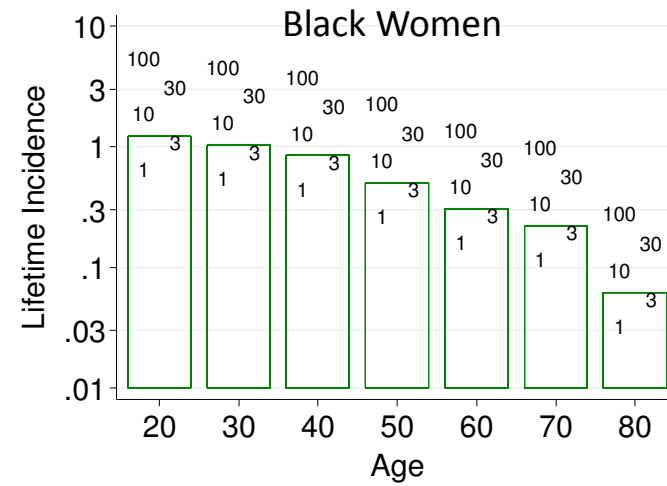
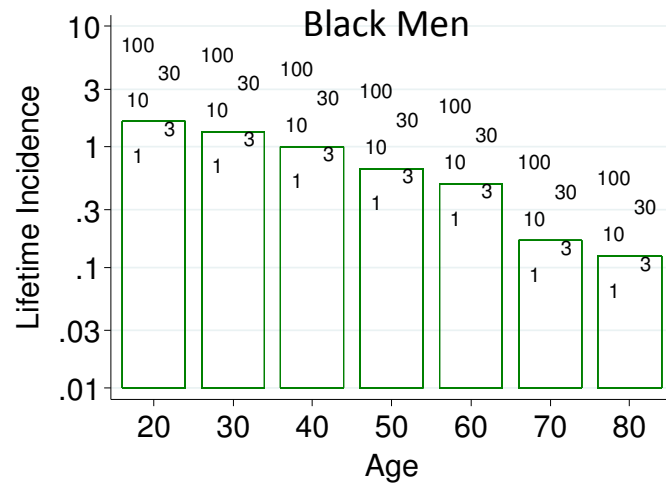
Table 2. Meta-Analysis of Multivariable-Adjusted Hazard Ratios That Estimate the Association of Baseline Characteristics with ESRD.*

Characteristic	Hazard Ratio (95% CI)	$\beta \pm SE$	Population Cohort						
			NHANES	ARIC	VA	ICES KDT	Maccabi	Mount Sinai	Geisinger
eGFR per decrease of 15 ml/ min/1.73 m ²									
<60 ml/min/1.73 m ²	6.61 (4.87–8.96)	1.89±0.16	12.82 (0.35–463.68)	6.66 (1.85–23.97)	NA	10.47 (6.75–16.24)	6.00 (4.74–7.60)	2.47 (0.64–9.55)	5.50 (3.25–9.30)
60–89 ml/min/1.73 m ²	1.63 (1.53–1.74)	0.49±0.03	1.05 (0.33–3.36)	1.51 (1.01–2.25)	1.50 (1.32–1.70)	1.59 (1.39–1.82)	1.72 (1.54–1.93)	1.65 (1.03–2.64)	1.85 (1.51–2.26)
90–119 ml/min/1.73 m ²	1.02 (0.85–1.23)	0.02±0.09	0.83 (0.32–2.14)	1.67 (0.87–3.20)	0.98 (0.81–1.17)	0.77 (0.68–0.88)	0.96 (0.81–1.15)	1.35 (0.81–2.27)	1.27 (0.99–1.62)
≥120 ml/min/1.73 m ²	0.79 (0.56–1.10)	−0.24±0.17	1.18 (0.47–2.94)	NA	0.50 (0.34–0.72)	1.62 (1.04–2.52)	0.72 (0.52–1.00)	0.82 (0.45–1.47)	0.59 (0.47–0.75)
Systolic blood pressure, per increase of 20 mm Hg	1.42 (1.27–1.58)	0.35±0.06	2.90 (1.74–4.82)	1.40 (1.04–1.88)	1.27 (1.15–1.41)	NA	1.45 (1.33–1.57)	1.29 (0.91–1.84)	1.47 (1.25–1.72)
Antihypertensive drug use	1.35 (1.01–1.82)	0.30±0.15	0.31 (0.07–1.31)	1.18 (0.74–1.88)	1.17 (1.01–1.36)	NA	1.90 (1.68–2.16)	2.04 (1.19–3.49)	1.16 (0.90–1.49)
Noninsulin-dependent diabetes mellitus	3.01 (1.91–4.74)	1.10±0.23	9.73 (2.97–31.88)	2.95 (1.79–4.85)	NA	NA	2.21 (1.97–2.48)	1.49 (0.79–2.81)	4.50 (3.45–5.88)
Body-mass index, per 5-point increase									
≤30	0.98 (0.81–1.17)	−0.02±0.09	2.40 (1.11–5.21)	1.20 (0.74–1.95)	0.91 (0.80–1.02)	NA	NA	0.94 (0.62–1.40)	0.87 (0.71–1.08)
>30	1.16 (1.04–1.29)	0.15±0.05	0.95 (0.40–2.24)	1.30 (0.95–1.79)	1.26 (1.13–1.40)	NA	NA	0.99 (0.83–1.18)	1.18 (1.06–1.30)
Smoking status									
Former smoker	1.45 (1.23–1.71)	0.37±0.08	1.98 (0.73–5.37)	1.75 (1.02–3.00)	NA	NA	1.35 (1.03–1.79)	1.12 (0.62–2.02)	1.51 (1.18–1.94)
Current smoker	1.76 (1.29–2.41)	0.57±0.16	4.44 (1.49–13.27)	3.51 (1.81–6.78)	NA	NA	1.35 (1.17–1.56)	1.42 (0.77–2.63)	1.60 (1.22–2.09)
Urinary albumin-to-creatinine ratio, per increase of 10×	2.94 (0.99–8.75)	1.08±0.56	5.48 (2.37–12.71)	1.80 (1.26–2.56)	NA	NA	NA	NA	NA

