Race and Kidney Function: What's The Fuss?

Neil R. Powe, MD, MPH, MBA

Chief of Medicine, Zuckerberg San Francisco General Hospital

Constance B. Wofsy Distinguished Professor and

Vice-Chair of Medicine, University of California San Francisco

Northern California
American College of Physicians 2020 Meeting
October 17, 2020
9:00-10:00 AM

UCSF
University of California
San Francisco

PRISCILLA CHAN AND MARK ZUCKERBERG SAN FRANCISCO GENERAL
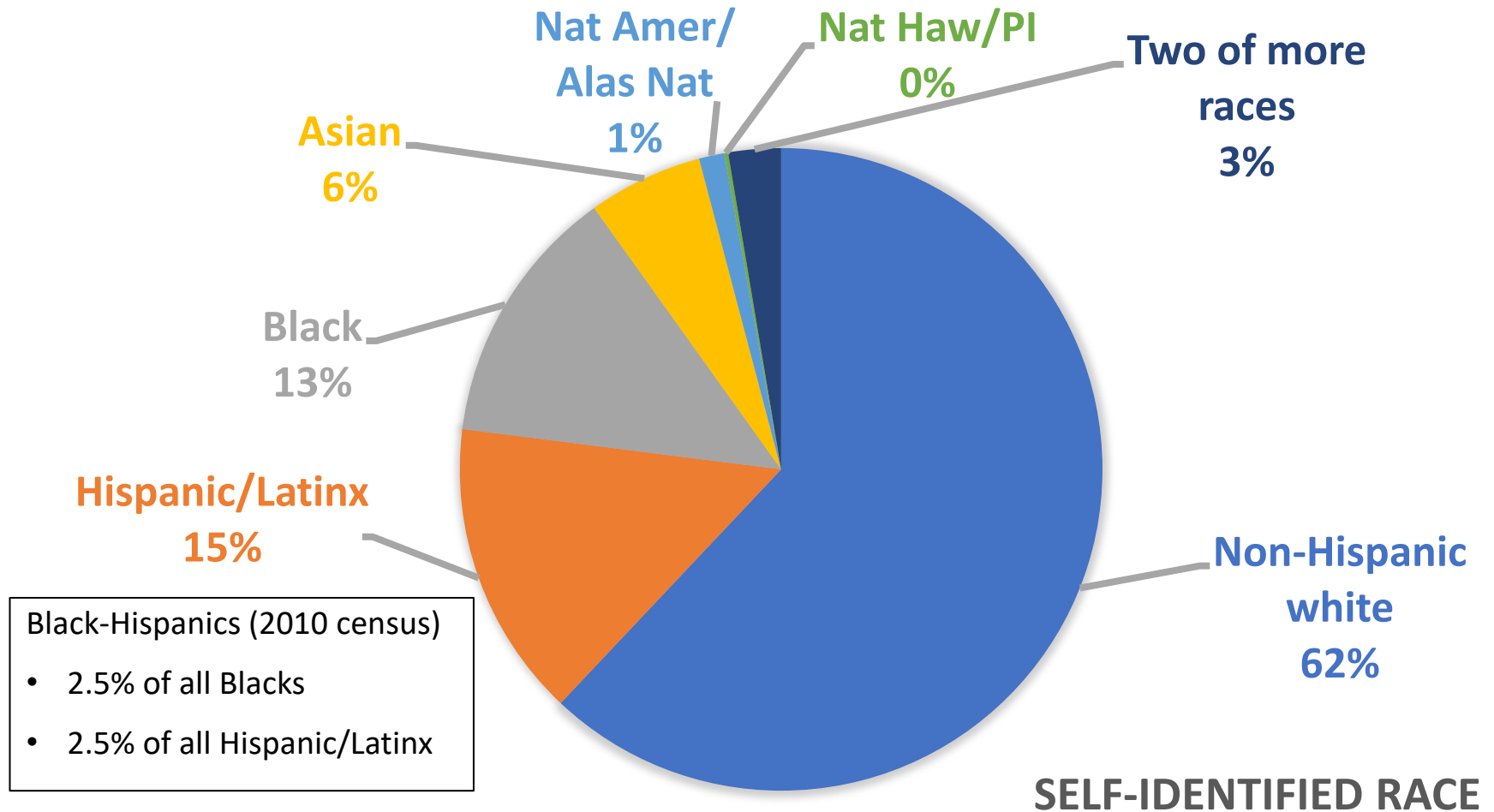Hospital and Trauma Center

Objectives

- Describe the fuss and fuzziness about race and kidney function measurement

- Describe forces that got us to this moment

- Describe potential clinical consequences of removing race from eGFR equations

- Examine claims on whether incorporation of race into equations generated disparities?

- Describe approaches (and challenges) to mitigate use of race in estimating or reporting GFR

Powe NR. Black Kidney Function Matters: Use or Misuse of Race. JAMA 2020 Published online July 29, 2020
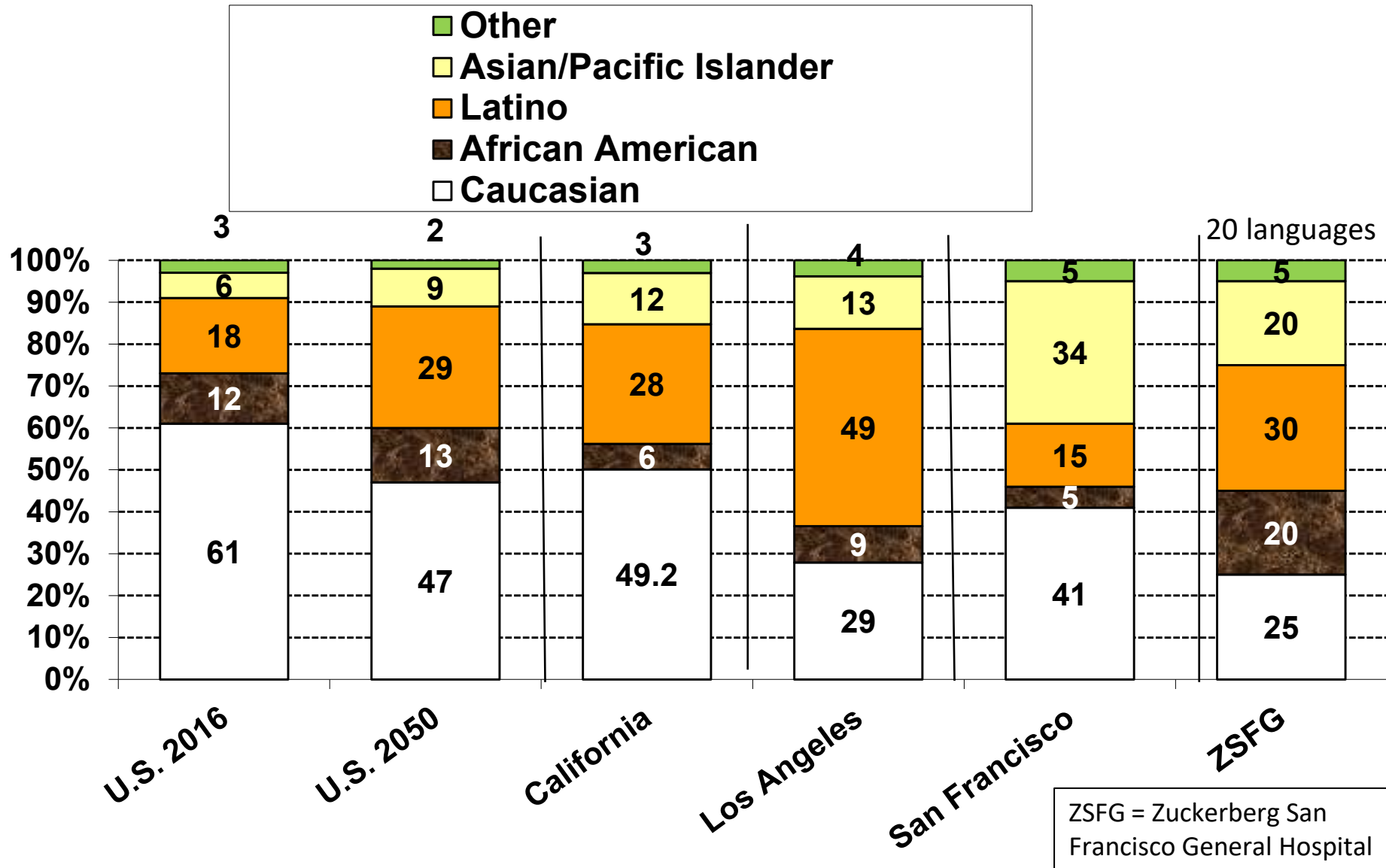**Conversations with Howard Bauchner: JAMA Podcast**

Race and Ethnicity Composition of the United States: ~330 million

Nat Amer/ Alas Nat
1%

Nat Haw/PI
0%

Two of more races
3%

Asian
6%

Black
13%

Hispanic/Latinx
15%

Non-Hispanic white
62%

Black-Hispanics (2010 census)
- 2.5% of all Blacks
- 2.5% of all Hispanic/Latinx

2019 Census Bureau Estimates

SELF-IDENTIFIED RACE

The Fuss: Race/Ethnic Composition United States and California

Legend:
- Other (green)
- Asian/Pacific Islander (yellow)
- Latino (orange)
- African American (brown)
- Caucasian (white)

	U.S. 2016	U.S. 2050	California	Los Angeles	San Francisco	ZSFG (20 languages)
Other	3	2	3	4	5	5
Asian/Pacific Islander	6	9	12	13	34	20
Latino	18	29	28	49	15	30
African American	12	13	6	9	5	20
Caucasian	61	47	49.2	29	41	25

ZSFG = Zuckerberg San Francisco General Hospital

Fussier: Health Disparities among racial and ethnic minorities have been recognized for many years

September 1985

- US DHHS landmark 'Heckler report'

- Documented health disparities

- *"An affront both to our ideals and to the ongoing genius of American medicine."*

- Driving force for quest to end health disparities and advance health equity

March 2002

- National Academy of Medicine Report to Congress

- Large body of consistent research
  - Variation in rates of medical procedures and quality of health services by race

- Recommendations: 1) increase awareness; 2) use "evidence-based" guidelines; 3) interpreters should be available and; 4)more minority providers
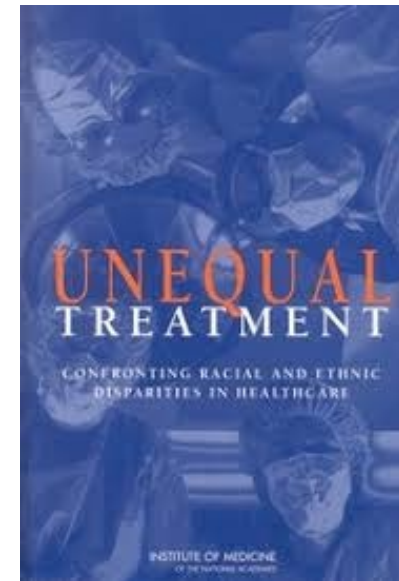
The Fussiest: **A Contrast in Progress:**

