Moving Away From Race-Based Medicine: *The New eGFR Equation*

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MEDICINE AND SOCIETY

Debra Malina, Ph.D., *Editor*

Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms

Darshali A. Vyas, M.D., Leo G. Eisenstein, M.D., and David S. Jones, M.D., Ph.D.

VIEWPOINT

Reconsidering the Consequences of Using Race to Estimate Kidney Function

Health inequities and the inappropriate use of race in nephrology

Nwamaka D. Eneanya[1], L. Ebony Boulware[2], Jennifer Tsai[3], Marino A. Bruce[4], Chandra L. Ford[5], Christina Harris[6], Leo S. Morales[7], Michael J. Ryan[7], Peter P. Reese[1,8], Roland J. Thorpe Jr.[9], Michelle Morse[10], Valencia Walker[11], Fatiu A. Arogundade[12], Antonio A. Lopes[13] and Keith C. Norris[6]

Precision in GFR Reporting
Let's Stop Playing the Race Card

Vanessa Grubbs

CJASN 15: ●●●–●●●, 2020. doi: https://d

Annals of Internal Medicine

IDEAS AND OPINIONS

Race and the False Precision of Glomerular Filtration Rate Estimates

Ashwini R. Sehgal, MD

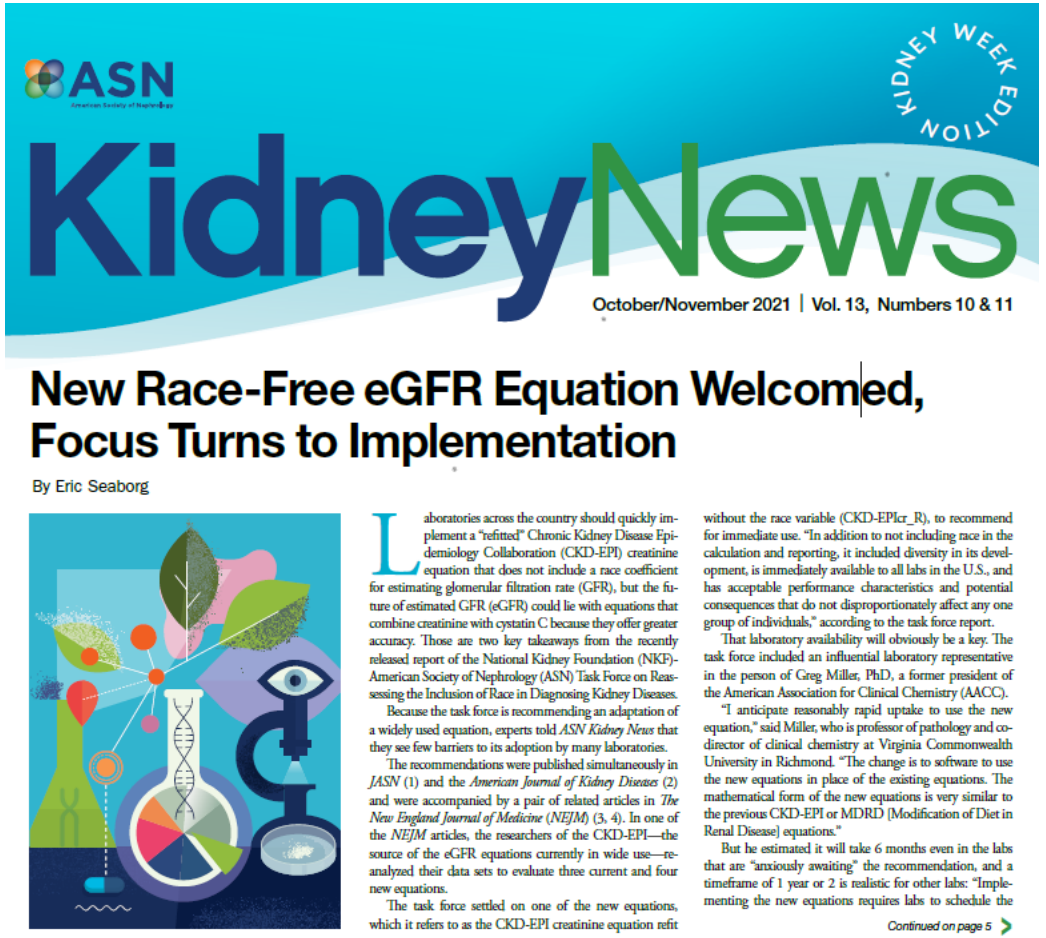
What Is the Role of Race in Medicine?

- Recommendations for utilizing race in healthcare:
  1. Use confers substantial benefit
  2. Benefit cannot be achieved through other feasible approaches
  3. Patients who reject race categorization are accommodated fairly
  4. Use of race is transparent

Eneanya et al, *JAMA* 2019;322:113-4

Impact in Nephrology

- Re-exploration of role of race variable in eGFR equations
- Development of a new consensus, race-free eGFR equation
  - Published 9/2021 and implementation underway across the country



ASN

KIDNEY WEEK EDITION

KidneyNews

October/November 2021 | Vol. 13, Numbers 10 & 11

New Race-Free eGFR Equation Welcomed, Focus Turns to Implementation

By Eric Seaborg

Laboratories across the country should quickly implement a "refitted" Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation that does not include a race coefficient for estimating glomerular filtration rate (GFR), but the future of estimated GFR (eGFR) could lie with equations that combine creatinine with cystatin C because they offer greater accuracy. Those are two key takeaways from the recently released report of the National Kidney Foundation (NKF)-American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases.

Because the task force is recommending an adaptation of a widely used equation, experts told *ASN Kidney News* that they see few barriers to its adoption by many laboratories.

The recommendations were published simultaneously in *JASN* (1) and the *American Journal of Kidney Diseases* (2) and were accompanied by a pair of related articles in *The New England Journal of Medicine* (*NEJM*) (3, 4). In one of the *NEJM* articles, the researchers of the CKD-EPI—the source of the eGFR equations currently in wide use—reanalyzed their data sets to evaluate three current and four new equations.

The task force settled on one of the new equations, which it refers to as the CKD-EPI creatinine equation refit without the race variable (CKD-EPIcr_R), to recommend for immediate use. "In addition to not including race in the calculation and reporting, it included diversity in its development, is immediately available to all labs in the U.S., and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals," according to the task force report.

That laboratory availability will obviously be a key. The task force included an influential laboratory representative in the person of Greg Miller, PhD, a former president of the American Association for Clinical Chemistry (AACC).

"I anticipate reasonably rapid uptake to use the new equation," said Miller, who is professor of pathology and co-director of clinical chemistry at Virginia Commonwealth University in Richmond. "The change is to software to use the new equations in place of the existing equations. The mathematical form of the new equations is very similar to the previous CKD-EPI or MDRD [Modification of Diet in Renal Disease] equations."