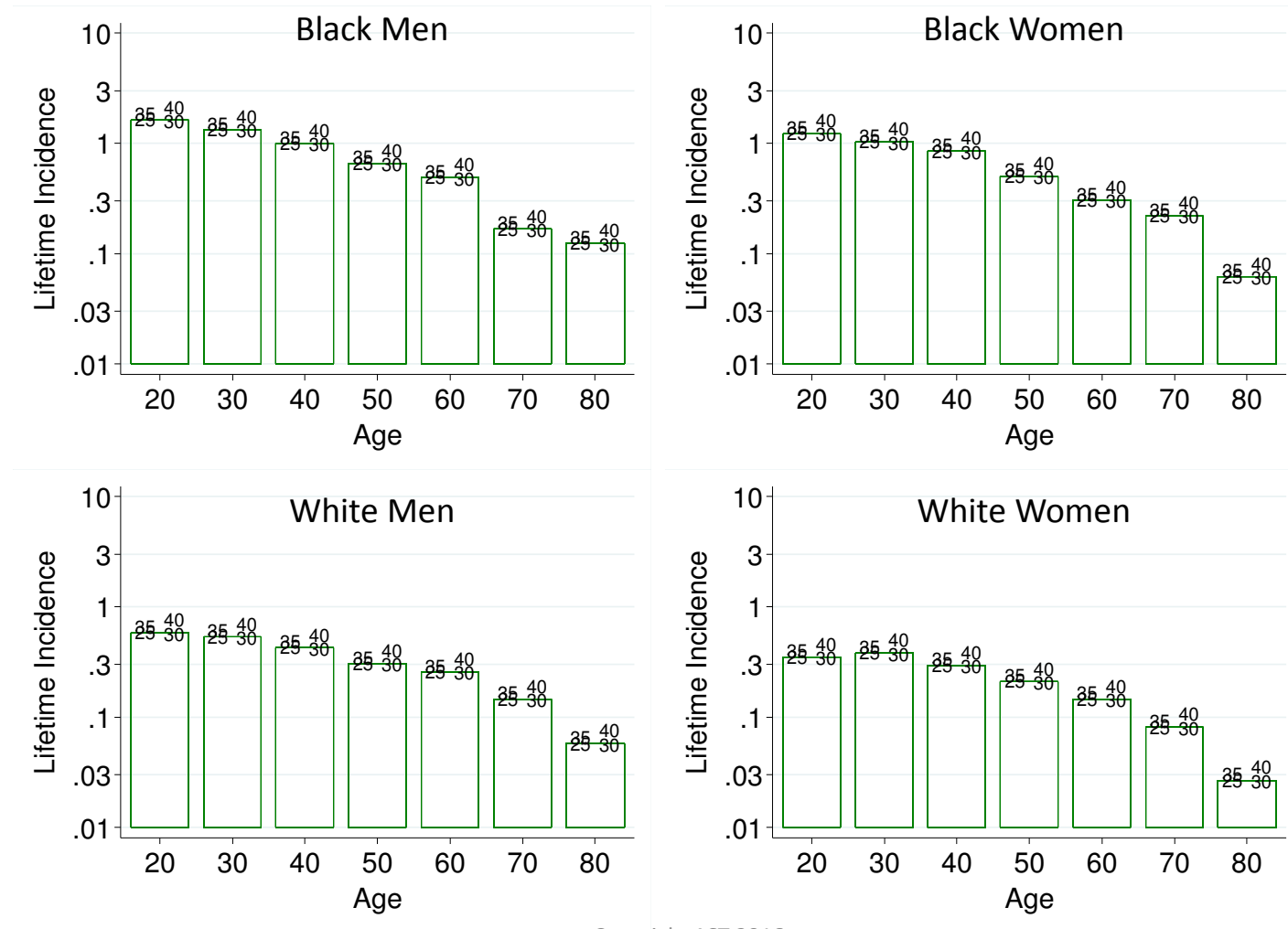
eGFR



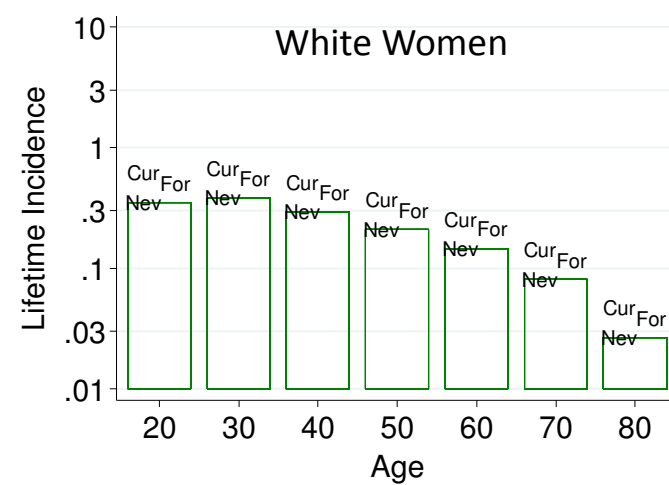
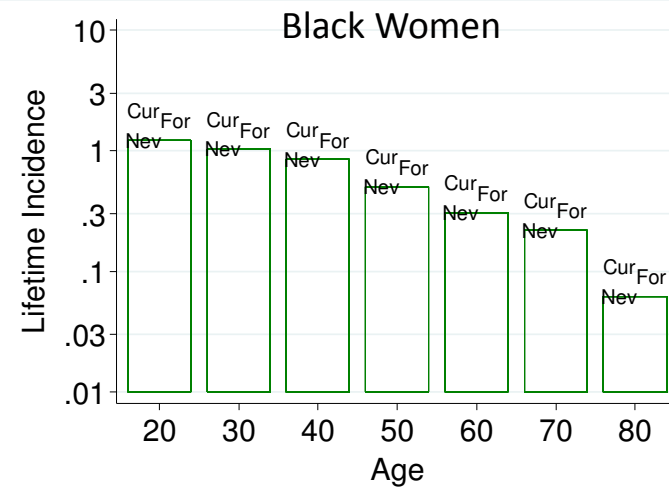
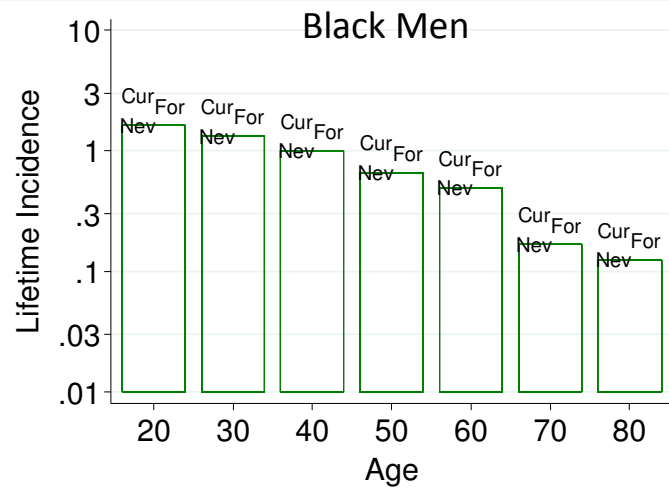
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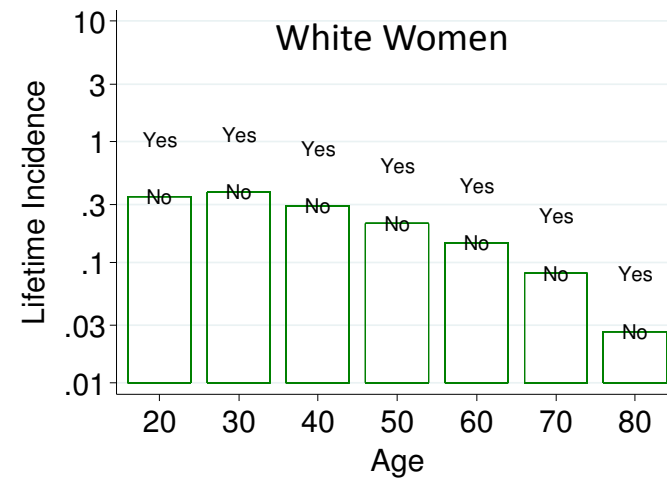
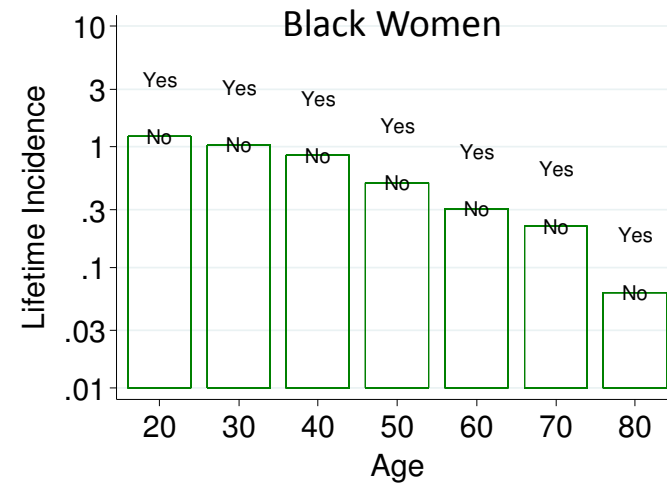
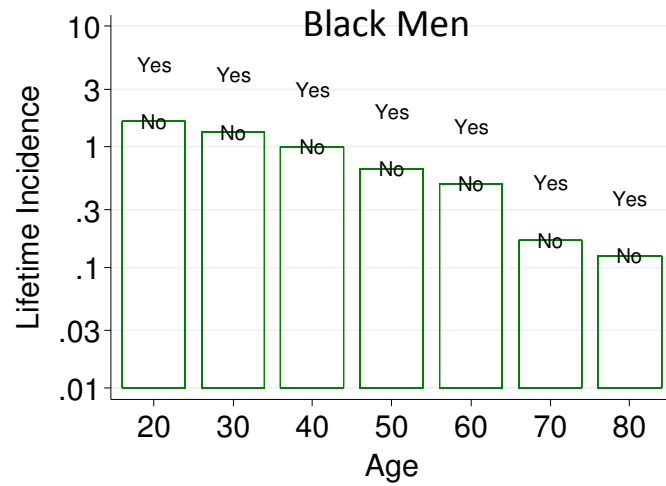
BMI



Smoking



NIDDM



ESRD Risk Tool for Kidney Donor Candidates

Projected Incidence of End-Stage Renal Disease:

0.04%

Pre-Donation 15-Year*

0.30%

Pre-Donation Lifetime*

?

Post-Donation 15-Year**

?

Post-Donation Lifetime**

blue: < 1%, green: 1-2%, yellow: 2-3%, orange: 3-5%, red: >5%

The pre-donation risks represent projections if a person does not donate a kidney. Details about estimating post-donation risk are provided below.

Patient Characteristics:

Age (18-80yrs)

40

Gender

Female

Race (White or Black)

White

eGFR (mL/min/1.73m²)

90

Systolic Blood Pressure (mmHg)

120

Hypertension Medication

No Medication

BMI (kg/m²)

25

Non-Insulin Dependent Diabetes

No Diabetes

Urine Albumin to Creatinine (mg/g)

click on units to change between mg/g and mg/mmol

4

Smoking History

Non-Smoker

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Millions of
healthy/CKD
patients

transplantmodels.com/esrisk

ESRD Risk Tool for Kidney Donor Candidates

Projected Incidence of End-Stage Renal Disease:

0.04%

Pre-Donation 15-Year*

0.30%

Pre-Donation Lifetime*

?

Post-Donation 15-Year**

?

Post-Donation Lifetime**

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Patient Characteristics:

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Gender

Female

Race (White or Black)

White

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90

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120

Hypertension Medication

No Medication

BMI (kg/m²)

25

Non-Insulin Dependent Diabetes

No Diabetes

Urine Albumin to Creatinine (mg/g)