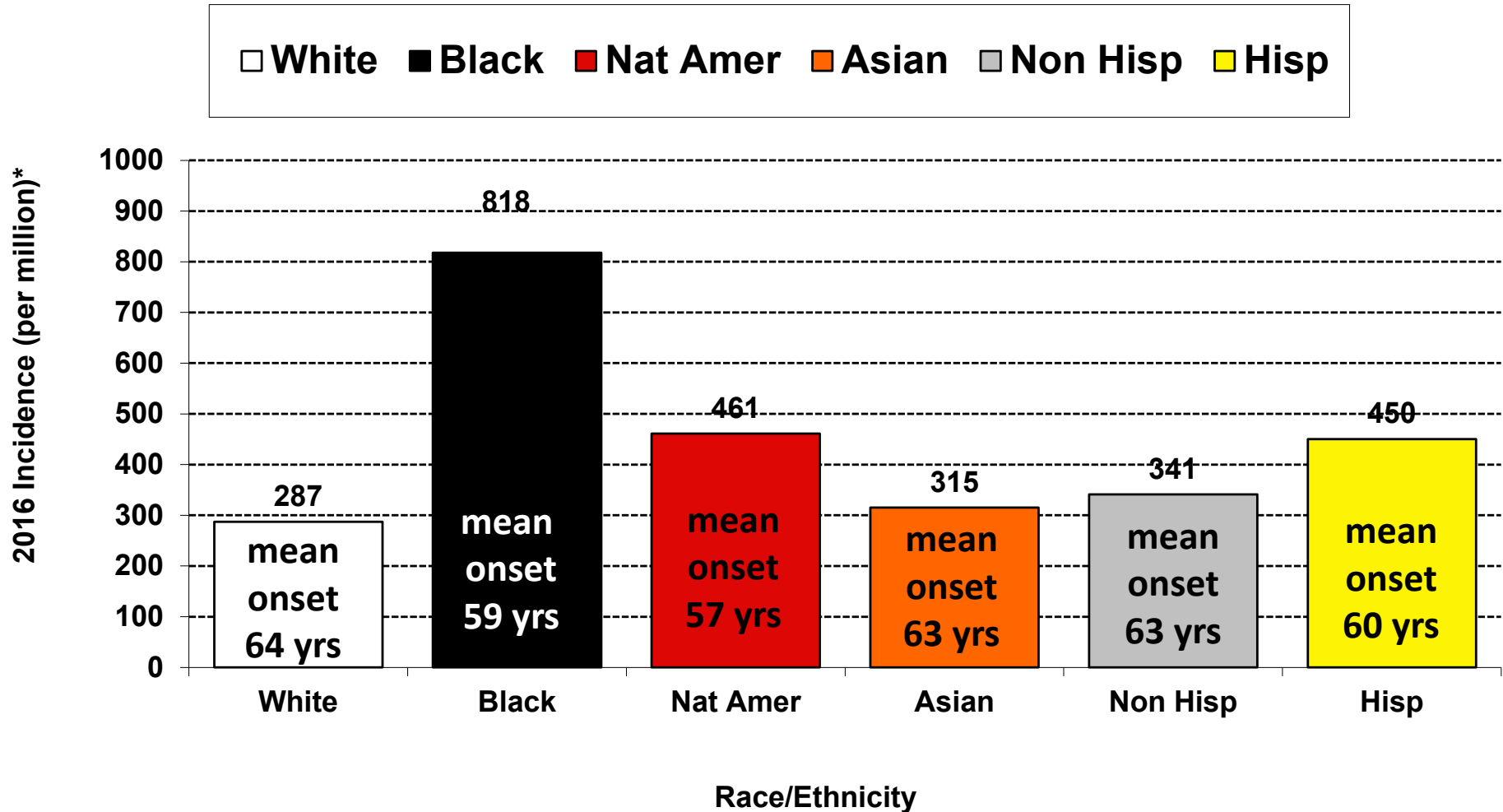Racial Disparities

Operation Glacial Pace

COVID-19

Operation Warp Speed

Black Kidney Function Matters
Kidney Failure (End Stage Renal Disease) is up to 3 times greater in racial/ethnic minorities 2016

Legend: □ White ■ Black ■ Nat Amer ■ Asian ■ Non Hisp □ Hisp

2016 Incidence (per million)*

Race/Ethnicity	Incidence	Mean onset
White	287	mean onset 64 yrs
Black	818	mean onset 59 yrs
Nat Amer	461	mean onset 57 yrs
Asian	315	mean onset 63 yrs
Non Hisp	341	mean onset 63 yrs
Hisp	450	mean onset 60 yrs

US Renal Data System Annual Data Report 2018; *adjusted for age, sex, race, ethnicity

Decline in eGFR~cys~ Differs by Race at Early Ages, with Faster Annualized Rates of Decline Among Blacks
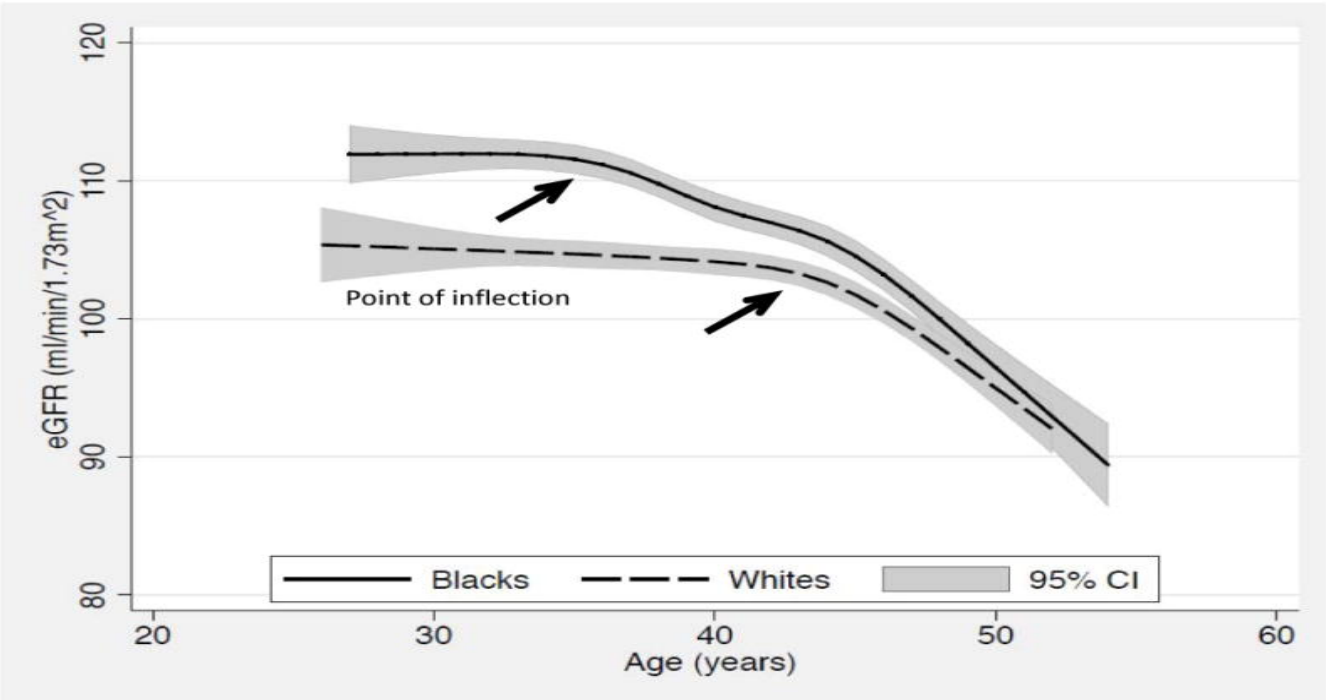
Age	P Value for Difference in Slope by Race
30	0.7
35	0.06
40	<0.001
45	0.09
50+	0.2

Peralta CA, Vittinghoff E, Bansal N, Jacobs D Jr, Muntner P, Kestenbaum B, Lewis C, Siscovick D, Kramer H, Shlipak M, Bibbins-Domingo K. Trajectories of kidney function decline in young black and white adults with preserved GFR: results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Kidney Dis. 2013 ;62(2):261-6.
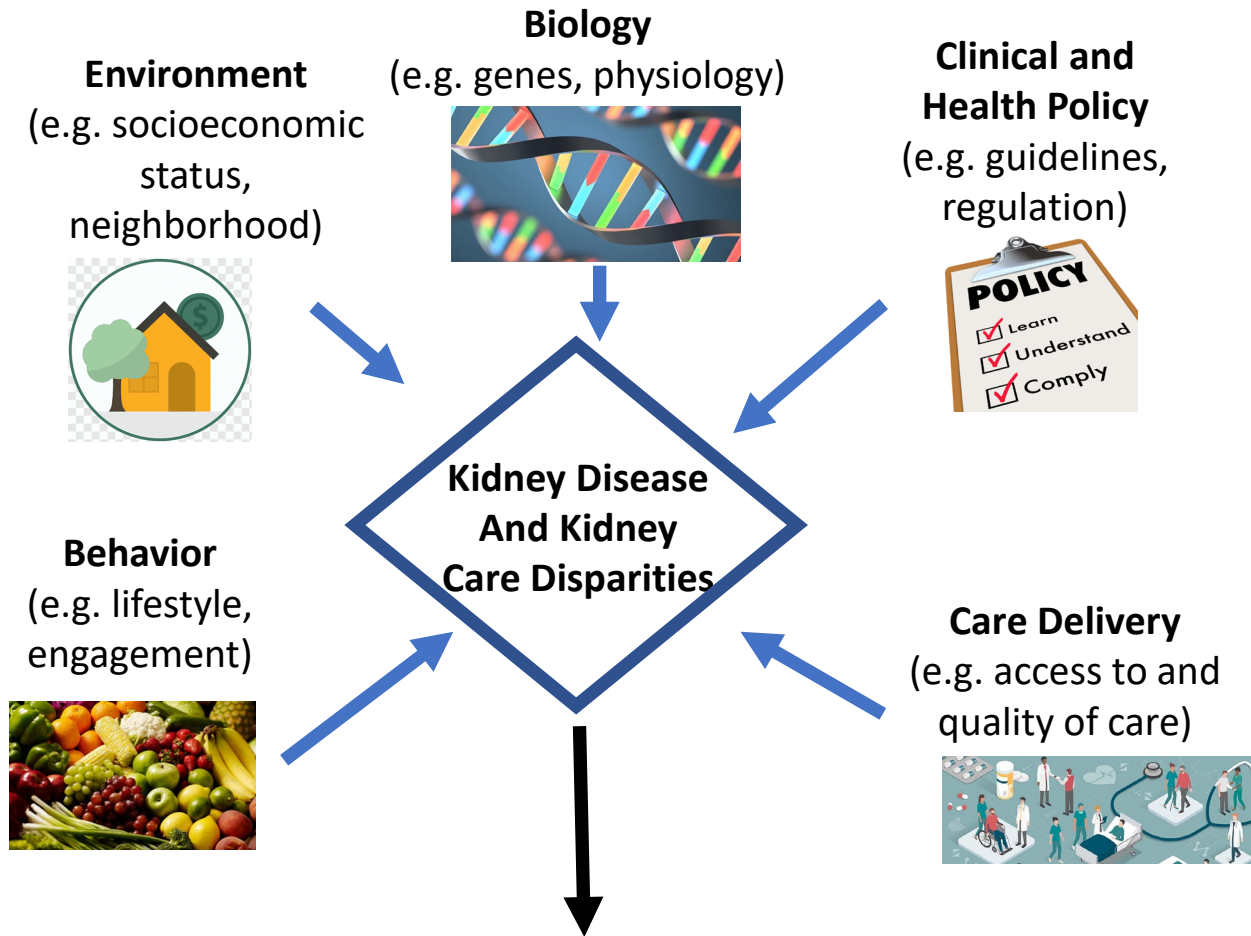
Ethnic Minorities versus Whites
Less likely to…

- see a nephrologist prior to dialysis[1]

- treated with home dialysis[2]

- be waitlisted and transplanted[3]

- receive live kidney transplants[4] (improving?)

1. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag, M, Levey A, Powe N. The Timing of Specialist Evaluation in Chronic Kidney Disease and Mortality *Annals of Internal Medicine* 2002;137:479-486
2. Mehrotra R, et al/ Racial and Ethnic Disparities in Use of and Outcomes with Home Dialysis in US. J Am Soc Nephrol. 2016 Jul;27(7):2123-34
3. United States Renal Data System 2015 Annual Report
4. Gore JL, Danovitch GM, Litwin MS, Pham PTT, Singer JS. Disparities in the Utilization of Live Donor Renal Transplantation. AJT 2009 9:1124-1133

Drivers of Disparities

Biology
(e.g. genes, physiology)

Environment
(e.g. socioeconomic status, neighborhood)

Clinical and Health Policy
(e.g. guidelines, regulation)

Behavior
(e.g. lifestyle, engagement)

Kidney Disease And Kidney Care Disparities

Care Delivery
(e.g. access to and quality of care)

Achieving Health Equity and Justice
Focus upstream on drivers
Tailor interventions to need
Implement palette of tools

Powe NR. The Pathogenesis of Race and Ethnic Disparities: Targets for Achieving Health Equity CJASN (under review)

Racism (oppression of a racial group to the social, economic, and political advantage of another) **can be a part of** drivers
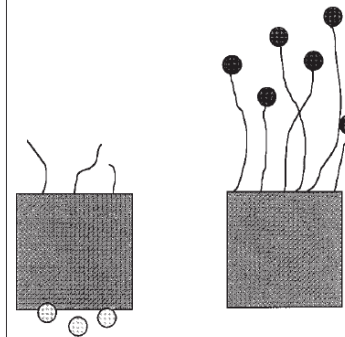
Environment

Care Delivery

Internalized racism
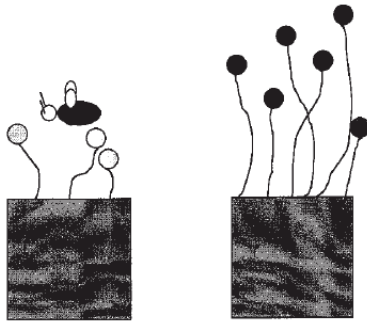
- Reflects systems of privilege
- Reflects societal values
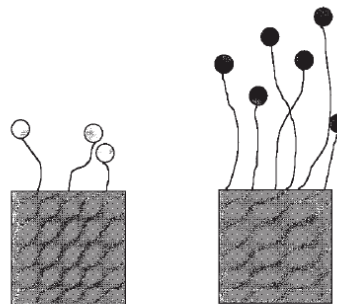- Erodes individual sense of value
- Undermines collective action

Personally mediated racism

- Intentional
- Unintentional
- Acts of commission
- Acts of omission
- Maintains structural barriers
- Condoned by societal norms

Clinical & Health Policy

Institutionalized racism

- Initial historical insult
- Structural barriers
- Inaction in face of need
- Societal norms
- Biological determinism
- Unearned privilege

Jones CP: Levels of racism: a theoretic framework and a gardener's tale", *American Journal of Public Health* 90, no. 8 (August 1, 2000): pp. 1212-1215.