But he estimated it will take 6 months even in the labs that are "anxiously awaiting" the recommendation, and a timeframe of 1 year or 2 is realistic for other labs: "Implementing the new equations requires labs to schedule the

Continued on page 5 >

Today's Objectives

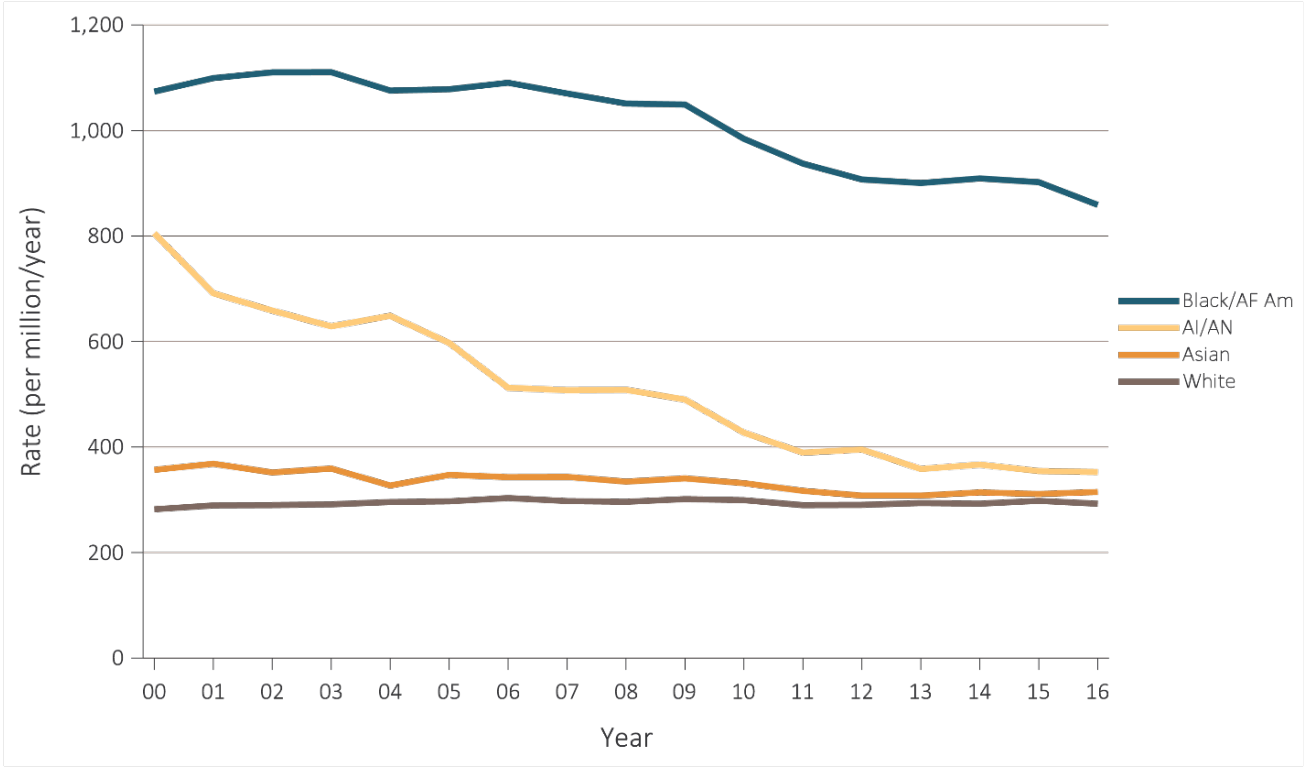
- Describe existing racial disparities in nephrology outcomes and care
- Describe the rationale for and development of the new consensus eGFR estimating equation
- Describe the potential clinical impact of implementation of the new eGFR estimating equation

Racial Disparities in Nephrology

Chronic Kidney Disease/Endstage Renal Disease

- African-Americans are 13% of US population but 32% of ESRD population → 4x risk for ESRD compared to Caucasians
- Contributions of socioeconomic differences, access to care, differences in risk factors (e.g. DM, HTN), other environmental factors
- Trends toward reducing disparities?

Trends in standardized ESRD incidence rate, by race, in the U.S. population, 2000-2016



USRDS.org

Kidney Transplantation

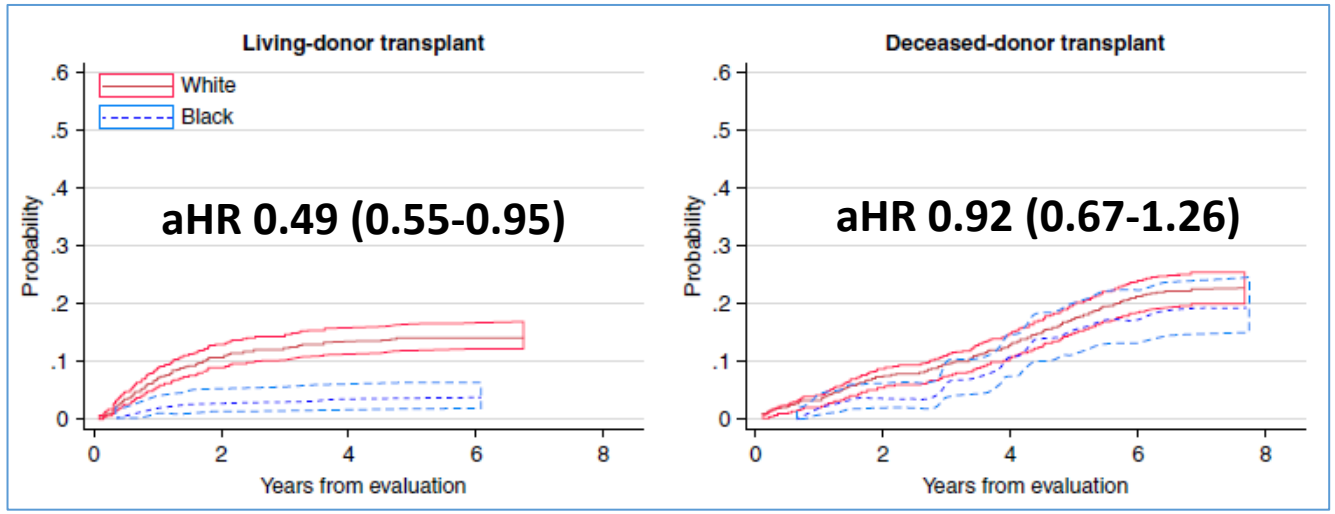
- Black pts 25% less likely to be waitlisted after adjusting for medical factors
- Black pts less likely to receive kidney transplant
- Black pts have worse outcomes following kidney transplantation

- Highlighting disparities has led to changes in organ allocation system, educational interventions
  - Some evidence of improvement in disparities