4

click on units to change between mg/g and mg/mmol

Smoking History

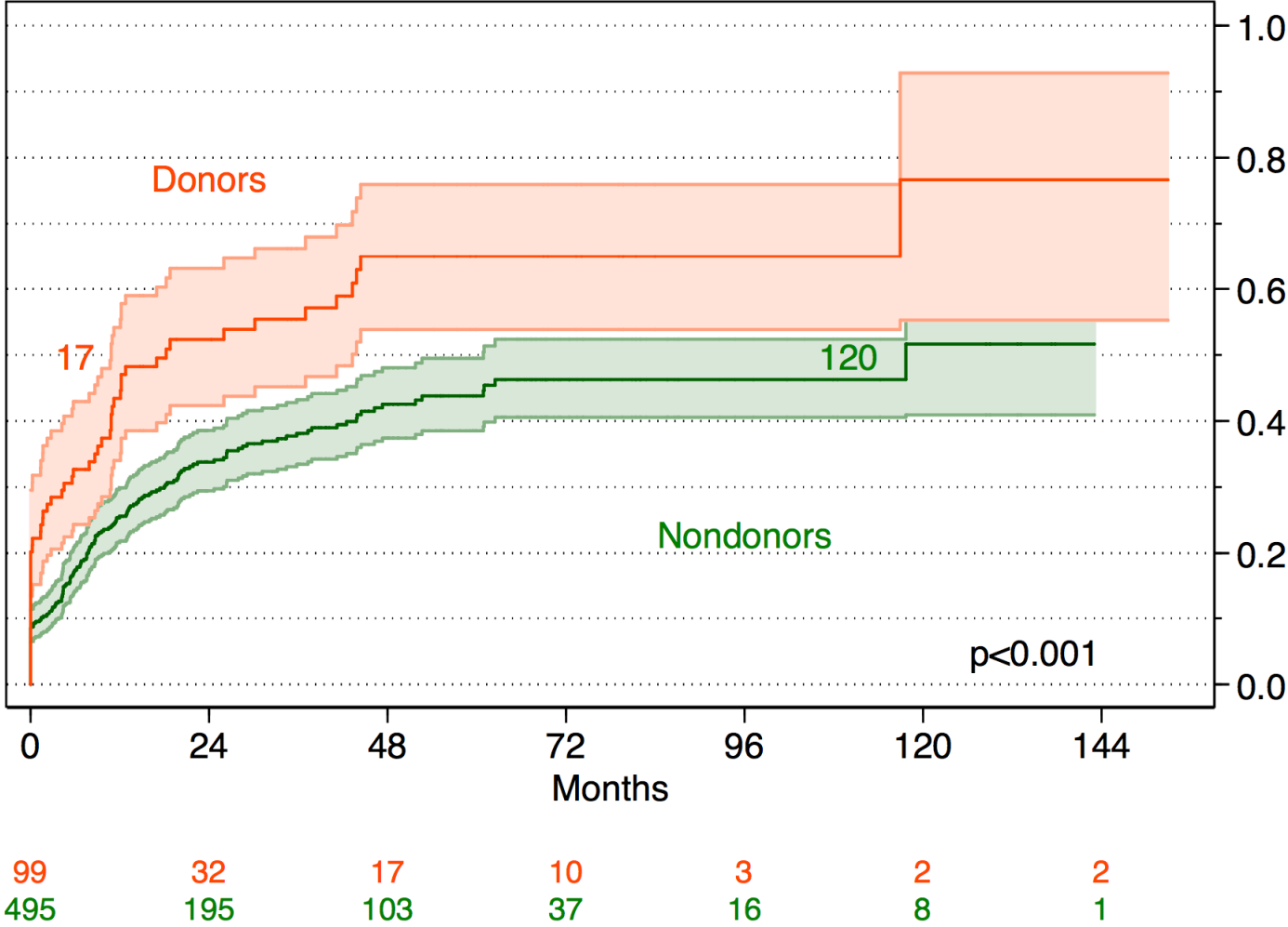
Non-Smoker

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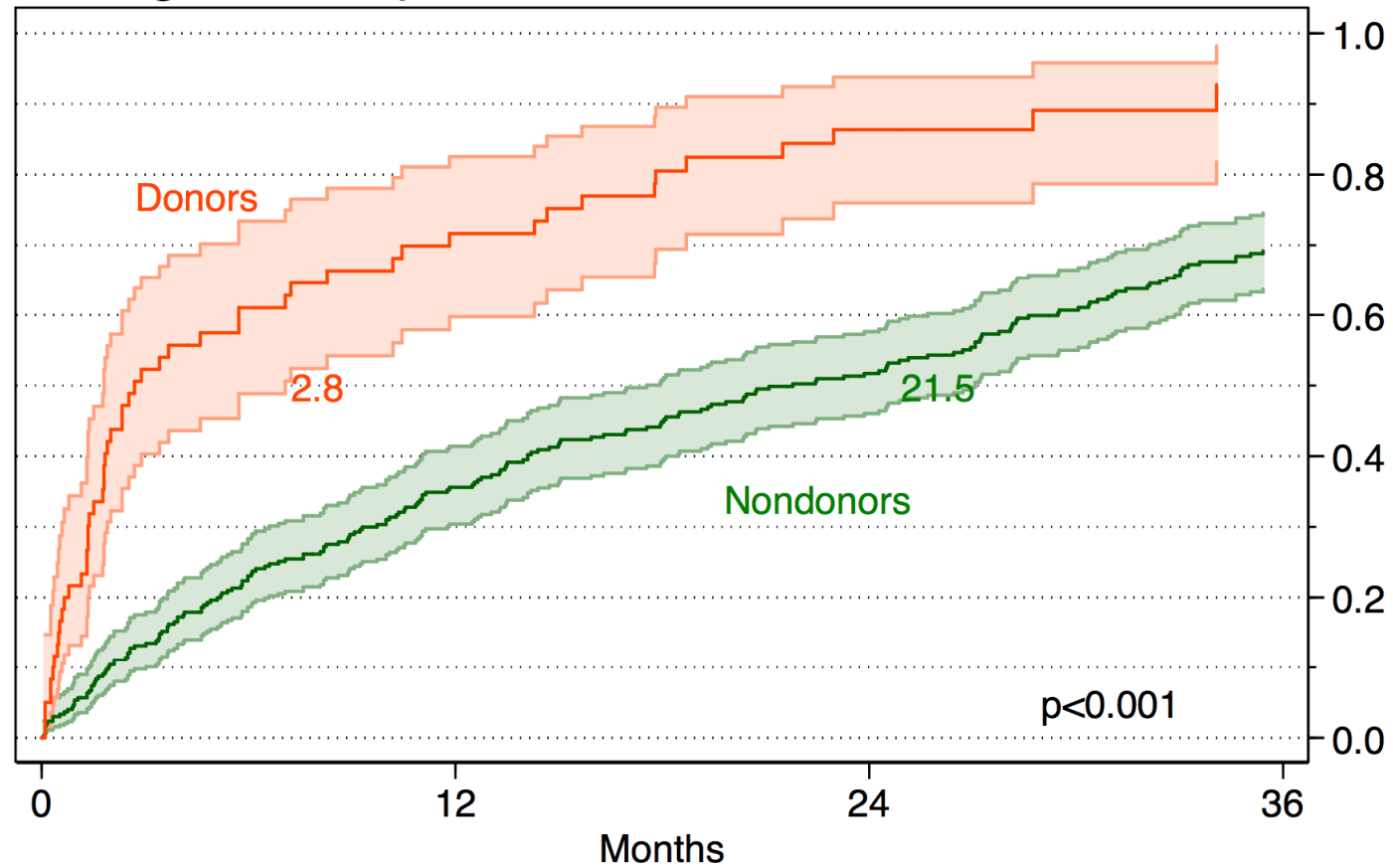
120,000+
actual donors