Timeline of Key eGFR Milestones

- 1976 Cockcroft-Gault equation developed in 249 white men

- 1999: MDRD eGFR equation (Scr, age, sex, race 1.21) published with inclusion of women and Blacks (Levey 1999)

- 2007: 50% penetration of eGFR reporting (MDRD) in U.S. clinical laboratories (CAP Survey)

- 2009: CKD-EPI equation (Scr, age, sex, race 1.16) published with inclusion of women, Blacks (few Asian and Hispanics) (Levey 2009)

- 2012: CKD EPI combined equation (Scr, Scys, age, sex, race 1.08) (Inker 2012)

- 2013: 90% penetration of eGFR reporting (MDRD>66%) in U.S. clinical laboratories (CAP Survey); standardized assessment of kidney function and equations incorporated into clinical practice guidelines (KDIGO 2013)

- 2017: First call for race removal from eGFR reporting

- 2020: More calls - half dozen institutions remove race from eGFR reporting

Estimation of GFR from Creatinine

- CKD Epidemiology (CKD EPI) Collaboration
  - $141 \times \min(SCr/k,1)^a \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if female}] \times [1.159 \text{ if African American}]$

- Modification of Diet in Renal Disease (MDRD) study
  - $1.86 \times SCr^{-1.154} \times Age^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if African American}]$
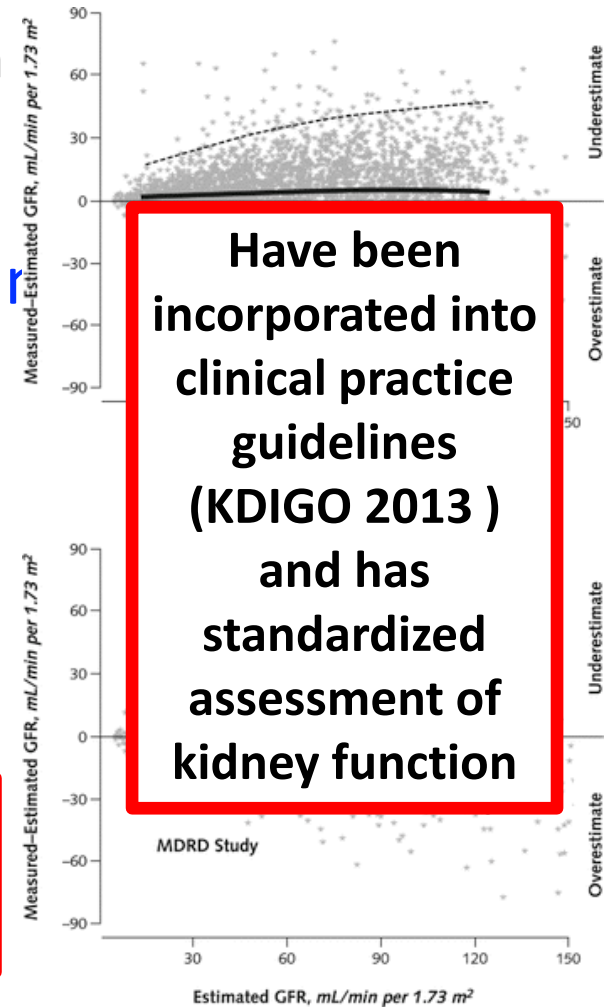
SCr = serum creatinine in mg/dL

k = 0.7 for females and 0.9 for males
a = -0.329 for females and -0.411 for males
min indicates the minimum of SCr/k or 1
max indicates the maximum of SCr/k or 1.

Race-Based or Evidenced-Based Medicine?

Have been incorporated into clinical practice guidelines (KDIGO 2013) and has standardized assessment of kidney function

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May 5;150(9):604-12.
Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (March 1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130 (6): 461–70.
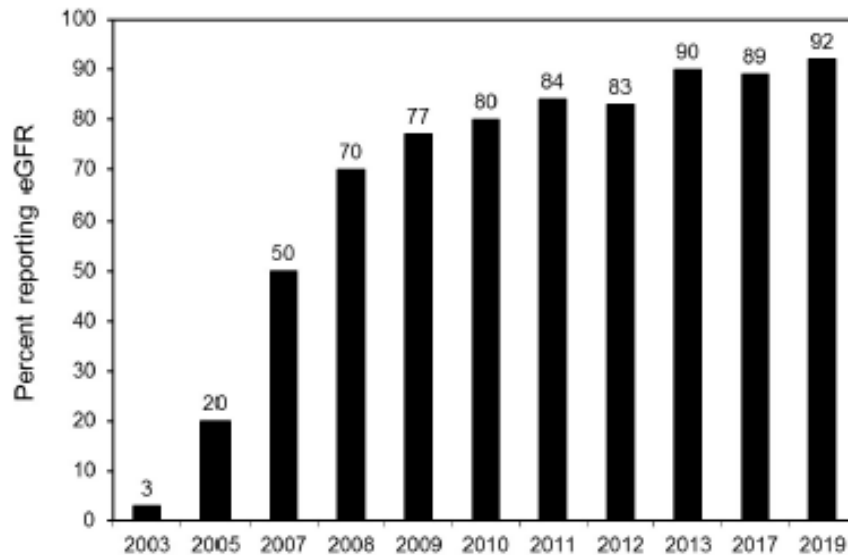
~280 Million Creatinines are performed each year in the U.S.
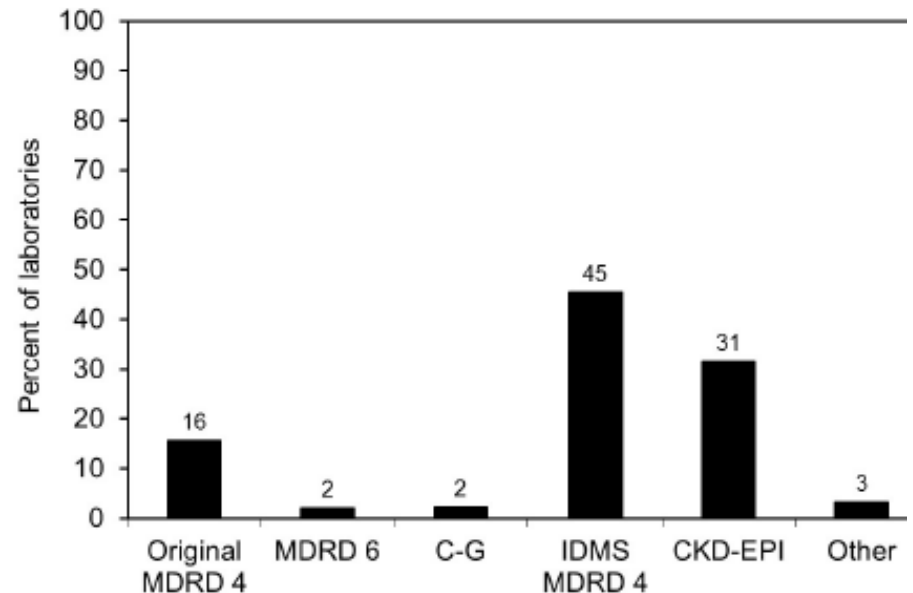# Standardized Kidney Function Measurement

Percent of laboratories reporting eGFR with SCr

Percent of laboratories using different eGFR equations

The Fuzziness:
Race - What do we mean?

- Race (rās) *n*. a group of people [u]
  together on the basis of commo[n]
  geographic distribution

  Webster's New World Dictionary, Revised Edit[ion]

- "a construct of human variability
  differences in biology, physical a[nd]
  behavior",-- not a biological real[ity]
  Medicine, United States

SKIN DEEP: THE SCIENCE OF RACE — DAWN OF THE WHITE MINORITY — US AND THEM: WHY WE DIVIDE — DRIVING WHILE BLACK

SPECIAL ISSUE

NATIONAL GEOGRAPHIC

Black and White
These twin sisters make us rethink everything we know about race

APRIL 2018

WHAT'S YOUR STORY? #IDefineMe

The Fuzziness: Ethnicity

- Shared social, cultural and historical experiences, stemming from common national or regional backgrounds; with relatively distinctive beliefs, values, and behaviors; and with some sense of identity of belonging to the subgroup

- Interpretations may vary: Hispanic & Latino
  - Two thirds say Hispanic is part of their 'racial background' (Pew Research Center 2015)
  - U.S. Census Bureau: "a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race". Hispanics or Latinos can be of any race, ancestry, ethnicity.

Racial background 11%

67%

Ethnic background 19%

Both, racial and ethnic background 56%

Don't know 13%
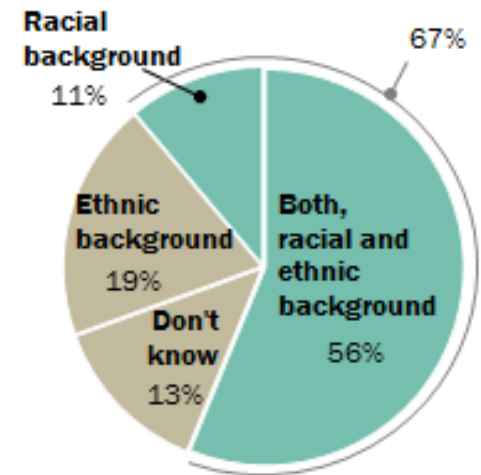
Ancestry: A clearer focus?

- **Ancestry:** Trail of where your family started and all the descendants that followed

- **Genetic Ancestry:** architecture of genome variation between populations

DNA variations provide clues about where a person's ancestors might have come from and about relationships between families.

Certain patterns of genetic variation are often shared among people of particular backgrounds

More closely related two individuals, families, or populations are, the more patterns of variation they typically share

Tests for genetic ancestry exploit findings of population genetics research to provide inferences about someone's genetic heritage.

"Information about genetic group membership captured by notions of race is, in general, less than that obtained by making inferences of ancestry from geographic or explicit genetic data" *Bamshad M. JAMA* 2005; 294:937-946.