Transplant outcomes by race, 1990-2009

Outcome	Caucasian recipients (%)	African American recipients (%)
Delayed graft function		
Overall	15.0	25.8
Deceased donor	22.4	31.2
Living donor	4.4	6.4
Acute rejection		
6 months	15.0	16.2
1 year	15.9	17.4
Overall	25.5	28.8
Graft loss		
1 year	5.60	9.96
3 years	10.10	17.61
5 years	14.68	25.07
Death		
1 year	3.96	4.84
3 years	8.93	10.85
5 years	15.17	18.28

Taber, *Kidney Int* 2016;90:878-871

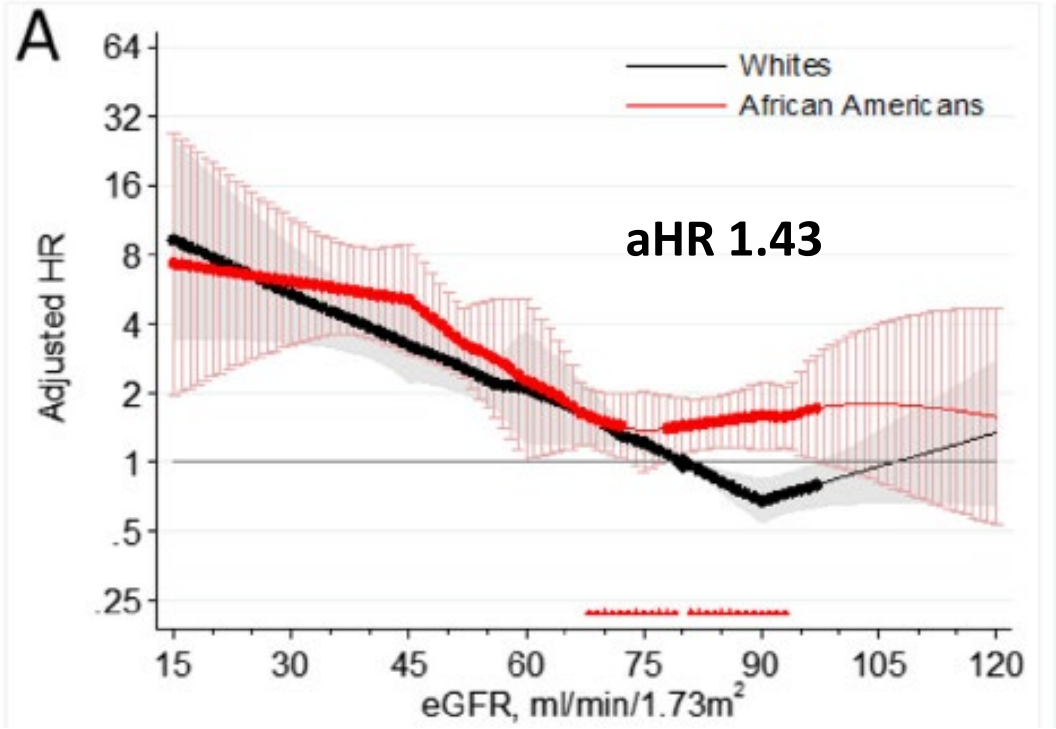


Wesselman, *CJASN* 2021;16:262-74

Acute Kidney Injury

- Black (compared to White) pts are at increased risk for AKI in a variety of settings: general population, hospitalized, post-PCI, post-surgery

- Reasons for disparity are uncertain
  - Persist after adjustment for comorbidities and other medical factors
  - Role of socioeconomic factors?
  - Role of systematic racism?



Grams, *AJKD* 2015;44:591-601

Race in Kidney Function Estimation

Clinical Utility of GFR

- Define/classify CKD and assess CKD prognosis
- Monitoring of kidney function
- Determine dosing for drugs with renal clearance
- Used in guidelines for referral and management of CKD
- Kidney transplantation eligibility

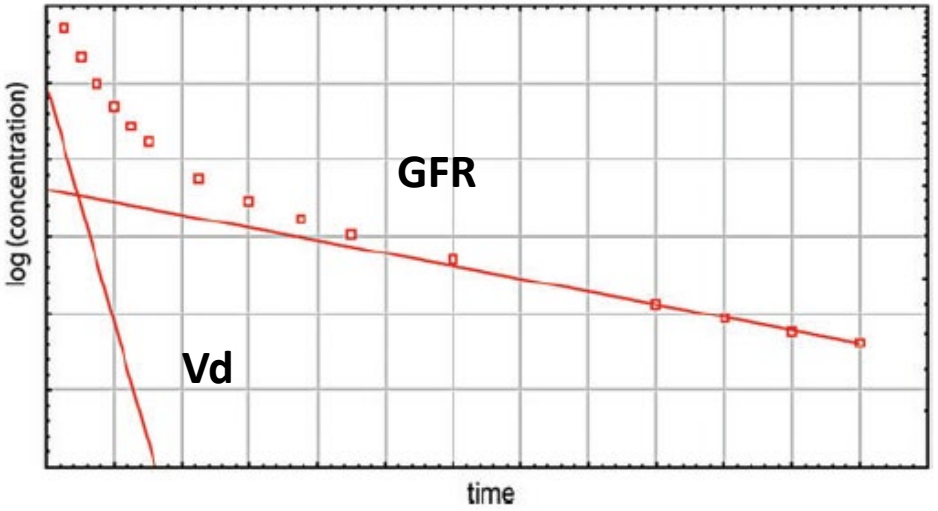
Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m^2) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