transplantmodels.com/esrdrisk

Dialysis-to-Listing



Listing-to-Transplant



60
300

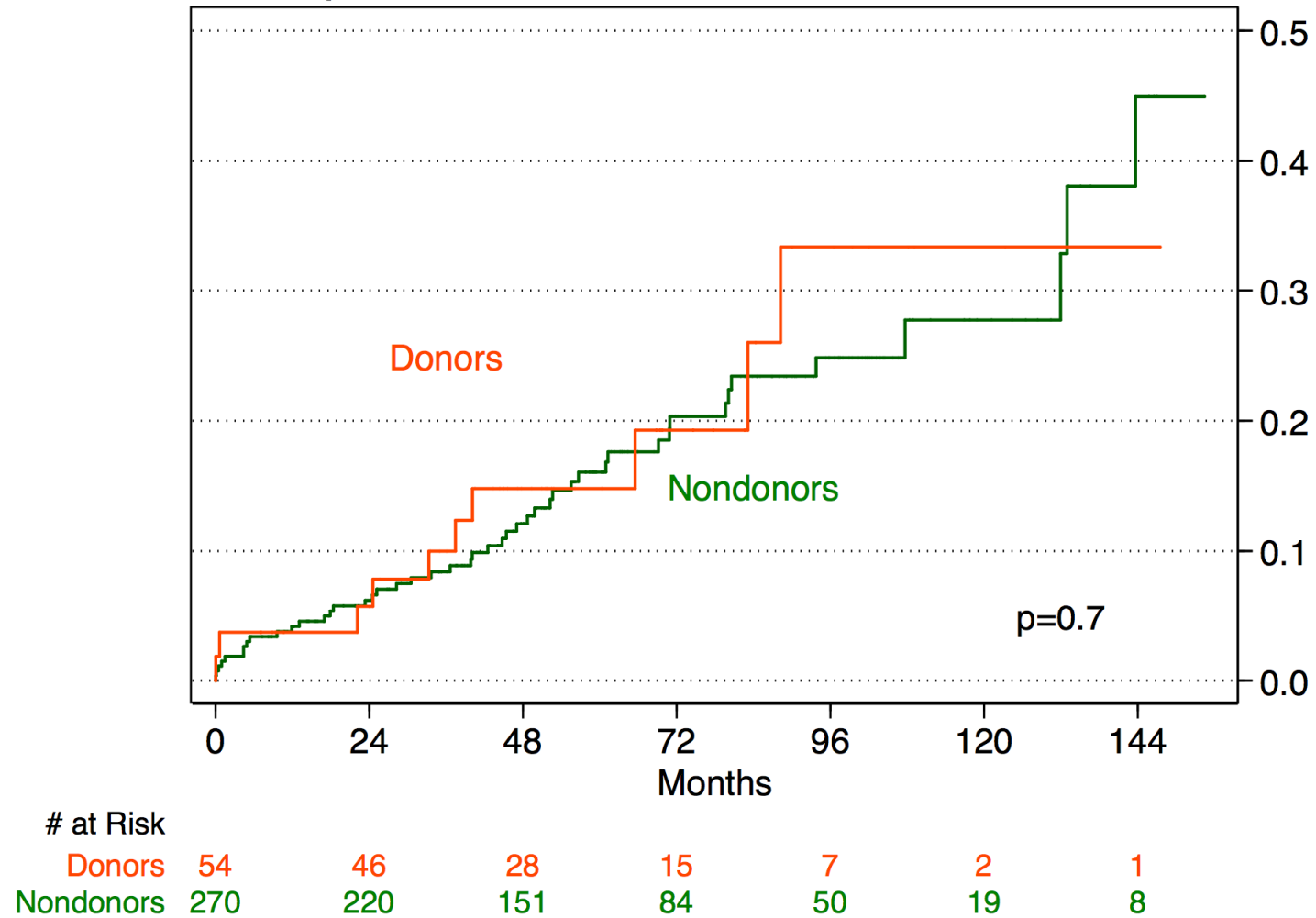
16
182

6
130

2
78

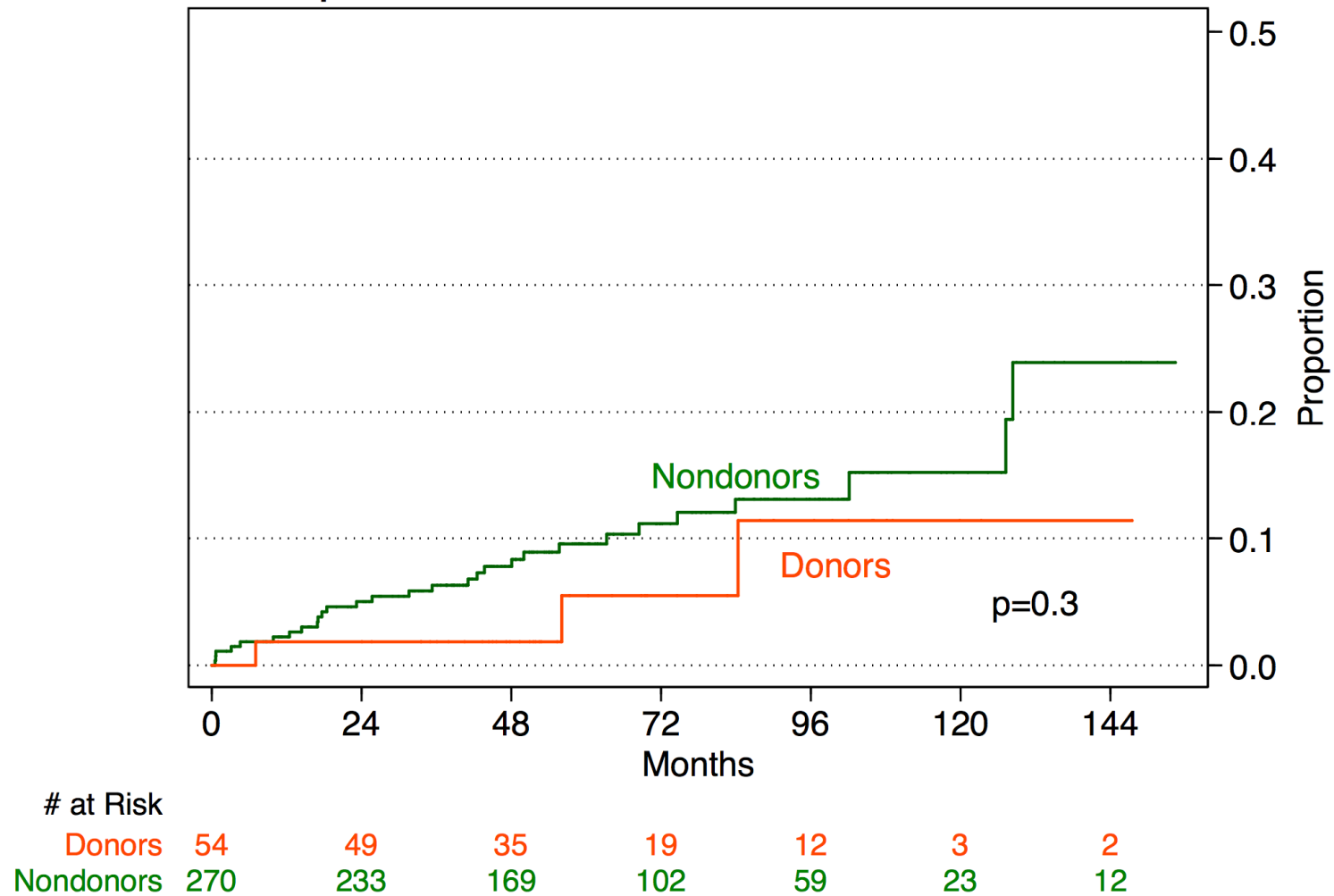