The Fuzziness: Inference of Individual Ancestry Proportions From Genetic Data

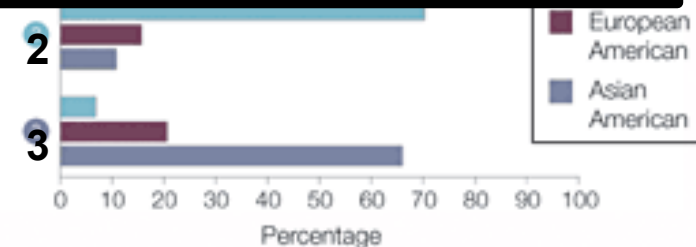A Network of Genetic Relatedness

African Americans (n=20)

Genetic Distance
— Between Populations

C Inferred Ancestry

African American Ancestor

Race is a Human Invention

- Subjective: society defines you by the color of your skin

- Objective: genetic ancestry: science defines you by your DNA
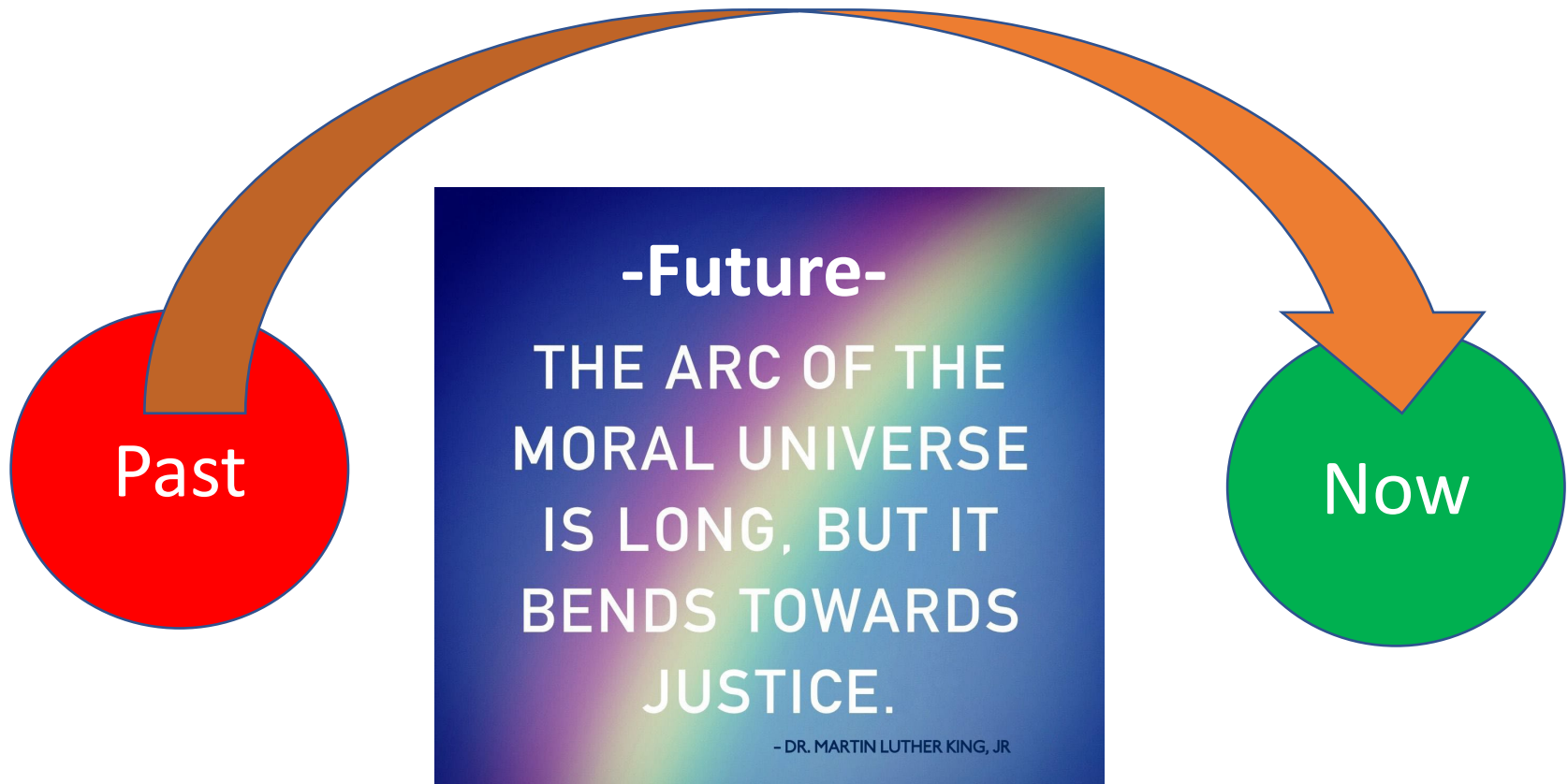
B Examples of Genetic Distance

Between Individuals Within the Same Population   1 ———————— 2

Between Individuals From Different Populations   2 ———————— 3

2
3

European American

Asian American

0 10 20 30 40 50 60 70 80 90 100
Percentage

Bamshad, M. JAMA 2005;294:937-946.

Arguments/Claims about Use of Race in Clinical Algorithms

- Race is a social construct that does not reflect biological function
- Incorporation of race caused disparities (waitlisting, nephrology referral)
- Using race institutionalizes racism
- Displaying race makes clinicians feel they are applying race in an unfair way
- Race is difficult to obtain and ascertain
- Inter-racial/ethnicity children are increasing
- Patients are reluctant to divulge race to protect privacy

The science that got us here

Past

Now

-Future-

THE ARC OF THE MORAL UNIVERSE IS LONG, BUT IT BENDS TOWARDS JUSTICE.

– DR. MARTIN LUTHER KING, JR

Evidence on Use of Race in eGFR

- Equations derived empirically using pooled data from studies measuring creatinine and GFR

    - 8254 participants in 10 studies (equation development data set)

    - 3896 participants in 16 studies (validation data set)

- Blacks were 30.5% (2601) of derivation and 12% (451) of validation; 1807 from African American Study of Kidney Disease

- Race/ethnicity was self-reported (not provider assigned)

- In the development data set coefficients were:

    - African Americans 1.16

    - Asians 1.05

    - Hispanics and Native Americans 1.01

- However, eGFR equations do not perform well in some populations from Africa and Asia

Levey AS et al A new equation to estimate GFR. Annals of Internal Medicine 2009; 150: 604-612
Stevens LA et al. Evaluation of the CKD Epidemiology Collaboration equation for estimating the GFR in multiple ethnicities. Kidney Int. 2011;79(5):555-62.

Scr in U.S. Population by Race, Age and Sex: NHANES III 1988-1994

Ethnicity	Age (yr)	Men			Women		
		Mean	Median	95th	Mean	Median	95th
Total US	All	1.16	1.09	1.40	0.96	0.89	1.18
	12-19	1.00	0.95	1.24	0.88	0.83	1.01
	20-39	1.15	1.09	1.33	0.92	0.87	1.08
	40-59	1.17	1.11	1.38	0.96	0.90	1.14
	60+	1.29	1.18	1.75	1.08	0.97	1.44
Non-Hispanic white	All	1.16	1.09	1.39	0.97	0.90	1.19
	12-19	0.99	0.94	1.23	0.89	0.84	1.02
	20-39	1.14	1.09	1.30	0.93	0.88	1.08
	40-59	1.16	1.11	1.36	0.97	0.90	1.15
	60+	1.28	1.18	1.72	1.07	0.97	1.43
Non-Hispanic black	All	1.25	1.16	1.53	1.01	0.92	1.23
	12-19	1.06	1.03	1.30	0.90	0.85	1.04
	20-39	1.25	1.18	1.46	0.97	0.91	1.13
	40-59	1.28	1.17	1.55	1.04	0.94	1.20
	60+	1.49	1.26	2.12	1.20	1.06	1.71

Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH, Coresh J, Salive M, Jones CP, Agodoa LY. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis. **1998** Dec;32(6):992-9.

Conclusion on serum creatinine levels in the US population

"Mean serum creatinine values are higher in men, non-Hispanic blacks, and older persons and are lower in Mexican-Americans. In the absence of information on glomerular filtration rate (GFR) or lean body mass, it is not clear to what extent the variability by sex, ethnicity, and age reflects normal physiological differences rather than the presence of kidney disease. Until this information is known, the use of a single cutpoint to define elevated serum creatinine values may be misleading."

Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH, Coresh J, Salive M, Jones CP, Agodoa LY. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis. **1998** Dec;32(6):992-9.

Mean Scr is greater in Black prevalent U.S. hemodialysis patients (n=3009)

| Race/Ethnicity	n	Mean Adjusted* Scr mg/dl
Whites	1304	9.9
Hispanics	190	10.8
Other Race/Ethnicity	34	10.3
Blacks	1371	11.7

Adjustment for case mix (age, gender, diabetes, and vintage) blacks 11.9 *versus* nonblacks 9.9 mg/dl; *P* < 0.0001) and after *adjustment for nutritional variables (including serum albumin, phosphorus, glucose, predialysis blood urea nitrogen, and transferrin; body weight, and <u>reactance and resistance by bioelectrical impedance</u>, blacks 11.7 versus nonblacks 10.0 mg/dl.

Hsu J, Johansen KL, Hsu CY, Kaysen GA, Chertow GM. Higher serum creatinine concentrations in black patients with chronic kidney disease: beyond nutritional status and body composition. *Clin J Am Soc Nephrol*. 2008;3(4):992-997.

Serum creatinine varies with the proportion genetic African ancestry

Udler MS, Nadkarni GN, Belbin G, Lotay V, Wyatt C, Gottesman O, Bottinger EP, Kenny EE, Peter I. Effect of Genetic African Ancestry on eGFR & Kidney Disease. J Am Soc Nephrol. 2015 (7):1682-92.

Peralta CA, Risch N, Lin F, Shlipak MG, Reiner A, Ziv E, Tang H. Siscovick D.[e] · Bibbins-Domingo K. Association of African Ancestry and **elevated creatinine** (>1.3 mg/dl in men and 1.1 mg/dl in women) in the Coronary Artery Risk Development in Young Adults (CARDIA) Study.
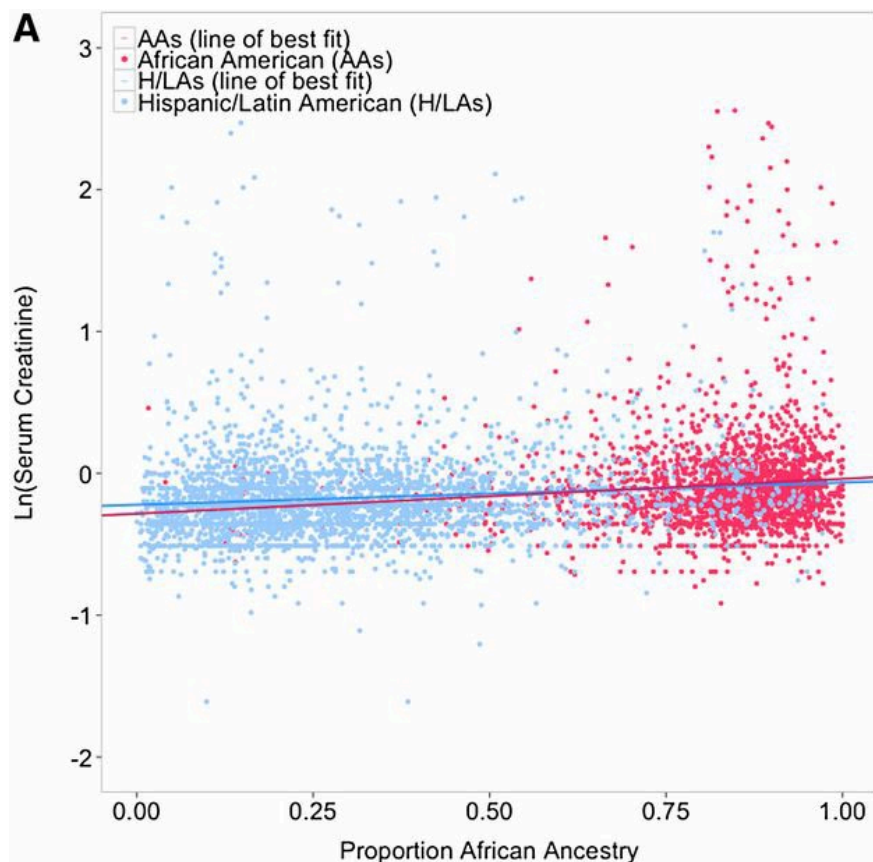
Whites (combined) and blacks by African ancestry group	n	Unadjusted odds ratio (95% CI)	Adjusted[1] odds ratio (95% CI)
Men			
Self-reported white (ref.)	884	1.0	1.0
African ancestry			
<40%	19	*	*
40–70%	134	4.44 (2.36–8.36)	4.27 (2.26–10.06)
70–80%	150	7.33 (4.21–12.74)	8.09 (4.19–15.61)
>80%	180	7.64 (4.52–12.91)	9.05 (4.81–17.02)
Women			
Self-reported white (ref)	989	1.0	1.0
African ancestry			
<40%	28	2.12 (0.27–16.49)	2.11 (0.25–18.11)
40–70%	110	3.04 (1.43–6.44)	2.05 (0.79–5.32)
70–80%	252	2.12 (0.93–4.81)	1.95 (0.73–5.23)
>80%	239	3.56 (1.73–7.33)	3.46 (1.41–8.50)

* There were no black men with African ancestry <40% and elevated creatinine.
[1] Adjusted for age, income, education, smoking, systolic blood pressure, cardiovascular disease, diabetes, hypertension, BMI, fasting glucose, LDL cholesterol, C-reactive protein, and clinical site.