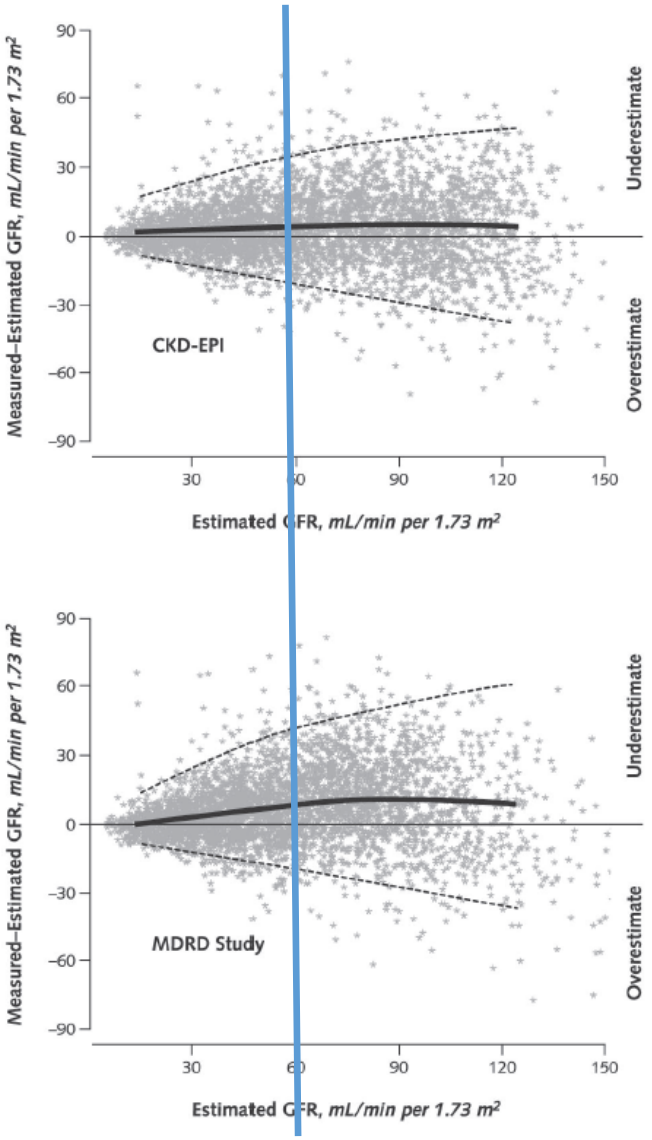
GFR Measurement

- Inulin clearance: “ideal GFR marker”
  - Requires constant infusion and timed urine collections
- Iothalamate urinary or plasma clearance
- Iohexol plasma disappearance method
  - Multiple different protocols described
  - Injection of iohexol followed by serial plasma level measurements and calculation of AUC
- Creatinine clearance measurement
  - Timed urine collection
  - By definition, is an overestimate of GFR



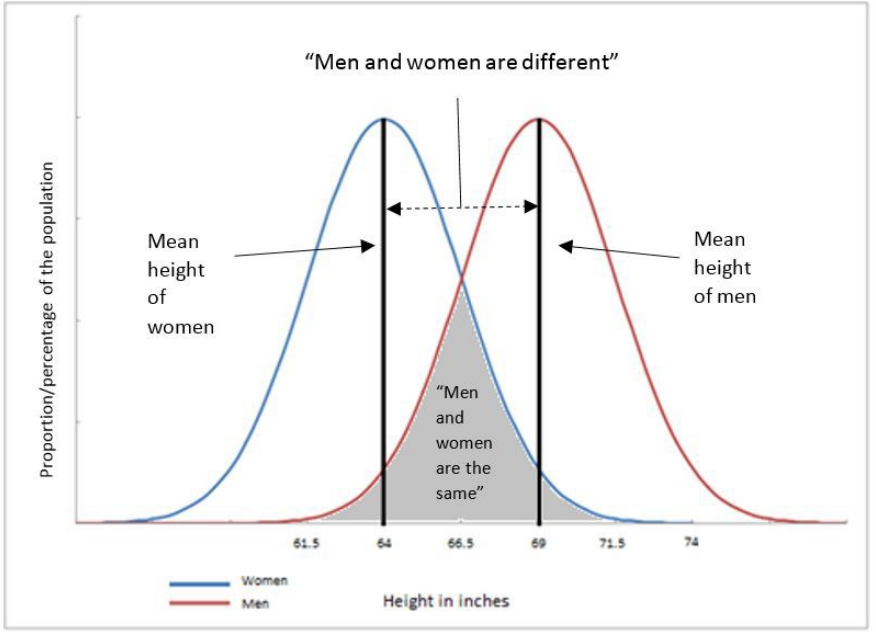
How Do We Estimate GFR (eGFR)?

- MDRD equation (1999): RCT (n=1628) in patients with CKD → baseline iothalamate urine clearance
  - Supplanted CrCl (Cockroft-Gault formula)
- CKD-EPI equation (2009): Pooled data from studies (n=8254 development; n=3896 external validation)
  - Specific goal to increase accuracy in higher GFR range
  - Multiple linear regression
  - eGFR = 141 * min(SCr/k,1)^{a} * max(SCr/k,1)$^{-1.209}$ * 0.993^{age} * 1.018 (if female) * **1.159 (if black)**
- Cystatin C: Produced by all nucleated cells
  - Thought not affected by muscle mass
  - No race variable
  - Challenges with availability/familiarity, lab standardization and potential confounding factors