Muzaale/Segev, Transplantation, 2015

Transplant-to-Graft Failure



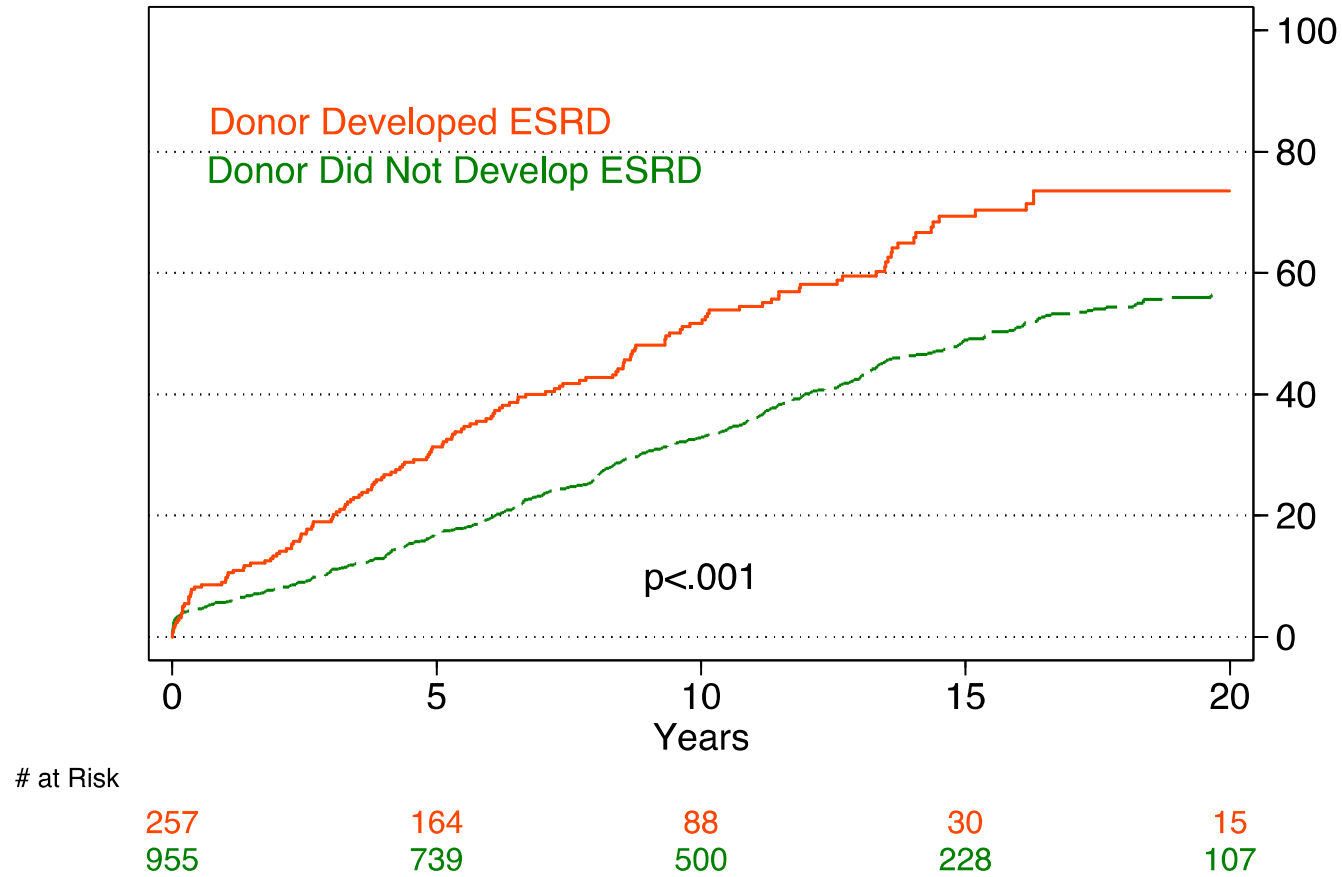
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Transplant-to-Death