Correspondence between self-reported race/ethnicity and genetic ancestry

Banda Y, Kvale MN, Hoffmann TJ, et al. **Characterizing Race/Ethnicity and Genetic Ancestry for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort**. *Genetics*. 2015;200(4):1285-1295.

**91,502 (93.9%) reported single; 5475 (5.9%) two race/ethnicities**

- All 100% who self-identified as European/West Asian had (evidence of) European/West Asian (genetic) ancestry

- Nearly all 99.7% self identifying as African/African American race/ethnicity had African ancestry; but 91% had European ancestry

- For self-reported East Asians, all had East Asian ancestry

- Latinos, nearly all European/West Asian ancestry; high proportion (94.2%) Native American ancestry, and 27.7% had African ancestry

- Among self identified Native American race/ethnicity, 14.4% have Native American ancestry, and all have European/West Asian ancestry

Reflect historical & recent mating practices and geography on genetic variation
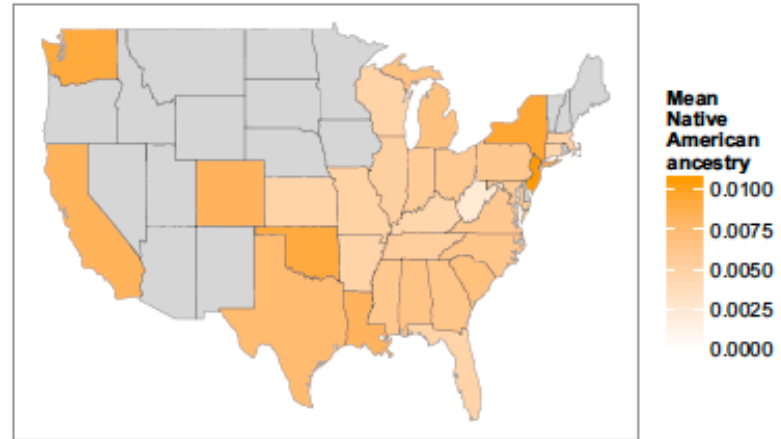**Ancestral genes may or may not have important functional significance**

Distribution of Ancestry of Self Reported African Americans across the U.S.

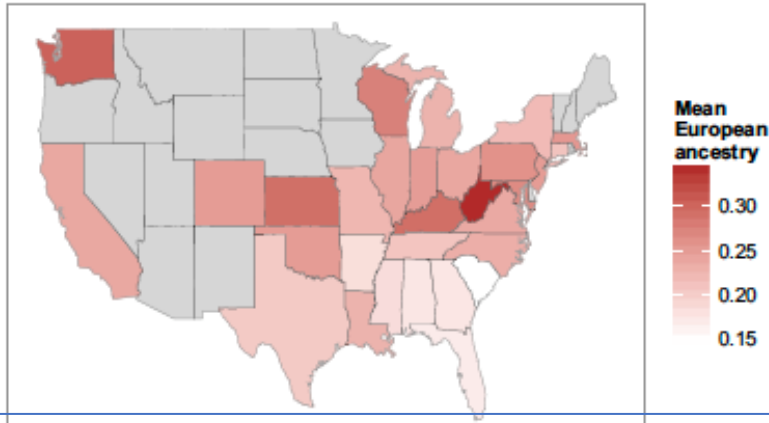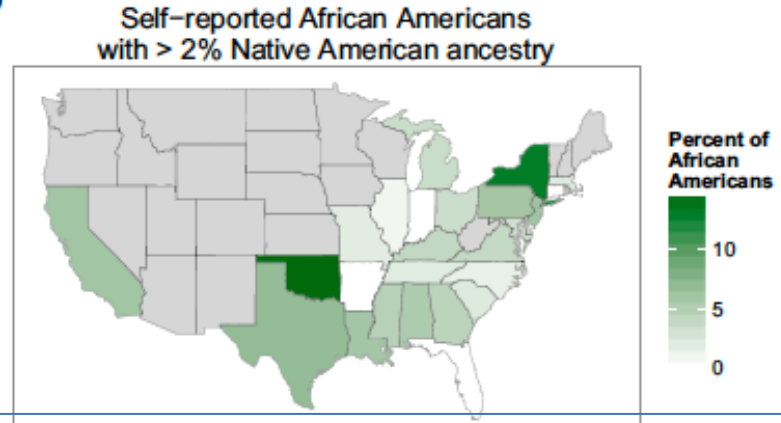**73.2% African, 24.0% European, and 0.8% Native American ancestry**
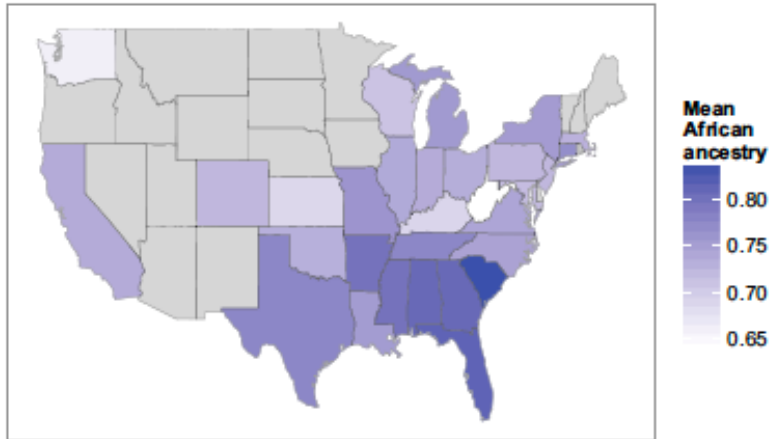
Bryc K, Durand EY, Macpherson JM, Reich D, Mountain JL. The genetic ancestry of African Americans, Latinos, and European Americans across the U.S. Am J Hum Genet. 2015 ;96(1):37-53

No differences in sCr levels found between racial groups in Brazil

Serum creatinine levels (mg/dL) stratified according to sex, race and age ranges.

Age (years)	Females			Males		
	White (n = 254)	Mixed race (n = 287)	Black (n = 214)	White (n = 179)	Mixed race (n = 248)	Black (n = 121)
20-39	0.76±0.14	0.74±0.14	0.77±0.15	1.0±0.15 *	0.97±0.18 *	0.97±0.18 *
40-59	0.75±0.13	0.76±0.15	0.78±0.15	0.97±0.19 *	0.97±0.18 *	1.05±0.52 *
> 60	0.83±0.23	0.83±0.18	0.93±0.26 **	1.14±0.45 *	1.08±0.25 *	1.17±0.29 *
All	0.78±0.17	0.78±0.16	0.81±0.19	1.02±0.27 *	0.99±0.19 *	1.07±0.44 *

$*$ $p < 0.05$ males vs. females in the same age range;

$**$ $p < 0.05$ vs. mixed race females.

Association between variables and serum creatinine levels in the linear regression analysis.

Variable	β coefficient (95%CI)	p-value
Age (decade)	0.035 (0.026; 0.043)	< 0.001
Sex (male)	0.222 (0.197; 0.248)	< 0.001
Race (non-white)	0.09 (-0.05; 0.22)	0.201

95%CI: 95% confidence interval.

Barcellos RC, Matos JP, Kang HC, Rosa ML, Lugon JR. Comparison of serum creatinine levels in different color/race categories in a Brazilian population. Cad Saude Publica. 2015;31(7):1565-9.

Intercontinental Differences in Study Findings: Possible reasons

- Social and environmental factors are drivers
- Genetic ancestral differences between populations
- Methods, including patient selection, in research
- Differences in self-identification of race

Associations do not prove causality of possible drivers of creatinine or GFR

Subjective

Objective

Social
Customs
Behavioral

Race Ethnicity

Genetic Ancestry

Genetics
Physiology

- Diet
- Other?

- Muscle mass
- Tubular secretion
- Extra-renal elimination
- Other?

Still poorly understood!

Potential Clinical & Health Consequences of Removing Race Coefficent from eGFR equations:

Increase in persons with CKD and more severe stages
Past underdiagnosis, or with change, overdiagnosis?

Benefit   **Balance sheet?**   **Harm**

↓Living kidney donation

↑**Referral to specialists**

↑**Access to transplant waitlist**

↓Drug use or dosing: **metformin,** SGLT2 Inh, pain meds (analgesics, opioids), ACE inhibitors, antibiotics, chemotherapy (e.g. carboplatin)

↑Access to Medicare services:
  ↑nutrition therapy
  ↑CKD education

↓Contrasted Imaging procedures

↓Access to clinical trials

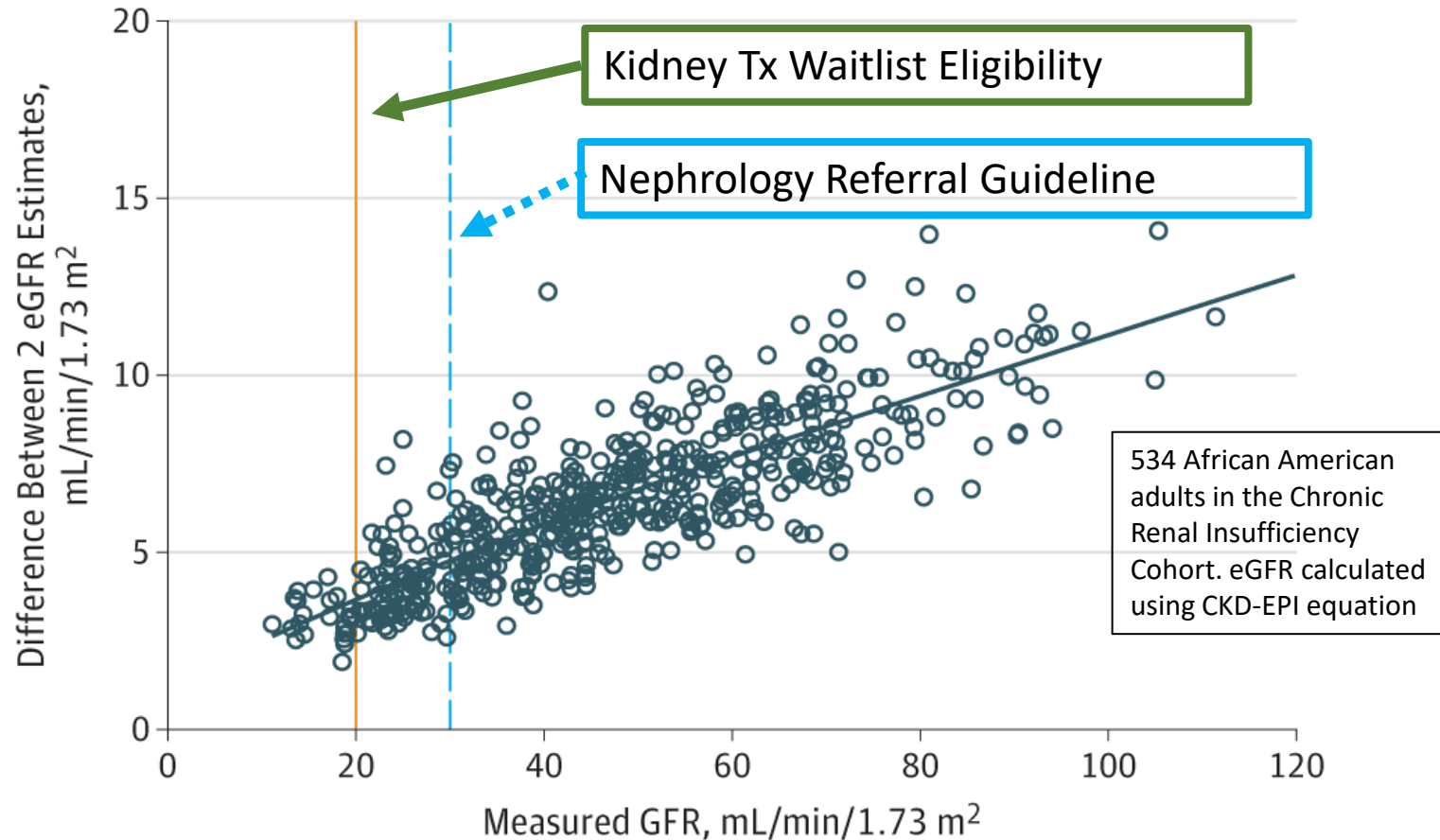↑More aggressive CKD mgmt

↑Anxiety (labeling)