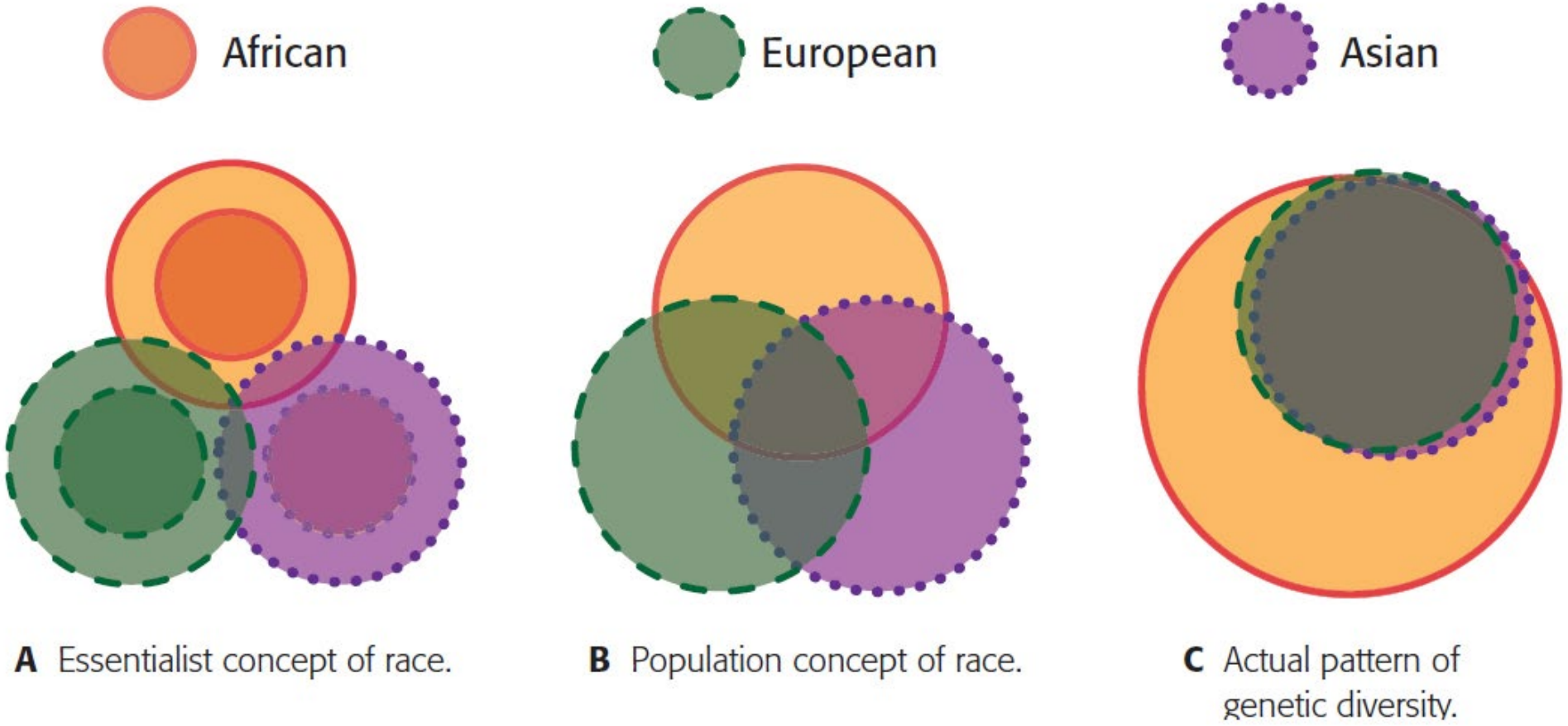


Race as a Component of eGFR

- In the MDRD study race was either self-reported or recorded by investigators
  - No specific rationale given for inclusion
- In the CKD-EPI study, race was included because of MDRD
  - Found that, on average, Black patients had 16% higher GFR compared to non-Black patients after adjusting for other factors
- Race variable = Black (African-American) or Other
- No discussion about how to apply for different African origins or inter-racial individuals



Race is a Social Construct



A Essentialist concept of race.

B Population concept of race.

C Actual pattern of genetic diversity.

Obasogie 2009; http://www.mixedracestudies.org/?p=25802

Problems with Use of Race in eGFR

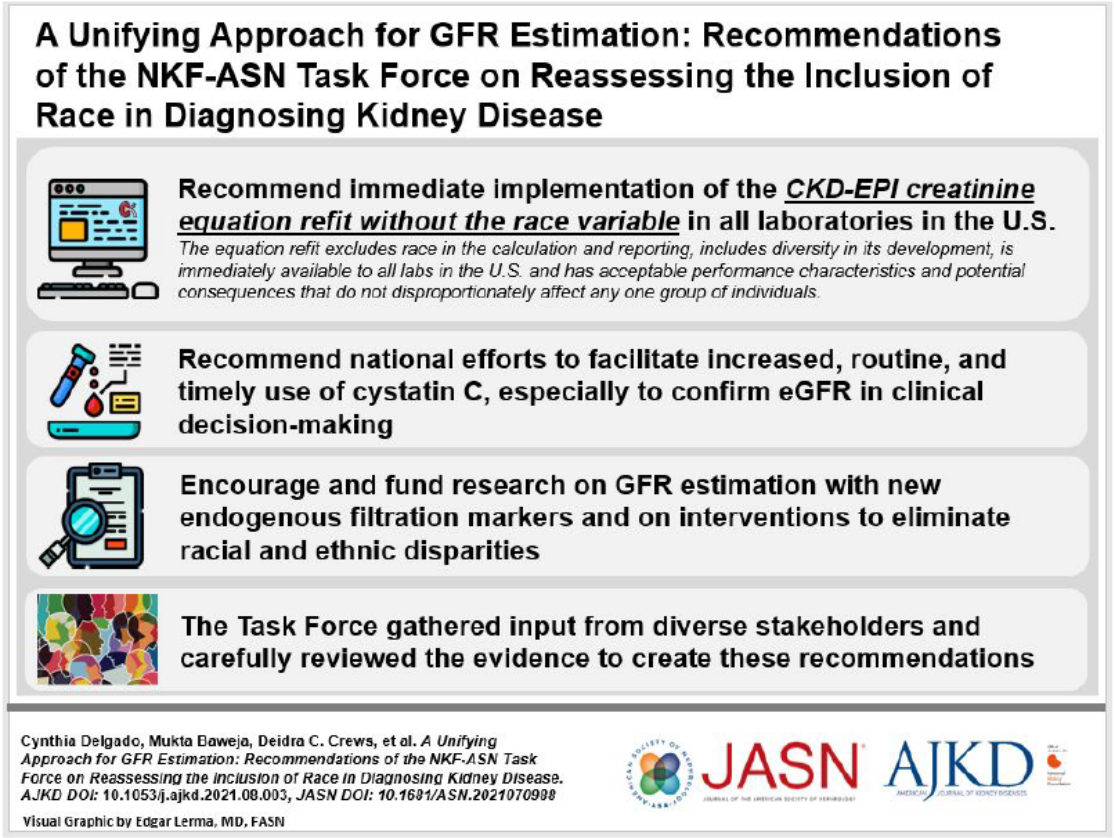
- Race is a social and not biologic construct
- No explanation for observed differences by race
  - Debunked “muscle mass” hypothesis
- Unnecessary identification/segregation by race
- No established approach to patients of mixed race
- Potential to disadvantage Black patients in some clinical situations