B

Death-Censored Graft Loss, %



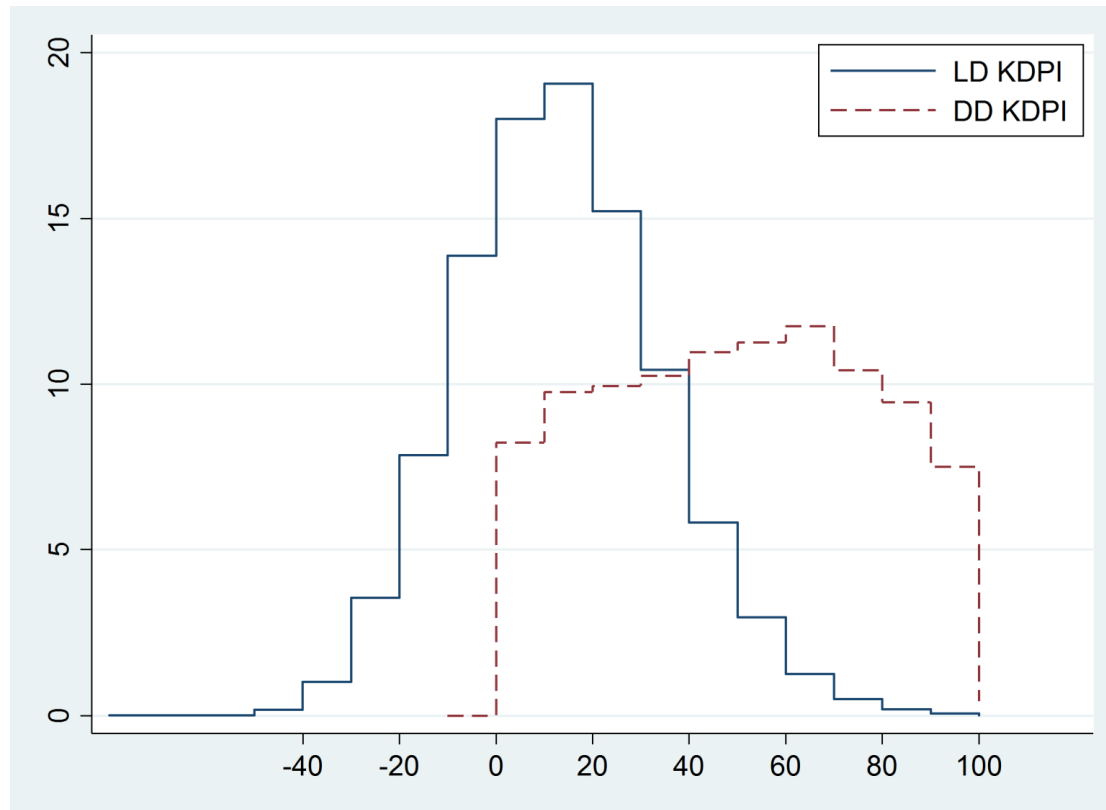
Live Donor KDPI

Donor characteristic	aHR		
LD: Age per year (over age 50)	1.02	1.02	1.03
LD: eGFR (per 10 units)	0.58	0.70	0.83
LD: BMI (per 10 units)	1.01	1.09	1.16
LD: Male donor to male recipient	0.75	0.81	0.87
LD: Black race	1.15	1.25	1.37
LD: ABO incompatible	1.03	1.27	1.58
LD: History of cigarette use	1.09	1.16	1.23
LD: Unrelated to recipient	0.84	0.90	0.97
LD: # HLA-B mismatches	1.03	1.08	1.14
LD: # HLA-DR mismatches	1.04	1.09	1.15

Adjusted for recipient characteristics. All coefficients p<0.05

Massie/Segev, AJT, 2016

Distribution of LKDPI



Conclusions

- Donor risk of death is very low (3:10,000) and there is no attributable risk beyond the operation at up to 12 years
- Donor risk of ESRD is very low (30:10,000) and there is attributable risk, which varies
- Baseline lifetime risk has be estimated from huge CKD populations
- Working on absolute/attributable lifetime risk

Implications

- We currently allow individuals to donate who have a very wide range of ESRD risk
- We currently decline potential donors who have conditions associated with a very wide range of ESRD risk
- We currently accept donors who have much higher risks than donors who we decline
- A new acceptable risk paradigm is coming

CKD-Prognosis Consortium

General Population Cohorts

Aichi

Hiroshi Yatsuya
Kentaro Yamashita
Hideaki Toyoshima
Koji Tamakoshi

AKDN:

Marcello Tonelli
Brenda Hemmelgarn
Matthew James
Tanvir C Turin

ARIC:

Josef Coresh
Kunihiro Matsushita
Morgan Grams
Yingying Sang

AusDiab:

Robert C Atkins
Kevan R Polkinghorne
Steven Chadban

Beaver Dam:

Anoop Shankar
Ronald Klein
Barbara EK Klein
Kristine E Lee

Beijing:

HaiYan Wang
Fang Wang
Luxia Zhang
Li Zuo

CHS:

Michael Shlipak
Carmen Peralta
Ronit Katz

CIRCS:

Hiroyasu Iso
Akihiko Kitamura
Tetsuya Ohira
Kazumasa Yamagishi

COBRA:

Tazeen Jafar
Muhammad Islam
Juanita Hatcher
Neil Poulter
Nish Chaturvedi

ESTHER:

Dietrich Rothenbacher
Hermann Brenner
Heiko Müller
Ben Schöttker

Framingham:

Caroline S Fox
Shih-Jen Hwang
James B Meigs
Ashish Upadhyay

Gubbio:

Massimo Cirillo

HUNT:

Stein Hallan
Knut Aasæd
Cecilia M Øien
Marie Radtke

Ibaraki:

Fujiko Irie
Hiroyasu Iso
Toshimi Sairenchi
Kazumasa Yamagishi

KSHS:

Eliseo Guallar
Seungcho Ryu
Yoosoo Chang
Juhee Cho
Hocheol Shin

Maccabi:

Gabriel Chodick
Varda Shalev
Yair C Birnbaum
Anat Bet-Or

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Mark J Sarnak
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Holly J Kramer

MRC Older People:

Paul Roderick
Dorothea Nitsch
Astrid Fletcher
Christopher Bulpitt

NHANES III:

Brad Astor
Josef Coresh
Kunihiro Matsushita

Ohasama:

Takayoshi Ohkubo
Hirohito Metoki
Masaaki Nakayama
Masahiro Kikuya
Yutaka Imai

Okinawa 83 & 93:

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Gihad Nesrallah
Joseph Kim

PREVEND:

Ron T Gansevoort
Paul E de Jong
Bakhtawar K Mahmoodi
Hans Hillege

Rancho Bernardo:

Simerjot K Jassal
Elizabeth Barrett-Connor
Jaclyn Bergstrom

REGARDS:

David G Warnock
Paul Muntner
Suzanne Judd
William M McClellan

Severance:

Sun Ha Jee
Heejin Kimm
Jaeseong Jo
Yejin Mok
Eunmi Choi

Taiwan:

Chi-Pang Wen
Sung-Feng Wen
Chwen-Keng Tsao
Min-Kuang Tsai

ULSAM:

Johan Ärnlöv
Lars Lannfelt
Anders Larsson



CKD Prognosis Consortium

CKD Prognosis Consortium

High Risk Cohorts

ADVANCE:

Mark Woodward
John Chalmers
Stephen MacMahon
Hisatomi Arima

AKDN ACR:

Marcello Tonelli
Brenda Hemmelgarn
Aminu Bello
Matthew James

CARE:

Marcello Tonelli
Frank Sacks
Gary Curhan

KEEP:

Allan J Collins
Joseph A Vassalotti
Suying Li
Shu-Cheng Chen

KP Hawaii:

Brian J Lee

MRFIT:

Areef Ishani
James Neaton

NZDCS:

C Raina Elley
Tim Kenealy
Simon Moyes
John Collins
Paul Drury

Pima Indian:

Robert G Nelson
William C Knowler

ZODIAC:

Henk J Bilo
Hanneke Joosten
Nanne Kleefstra
Klaas H Groenier
Iefke Drion

AASK:

Jackson Wright
Lawrence Appel
Tom Greene
Brad C Astor

British Columbia CKD:

Adeera Levin
Ognjenka Djurdjev

CCF:

Sankar Navaneethan
Joseph Nally
Jesse Schold

CRIB:

David C Wheeler
Martin J Landray
Jonathan N Townend
Jonathan Emberson

GCKD

Kai-Uwe Eckardt
Anna Kottgen
Florian Kronenberg
Stephanie Titze

Geisinger

Robert Perkins
H Les Kirchner

GLOMMS 1:

Corri Black
Angharad Marks
Nicholas Fluck
Gordon Prescott

Gonryo CKD

Sadayoshi Ito
Mariko Miyazaki
Masaaki Nakayama
Gen Yamada

CKD Cohorts

KP Northwest:

David H Smith
Eric S Johnson
Micah L Thorp
Jessica Weinstein

MASTERPLAN:

Jack F Wetzels
Peter J Blankestijn
Arjan D van Zuilen

MDRD:

Mark Sarnak
Andrew S Levey
Lesley Inker
Vandana Menon

MMKD:

Florian Kronenberg
Barbara Kollerits
Eberhard Ritz

NephroTest:

Marc Froissart
Benedicte Stengel
M. Metzger
JP Haymann
P Houillier
M. Flamant

RENAAL:

Hiddo J Lambers Heerspink
Barry Brenner
Dick de Zeeuw

SRR-CKD

Marie Evans
Maria Stendahl

STENO CKD:

Peter Rossing
Hans-Henrik Parving

Sunnybrook:

David Naimark
Navdeep Tangri

VA CKD:

Csaba P Kovesdy
Kamyar Kalantar-Zadeh





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Epidemiology Research Group in Organ Transplantation (D Segev, Director)

Core Research Group

Medicine/Surgery

Morgan Grams, MD PhD
Nephrology Faculty; K08
Christine Durand, MD
ID Faculty; R01 Pending
Rebecca Craig-Schapiro, MD
Surgery Resident
Jackie Garonzik-Wang, MD PhD
Surgery Resident; PhD Graduate (KL2)
Elizabeth King, MD
Surgery Resident; PhD Student (F32)
Babak Orandi, MD PhD MSc
Surgery Resident; PhD Graduate(F32)
Kyle Van Arendonk, MD PhD
Surgery Resident; PhD Graduate (KL2)

Medical/Graduate Students

Natasha Gupta
Medical Student (Doris Duke)
Lauren Kucirka, ScM
MD/PhD Student (F30)
Young Mee Choi
Epidemiology; MPH Student

Epidemiology/Biostatistics

Allan Massie, PhD
Epidemiology Faculty (K01 pending)
Mara McAdams-DeMarco, PhD
Epidemiology Faculty (K01)
Tanjala Purnell, PhD
Epidemiology Faculty
Abi Muzaale, MD, MHS
Epidemiology Postdoc
Megan Salter, PhD
Epidemiology Postdoc (T32)
Andrew Law, ScM
Epidemiology Staff
Xun Luo, MD ScM
Analytical Staff
Israel Olorunda, MBBS MPH
Analytical Staff
Anna Poon, MHS MS
Analytical Staff

Computational Science

Sommer Gentry, PhD
Computer Science Faculty (HRSA)
Eric Chow, MHS
Decision Process Programmer/Analyst
Corey Wickliffe, MHS
Geographic Systems Analyst

Research Assistants

Full-Time:
Jennifer Alejo
Amanda Brennan
Ryan Brown
Cassandra Delp
Erika Jones
Komal Kumar
Katie Marks
Part-Time:
Lindsay Adam
Saad Anjum
Kate Appel
Olivia Berman
Seal-Bin Han
Diana Cantu-Reyna
Maurice Dunn
Laura Grau
Teal Harrison
Sara Hawa
Billy Kim
Arnaldo Mercado-Perez
Ashley Millette
Sachin Patel
Ana Quintal
Katrina Rios
Michael Setteducato
Chelsea Sicat

Affiliated

Daniel Scharfstein, ScD
Biostatistics: Coinvestigator
Ravi Vardhan, PhD
Biostatistics: Coinvestigator
Lucy Meoni, ScM
Biostatistics: Coinvestigator
Josef Coresh, MD PhD
Epidemiology: Coinvestigator
Linda Kao, PhD
Epidemiology: Coinvestigator
Lauren Nicholas, PhD
Health Policy: Coinvestigator
Andrew Cameron, MD PhD
Surgery: Collaborator
Niraj Desai MD
Surgery: Collaborator
Bob Montgomery, MD PhD
Surgery: Collaborator
Nabil Dagher, MD
Surgery: Mentee
Elliott Haut, MD PhD
Surgery: Mentee (KL2; PCORI)
Kim Steele, MD PhD
Surgery: Mentee (K23)
Diane Schwartz, MD
Surgery: Mentee
Aliaksei Pustavoitau, MD
Anesthesiology: Mentee (R03 pending)