Clinical decisions can be affected by accuracy of GFR assessment among blacks
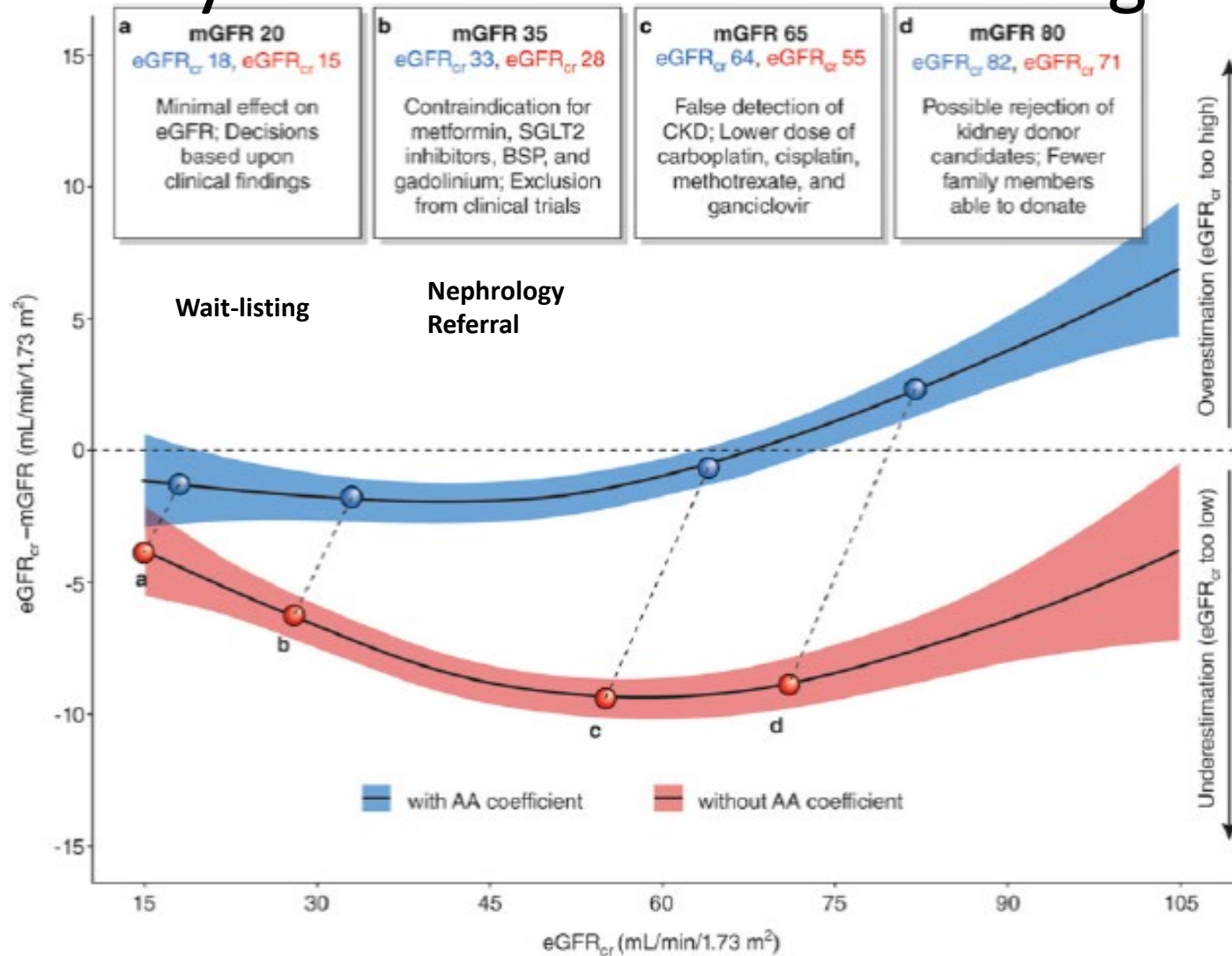
Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney Disease, Race, and GFR Estimation *Clin J Am Soc Nephrol*. 2020;CJN.12791019

Is Use of Race in Kidney Function Estimation Race-Based Medicine and Does it Restrict Access to Care?

534 African American adults in the Chronic Renal Insufficiency Cohort. eGFR calculated using CKD-EPI equation
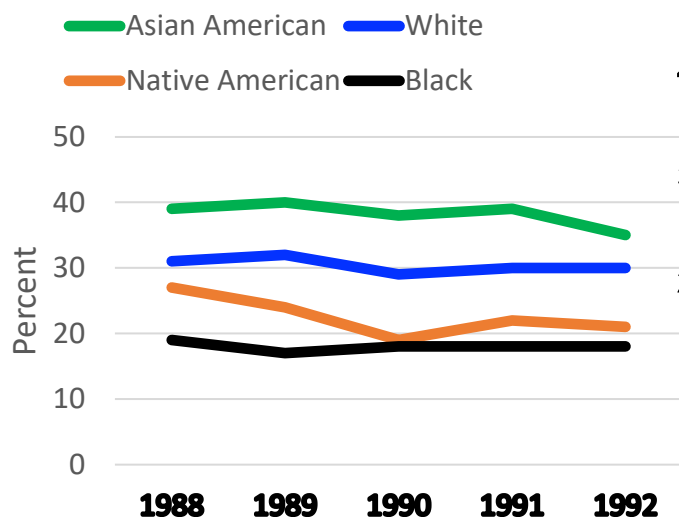
Black patients must have kidney function lower than the lines to be eligible for kidney transplant waiting list or nephrology referral.

Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. JAMA. 2019 Jul 9;322(2):113-114.

Disparities for Blacks in Wait-listing and Nephrology Referral Were Present Before Incorporation of Race into Equations

Wait-listing for Transplantation Within 1 Yr of Kidney Failure[1] (1988-1992)

Legend:
- Asian American (green)
- White (blue)
- Native American (orange)
- Black (black)

Percent (y-axis: 0, 10, 20, 30, 40, 50)

x-axis: 1988, 1989, 1990, 1991, 1992

Over One Third of Blacks Initiating Dialysis from 1995-1998 Received a Late Evaluation by a Nephrologist[2]

< 4 months before dialysis

CHOICE
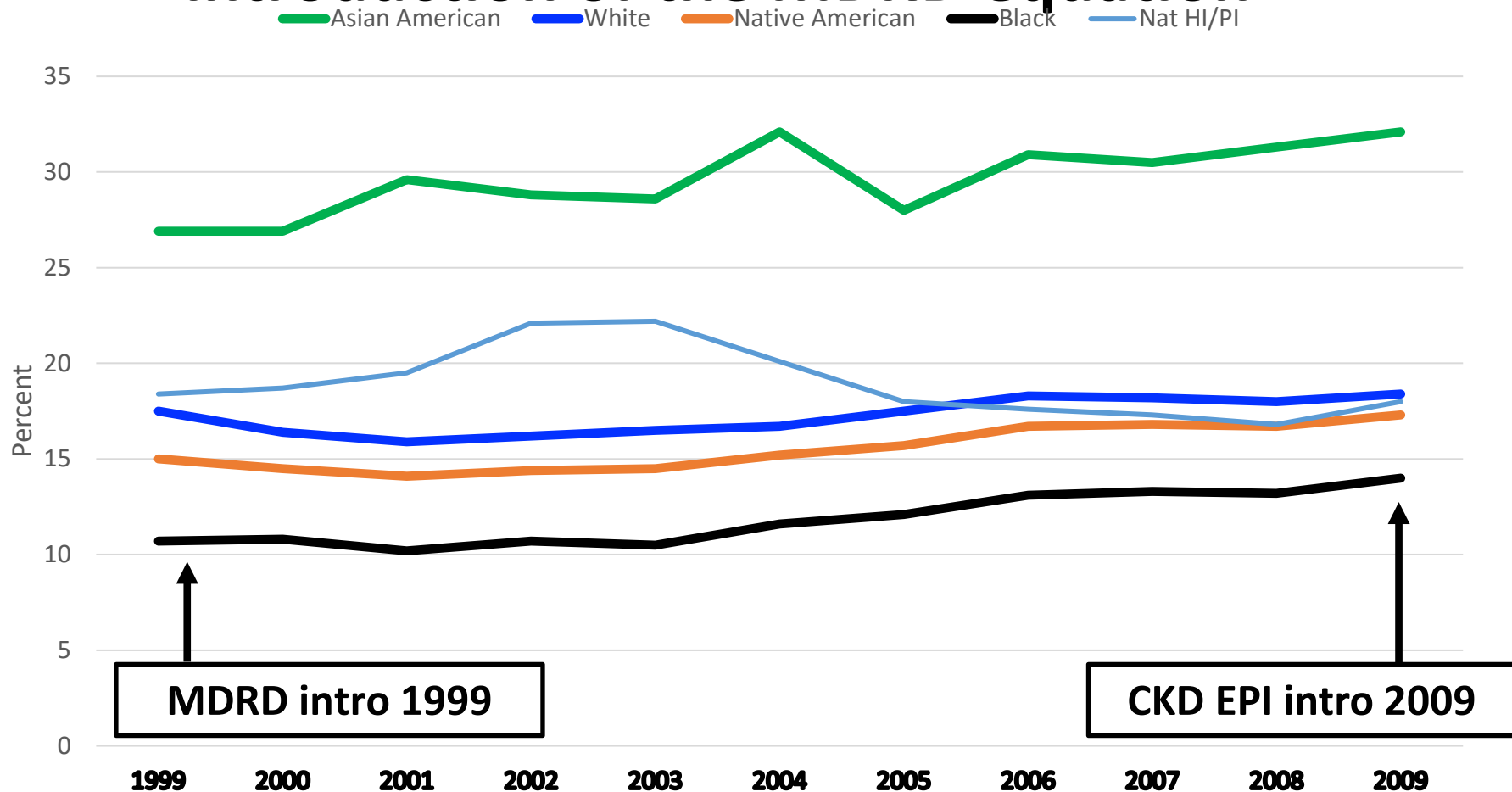CHOICE
CHOICE
CHOICE
CHOICE

Bar chart (y-axis: 0 to 50):
- WM: 25
- WF: 30
- BF: 38
- BM: 45
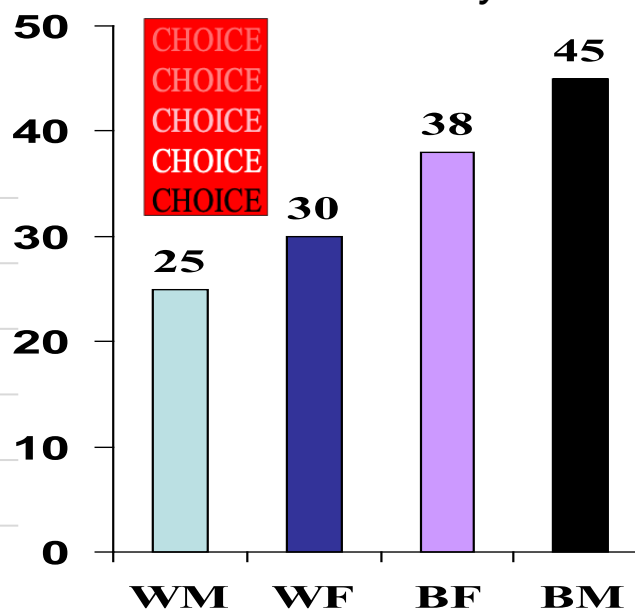
SCr Equations

Cockcroft-Gault Published 1976[3] (age, sex, wgt)