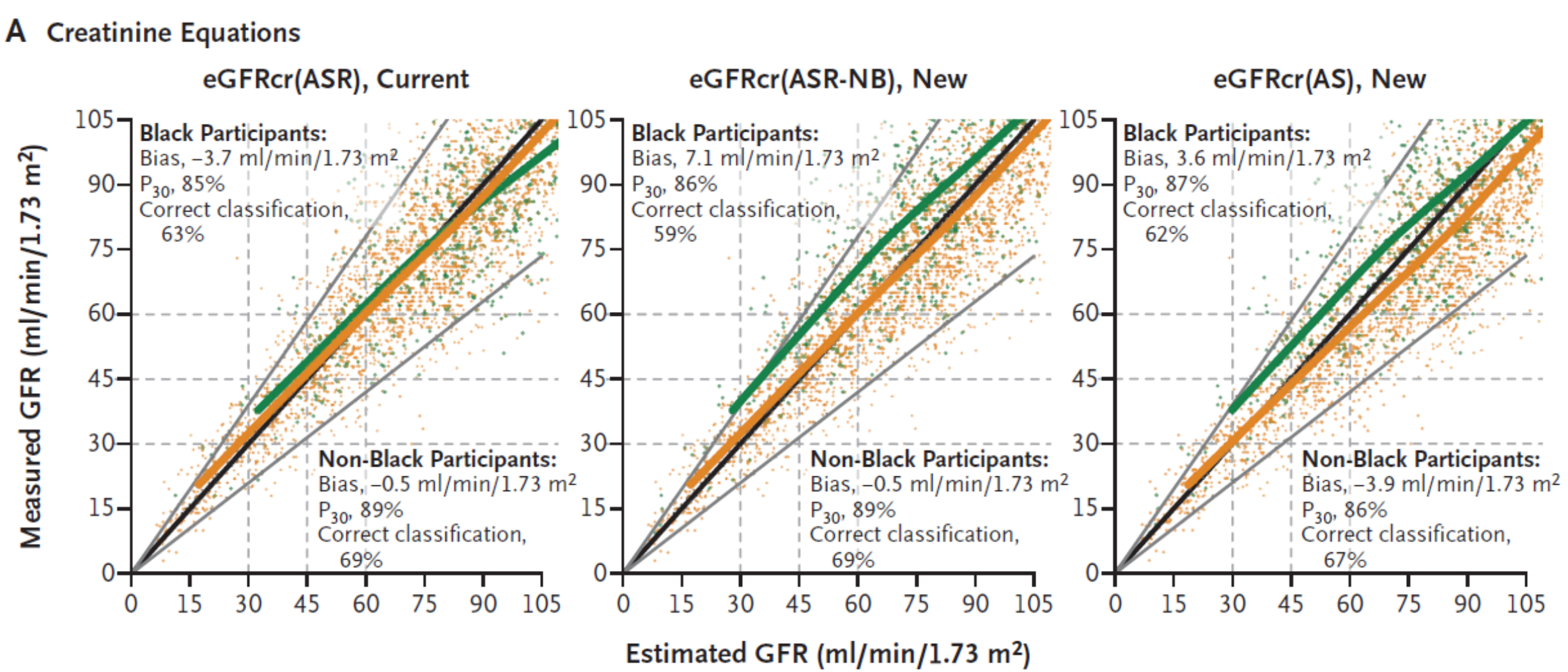
SPECIAL ARTICLE www.jasn.org

A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease

Cynthia Delgado,[1] Mukta Baweja,[2] Deidra C. Crews,[3] Nwamaka D. Eneanya,[4] Crystal A. Gadegbeku,[5] Lesley A. Inker,[6] Mallika L. Mendu,[7] W. Greg Miller,[8] Marva M. Moxey-Mims,[9] Glenda V. Roberts,[10] Wendy L. St. Peter,[11] Curtis Warfield,[12] and Neil R. Powe[13]

- NKF-ASN final report released 9/23/21
- Recommended use of new CKD-EPI eGFR equation that was refit without race variable
- UM laboratories implemented this new formula 1/4/22





- Agreement within 30% of mGFR using new CKD-EPI: 87.2% in Black vs 86.5% in Non-Black patients

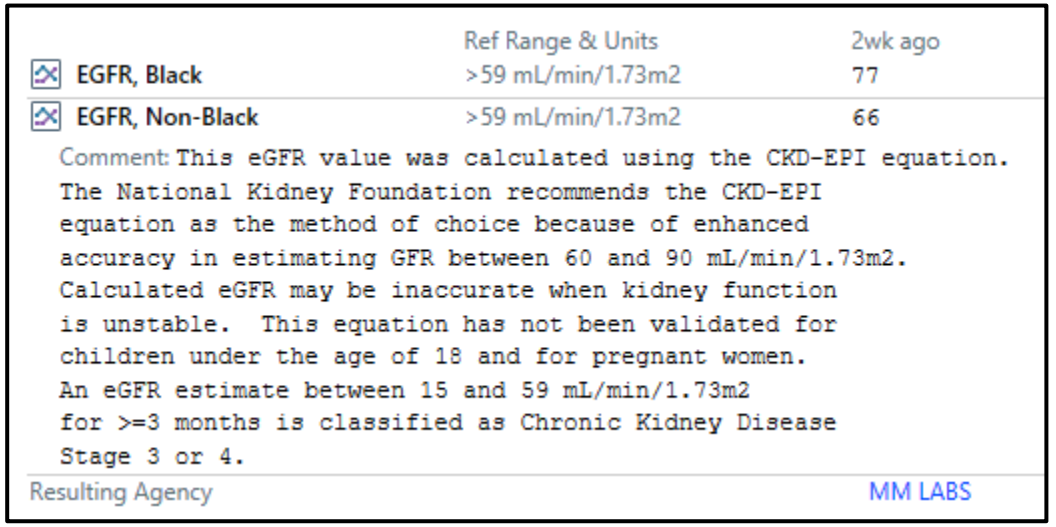
Inker, *NEJM* 2021

Scenario 1: Referral to Nephrology – Threshold vs Trend

- Recommended for eGFR <30
- In reality, increased referrals for eGFR<60 (“abnormal”) since advent of routine eGFR lab reporting

- Potential race implications: 55yo M with SCr 1.4
  - Black eGFR 65 → Observe
  - Non-Black eGFR 56 → Refer
  - New formula eGFR 59 → Refer

- Importance of within individual trends
  - eGFR 85 fell to 65 in 1yr → Refer
  - eGFR 56 and stable → Observe



	Ref Range & Units	2wk ago
EGFR, Black	>59 mL/min/1.73m2	77
EGFR, Non-Black	>59 mL/min/1.73m2	66

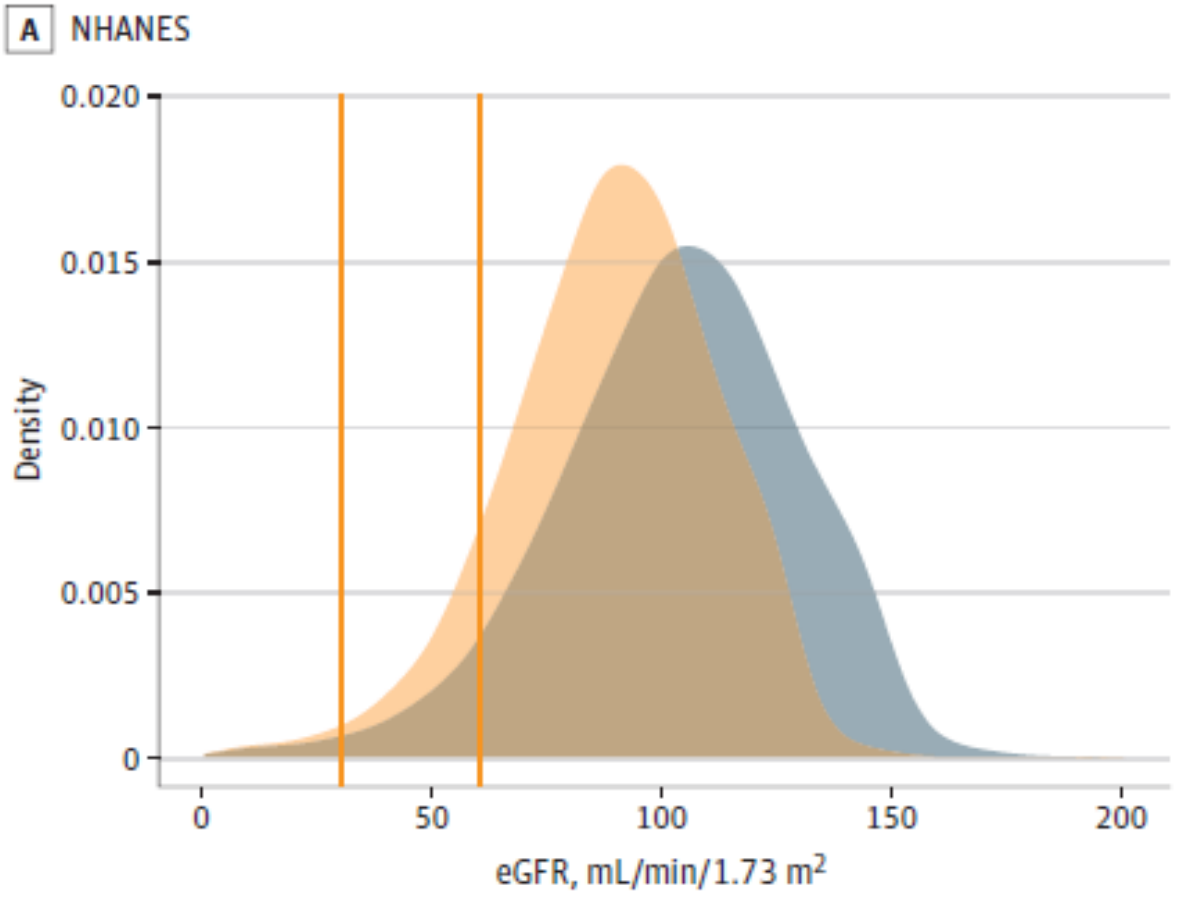
Comment: This eGFR value was calculated using the CKD-EPI equation. The National Kidney Foundation recommends the CKD-EPI equation as the method of choice because of enhanced accuracy in estimating GFR between 60 and 90 mL/min/1.73m2. Calculated eGFR may be inaccurate when kidney function is unstable. This equation has not been validated for children under the age of 18 and for pregnant women. An eGFR estimate between 15 and 59 mL/min/1.73m2 for >=3 months is classified as Chronic Kidney Disease Stage 3 or 4.