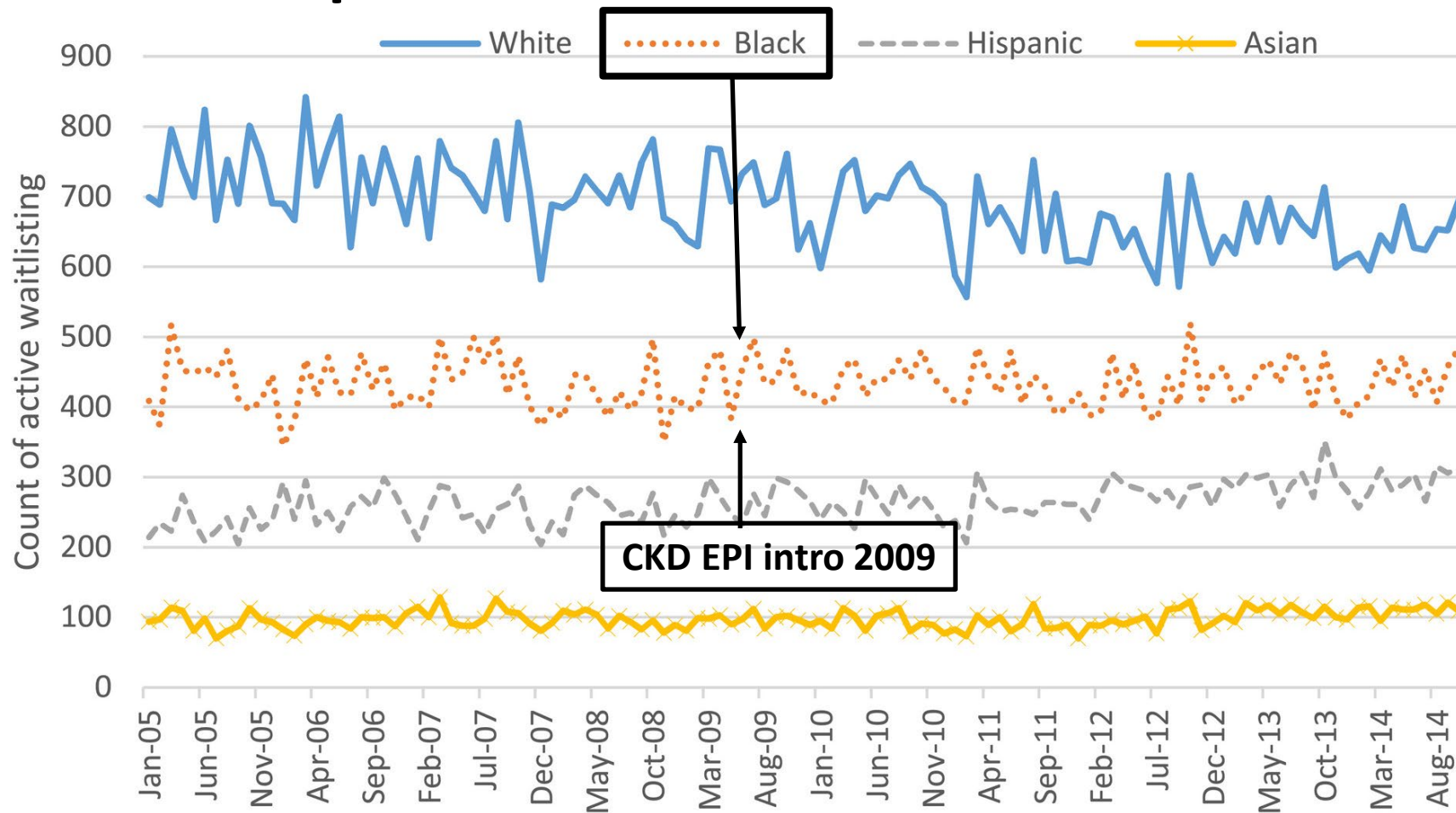*MDRD Published 1999[4]* (age, sex, **race**)

CKD Epi Published 2009[5] (age, sex, **race**)

1. Eggers PW. Racial differences in access to kidney transplantation. *Health Care Financ Rev*. 1995;17(2):89-103.
2. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag, M, Levey A, Powe N. The Timing of Specialist Evaluation in Chronic Kidney Disease and Mortality *Annals of Internal Medicine* 2002;137:479-486
3. Cockcroft, D.W. and M.H. Gault. Prediction of creatinine clearance from serum creatinine. Nephron. 1976. 16(1):31-41.
4. Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Annals of Internal Medicine, 130: 461-470, 1999
5. Levey AS, Stevens LA, Schmid CH, et al: A new equation to estimate GFR. Annals of Internal Medicine, 150: 604-612, 2009

Wait-listing (or receipt of a deceased donor transplant) within 1 Year of Kidney Failure did not decrease for Blacks following introduction of the MDRD equation

Legend: Asian American · White · Native American · Black · Nat HI/PI

Y-axis: Percent (0, 5, 10, 15, 20, 25, 30, 35)

X-axis: 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009

MDRD intro 1999

CKD EPI intro 2009

USRDS Annual Data Report 2012 Healthy People CKD 12 Objective

Monthly count of new wait-listing events were not decreased following introduction of CKD EPI equation Data from 2005 to 2015

Legend: White, Black, Hispanic, Asian

Y-axis: Count of active waitlisting (0 to 900)

X-axis: Jan-05 to Aug-14

CKD EPI intro 2009

Zhang X, Melanson TA, Plantinga LC, et al. Racial/ethnic disparities in waitlisting for deceased donor kidney transplantation 1 year after implementation of the new national kidney allocation system. *Am J Transplant*. 2018;18(8):1936-1946
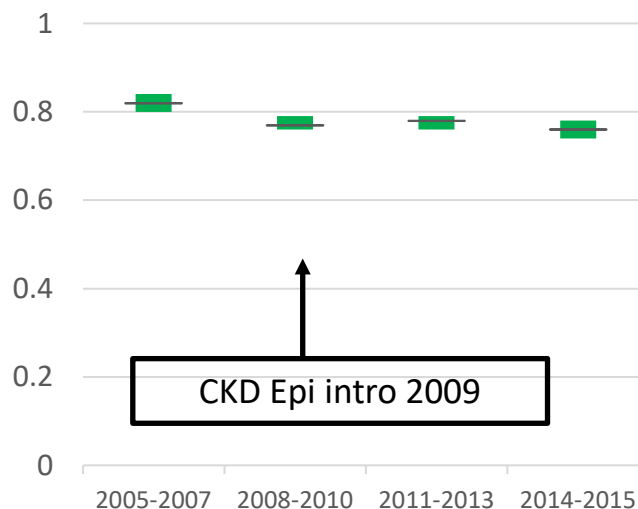
Ongoing Trends in Racial/Ethnic Disparities in Receipt of at Least 12 Months of Pre-dialysis Nephrology Care

Similar trend in race and no race coefficient minorities suggests disparities are driven by other factors

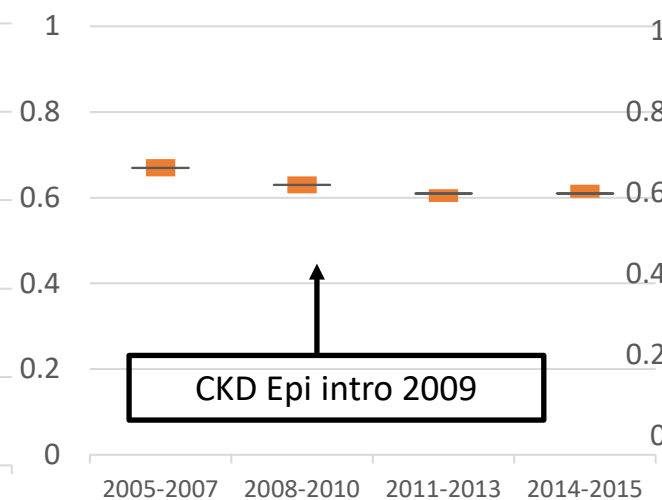### Race Coefficient
Blacks vs Whites
Odds Ratio* of Nephrology Referral 12 months prior to dialysis start

No Race Coefficient
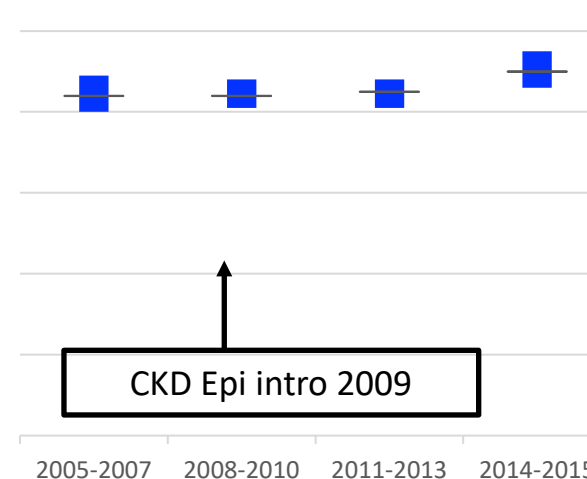#### Hispanics vs Whites
Odds Ratio* of Nephrology Referral 12 months prior to dialysis start

No Race Coefficient
Asians vs Whites
Odds Ratio* of Nephrology Referral 12 months prior to dialysis start

CKD Epi intro 2009

CKD Epi intro 2009

CKD Epi intro 2009

*Adjusted for age, sex, BMI, ESKD etiology

Purnell TS, Bae S, Luo X, Johnson M, Crews DC, Cooper LA, Henderson ML, Greer RC, Rosas SE, Boulware LE, Segev DL. National Trends in the Association of Race and Ethnicity With Predialysis Nephrology Care in the United States From 2005 to 2015. JAMA Netw Open. 2020 Aug 3;3(8):

Metformin Prescribing Disparities Eliminated after FDA's Serum Creatinine-based to eGFR (with race) Label Change

Steeper reduction in metformin prescriptions at eGFR<60 ml/min/1.73 m2 in Black than in White patients

Significant increase in metformin prescriptions only in Black patients with eGFR of 30-44 ml/min per 1.73 m2
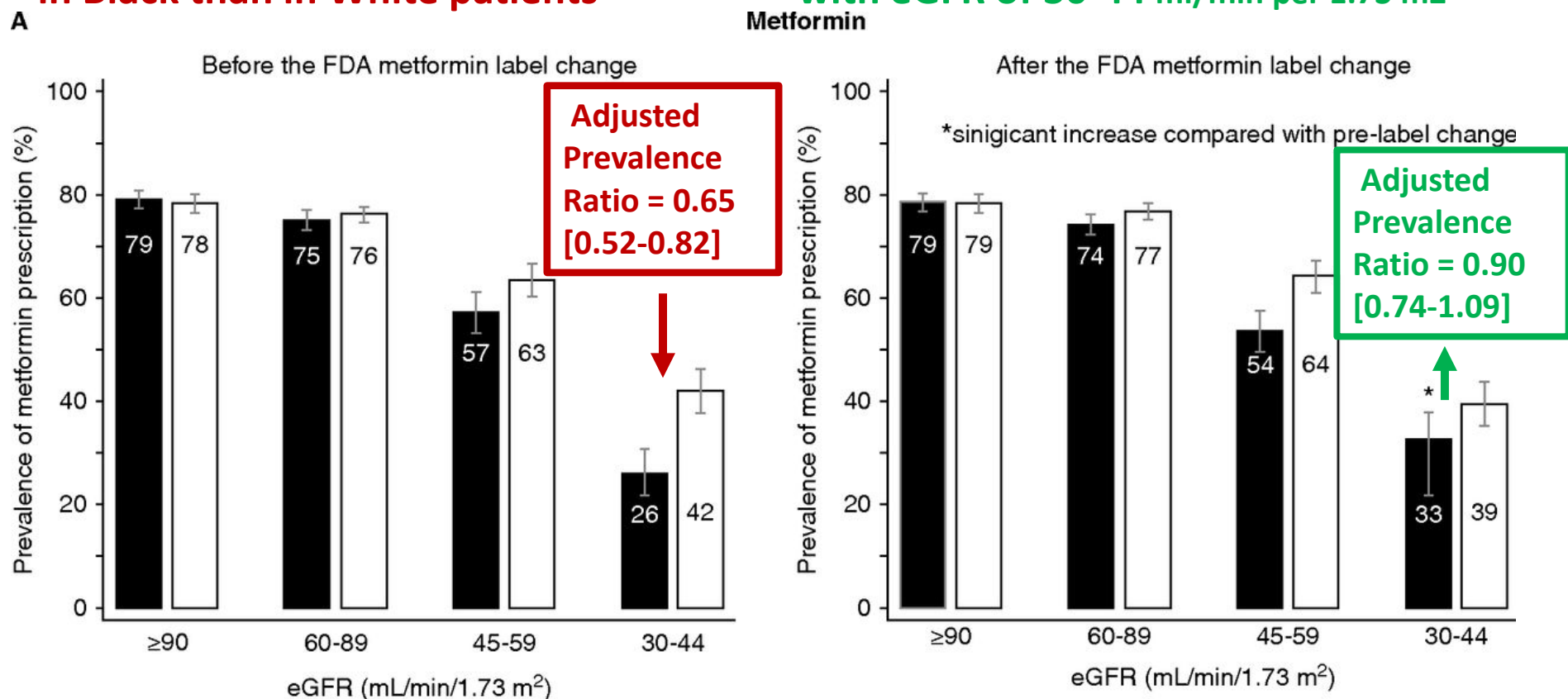
Shin JI, Sang Y, Chang AR, et al. The FDA Metformin Label Change and Racial and Sex Disparities in Metformin Prescription among Patients with CKD [*J Am Soc Nephrol*. 2020; ASN.2019101119. doi:10.1681/ASN.2019101119