Resulting Agency MM LABS

Epidemiologic Impact of Removing Race

- Based on NHANES data extrapolated to US population:
  - Increase in CKD (eGFR<60) prevalence from 5.8% to 10.4% among Black adults
  - 972,737 new cases!

- With new formula, some non-Black patients will no longer be classified as CKD



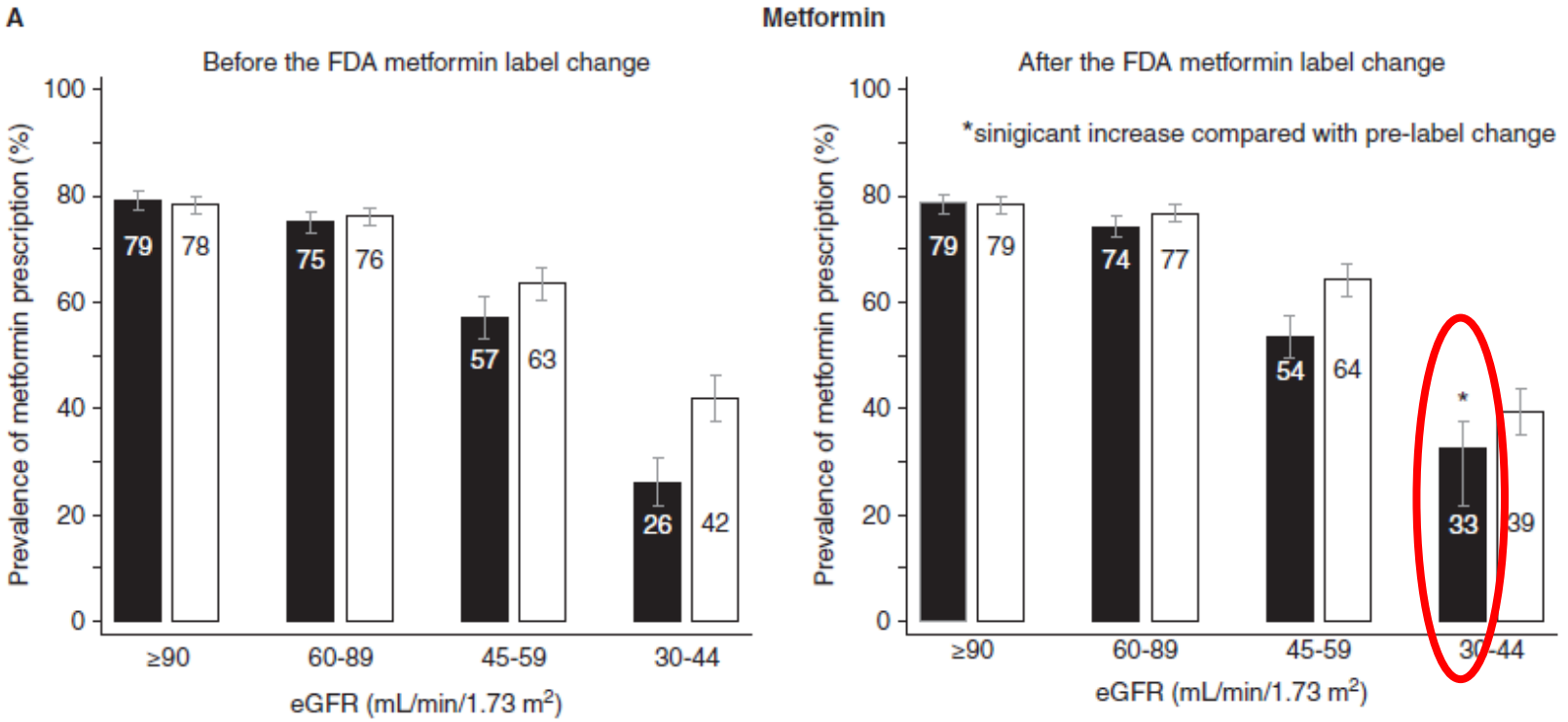
Bragg-Gresham, *JAMA Network Open* 2021;4(1):e2035636

Scenario 2: Medication Prescribing

- Many drugs have at least partial renal clearance and therefore may need to be dose adjusted (or avoided) when kidney dysfunction is present (acute or chronic)
- Metformin: Contraindicated for eGFR<30
- Potential race implications: 42yo F with SCr 2.1
  - Black eGFR 33 → Prescribe
  - Non-Black eGFR 28 → Avoid
- Using new formula
  - Black eGFR 33 → 30
  - Non-Black eGFR 28 → 30

Real World Impact

- Prior to 2016, metformin was contraindicated with Cr≥1.5 (men) or ≥1.4 (women) per FDA label (no race adjustment)
  - Updated to be contraindicated with eGFR<30mL/min/1.73m^2