Sulfonylurea Prescribing Before and After FDA's Serum Creatinine-based to eGFR Metformin Label Change
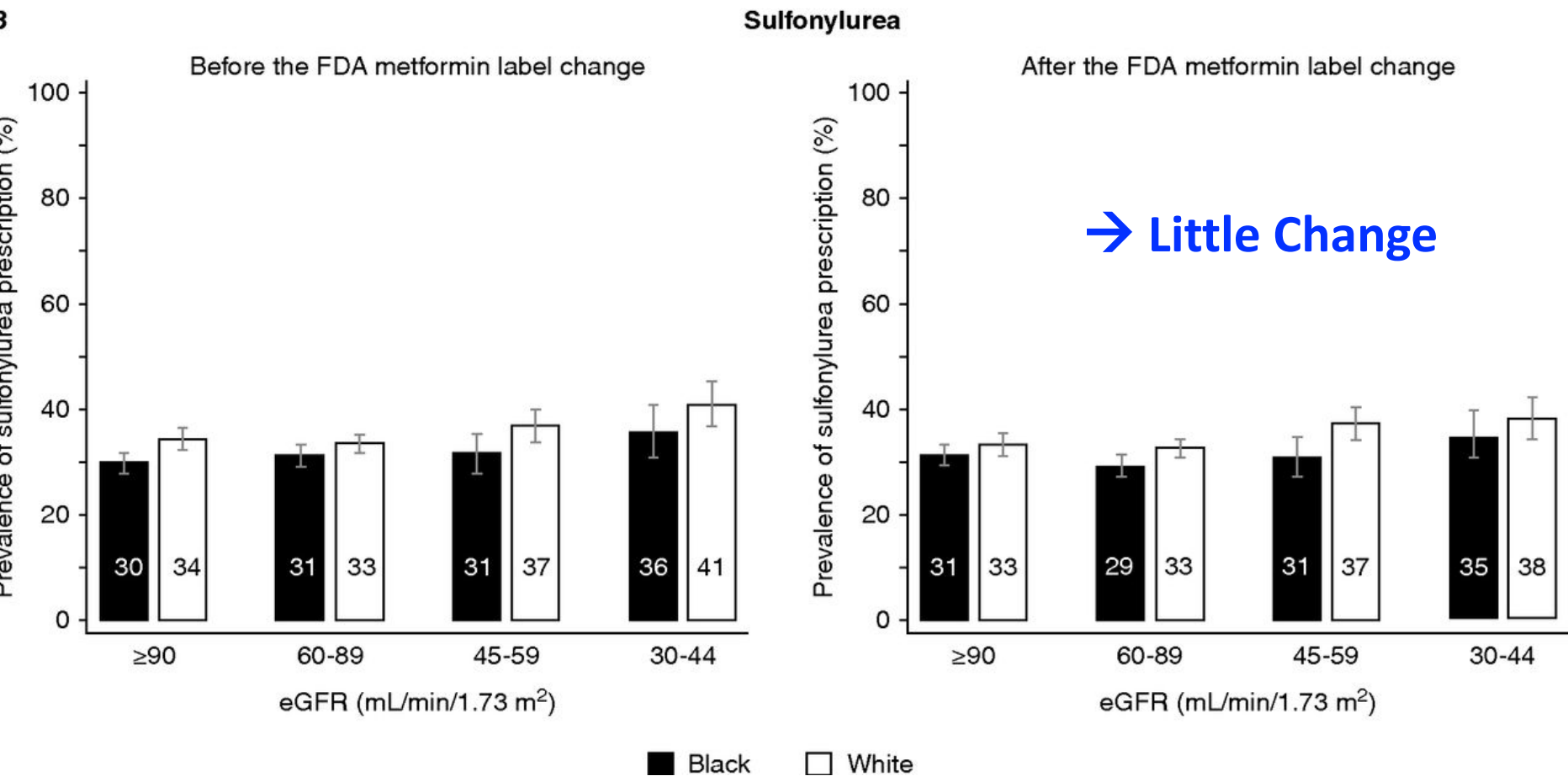
Jung-Im Shin et al. JASN
doi:10.1681/ASN.2019101119

Other Consequences of Race Removal

- Regulatory approval of drugs: pharmacokinetics

- Tracking kidney disease in the population

- Labelling, life or disability insurance access

- Research study participation (on CKD or studies using eGFR) by African Americans

Approaches to Mitigate Use of Race in Estimating or Reporting GFR in Routine Clinical Practice

- Return to the Past: Scr or CG

- Measure GFR: (e.g. iothalamate)

- Dominant Race Standard

- Substitute Phenotypes

- Blended Race Standard

- Rangeless Reporting

- Raceless Markers

- Your Approach?

Scr – serum creatinine alone
CG – Cockcroft-Gault equation
(Scr, weight, age, sex)

Powe NR. Black Kidney Function Matters: Use or Misuse of Race. JAMA 2020
Published online July 29, 2020 **Conversations with Howard Bauchner: JAMA Podcast**

Return to the (Raceless) Past

	Advantages *or Challenges*
Use serum creatinine level	Does not incorporate race in estimation or reporting. *Less accurate because does not take into account any factors (or proxies) affecting creatinine production or secretion.*
Use Cockcroft-Gault equation (Scr, weight, age, sex) to estimated creatinine clearance	Does not incorporate race in estimation or reporting. *Derivation did not include diverse populations (249 white males). Overestimates GFR in obesity (changes in population since development) and underestimates in older adults; Less accurate due to poor precision and bias.*

Approaches to Mitigate Use of Race in Estimating or Reporting GFR
Directly Measure Clearance or GFR (Raceless)

	Advantages *or Challenges*
Measure creatinine clearance	Does not incorporate race in estimation or reporting. *Less accurate than measured GFR More time/effort; low fidelity with 24-hour urine collection*
Measure GFR directly with filtration markers (e.g iothalamate)	Does not incorporate race in estimation or reporting. *More time, effort and cost*

Use when decision making could affect patient health and time permits

Dominant Race Standard

Approach	Advantages *or Challenges*
Discard race coefficient from equations and report the "non-black" estimate	Removes race in reporting. *Is discriminatory because it ignores data on blacks from studies included in equation derivation. Likely less accurate for blacks.*

→ **Institutionalizes Exclusion of Blacks from Research for Clinical Decision Making**

Dominant Race Standard

- CKD Epidemiology (CKD EPI) Collaboration
  - $141 \times \min(SCr/k,1)^a \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times$ [1.018 if female] $\times$ [1.159 if African American]

SCr = serum creatinine in mg/dL

k = 0.7 for females and 0.9 for males

a = 0.329 for females and -0.411 for males

min indicates the minimum of SCr/k or 1

max indicates the maximum of SCr/k or 1.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May 5;150(9):604-12.

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (March 1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130 (6): 461–70.

Dominant Race Standard

- CKD Epidemiology (CKD EPI) Collaboration
  - $141 \times \min(SCr/k,1)^a \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if female}]$

- Removes data contributed by 31% of Blacks in the 26 pooled studies that included a gold standard of directly measured GFR
  - Derivation n=8254: 2601 Blacks (31%), **1807 from African American Study of Kidney Disease**
  - Validation n=3896: 451 Blacks (12%)

$\times [1.159 \text{ if African American}]$

SCr = serum creatinine in mg/dL

k = 0.7 for females and 0.9 for males
a = 0.329 for females and -0.411 for males
min indicates the minimum of SCr/k or 1
max indicates the maximum of SCr/k or 1.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May 5;150(9):604-12.
Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (March 1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130 (6): 461–70.

GFR Estimating Equations: CKD EPI data set

- n=5653
- Non-African Americans

- 2601 **(1807)**
- African Americans
  (**African American Study of Kidney Disease**)

Risk Score for Coronary Artery Disease

Framingham Heart Study

Framingham Massachusetts

- 14,531 participants from 1948-1994, ongoing

- All European Americans

Jackson Heart Study

Jackson, Mississippi

- 5309 participants from 2000 - present

- All African Americans

Fox ER, Samdarshi TE, Musani SK, et al. Development and Validation of Risk Prediction Models for Cardiovascular Events in Black Adults: The Jackson Heart Study Cohort. *JAMA Cardiol*. 2016;1(1):15-25. Hurley LP, Dickinson LM, Estacio RO, Steiner JF, Havranek EP. Prediction of cardiovascular death in racial/ethnic minorities using Framingham risk factors. *Circ Cardiovasc Qual Outcomes*. 2010;3(2):181-187.

Racial Phenotyping

	Advantages *or Challenges*
Substitute "low muscle mass" and "high muscle mass' for "non black" and "black"	Removes race in reporting. Recognizes participation of blacks in derivation studies*. Assumes race is a proxy for muscle mass, (stereotyping all blacks as having high muscle mass), high muscle mass = higher creatinine, and we can measure muscle mass in clinical practice. Likely less accurate for blacks.*

→ **Institutionalizes Stereotyping**

All Possibilities

Blended Race Standard

	Advantages *or Challenges*
Develop new equation from CKD-EPI data using weighted average of ethnicity coefficients (e.g. 32% of black CKD EPI participants, 13% of blacks in U.S. or % of blacks at a health care institution)	Removes race in reporting. Recognizes participation of blacks in derivation studies. *Requires agreement on appropriate weights. Raises question whether same should be done for all race/ethnic groups. Likely less accurate for everyone.*

Powe NR. Black Kidney Function Matters: Use or Misuse of Race. JAMA 2020 Published online July 29, 2020
Conversations with Howard Bauchner: JAMA Podcast

Blended Race Standard Example

Proportional to Race in the U.S.

$$141 \times \min(SCr/k, 1)^a \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if female}] \boxed{\times \mathbf{0.87}}$$

+

$$141 \times \min(SCr/k, 1)^a \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if female}] \times [1.159] \boxed{\times \mathbf{0.13}}$$

African Americans comprise 13% of the U.S. Population

Blended equations have not been tested

1.159 is the Black coefficient
SCr = serum creatinine in mg/dL

k = 0.7 for females and 0.9 for males
a = 0.329 for females and -0.411 for males
min indicates the minimum of SCr/k or 1
max indicates the maximum of SCr/k or 1.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May 5;150(9):604-12.
Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (March 1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130 (6): 461–70.

Raceless Range Reporting

	Advantages *or Challenges*
Report two values currently generated by the CKD EPI equation, but not openly tag them with race descriptors	Removes race in reporting. Recognizes participation of blacks in derivation studies. *Underlying race distinction remains below the surface.* Leaves clinical correlation, nephrology consultation, and shared decision-making to ordering physicians.

Powe NR. Black Kidney Function Matters: Use or Misuse of Race. JAMA 2020 Published online July 29, 2020
Conversations with Howard Bauchner: JAMA Podcast

Newer Raceless Markers

	Advantages *or Challenges*
Using non-creatinine filtration markers for which race does not add greater precision (e.g cystatin C)	Does not incorporate race in estimation or reporting. *Higher cost, not widely available now, standardization improving. Uncertain performance in very ill patients*

Use when decision making could affect patient health

Powe NR. Black Kidney Function Matters: Use or Misuse of Race. JAMA 2020 Published online July 29, 2020
Conversations with Howard Bauchner: JAMA Podcast

Summary

- Elimination of race is a worthy aspiration, but consequences are far reaching

- Making changes is not a trivial task – seek "correct diagnosis" not "under or over diagnosis"
  → Avoid doing more harm than good (primum non nocere)

- Some approaches promulgated to remove race institutionalize discrimination, or may be racist
  - Newer raceless estimation markers may offer a path forward, but need to be scaled, widely adopted and monitored

- Solution should be <u>consistent</u>, <u>durable</u>, <u>evidence-based</u> and <u>devised with input</u> of clinicians, system leaders, social scientists and **patients**

Summary

- Elucidate relation between biology, social and environmental factors -- including race (subjective) and ancestry (objective); Advance genetic ancestry

- eGFR equations unlikely as cause of disparities in waitlisting or specialist referral; *evidence they helped eliminate metformin prescribing disparities*

- Health equity is the goal: Consider contribution of drivers to disparities with empirical evidence (not anecdotes or thought experiments) and focus on the <u>most important, evidence-based</u> drivers
  - e.g. endorse risk of outcomes (variable based on need) vs thresholds (fixed at same level): **Equity vs Equality**

Health Equity: Where should we set our sights and efforts?Look around!

Drivers of Disparities

eGFR Equations

THANK YOU!