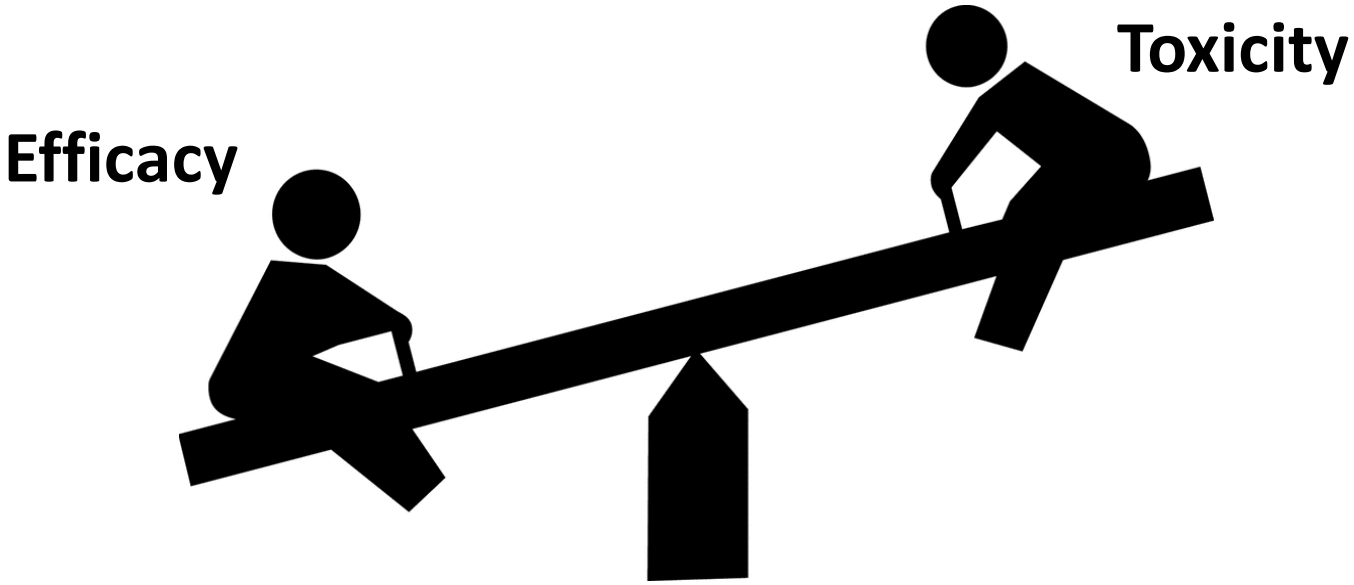


Conclusion: Use of eGFR labeling may have reduced racial disparities in metformin prescription

Shin et al, *J Am Soc Nephrol* 2020;31(8):1847-58

Medication Dosing

- Amoxicillin
- Potential race implications: 42yo F with SCr 2.1
  - Black eGFR 33 → Prescribe 875mg BID
  - Non-Black eGFR 28 → Prescribe 500mg BID
  - New equation eGFR 30 → 500mg BID



Scenario 3: Dialysis Initiation

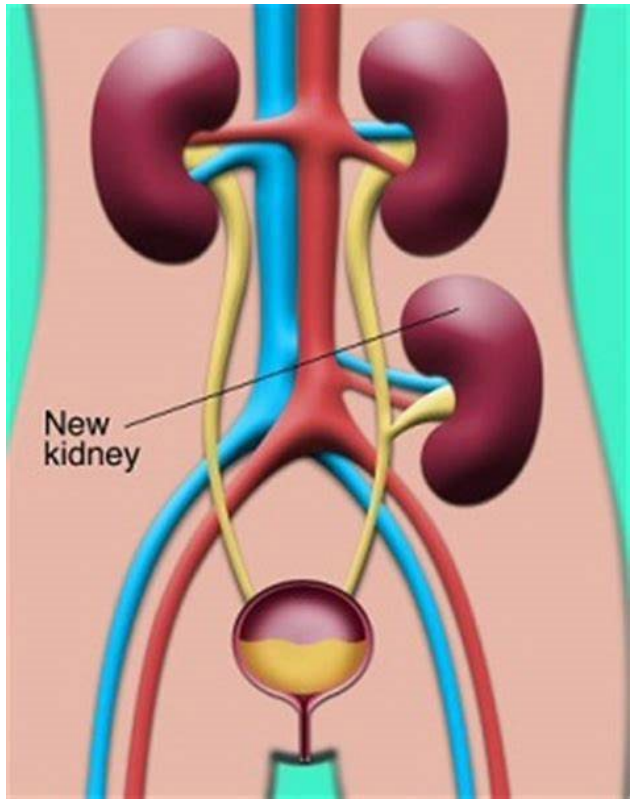
- On average, patients in U.S. initiate dialysis for end-stage renal disease with an eGFR ~10
- However, eGFR should not be used as sole determination for dialysis initiation
  - Clinical picture of uremia → symptoms
  - Sarcopenia can falsely lower Cr (increase eGFR)
- Potential race implications: 74yo F w SCr 4.2
  - Black eGFR 11, non-Black eGFR 10 → are they symptomatic?

Scenario 4: Kidney Transplant Wait-Listing

- Patients who meet clinical criteria as a kidney donor can join the waitlist for a deceased donor kidney transplant once their **eGFR is <20**

- Potential race implications: 65yo M w SCr 3.4
  - Black eGFR 21 → Monitor
  - Non-Black eGFR 18 → List
  - New formula eGFR → 19

- In U.S. there remain disparities in transplantation between Black versus White patients
  - Social determinants of health
  - Genetic factors (ABO and HLA compatibility)



Scenario 5: Kidney Transplant Living Donors

- Living donors must not have any significant comorbidities and have a GFR >80
  - Many centers will measure GFR for confirmation
- Potential race implications: 40yo M w SCr 1.2
  - Black eGFR 87 → Eligible
  - Non-Black eGFR 75 → Excluded
  - New formula eGFR → 78

Next Steps and Future Directions

- Standardized adoption and reporting across labs
- Search for better formulae/markers → availability of cystatin C
- Examining real world impact of change in eGFR reporting
  - Clinical decision-making, especially around thresholds
  - Impact on disparities (e.g. in transplant listing)
  - Use of alternative testing (e.g. cystatin C, timed urine collections)
  - Referral patterns to nephrology
  - Provider and patient perspectives

Summary

- Significant racial disparities exist in nephrology care and outcomes. Identifying disparities has helped to improve health equity.
- GFR is an important clinical concept that has helped inform clinical care, but has important limitations
- Trends in eGFR within an individual may be more important than thresholds. However, there are some specific scenarios where specific eGFR cutoffs make a difference in clinical decision-making.
- As part of efforts to eliminate race-based medicine, a new (race-free) eGFR equation has recently been introduced and adopted. The potential impact of this change is yet to be determined.