

PRIORITY UPDATES FROM THE RESEARCH LITERATURE (PURLs)

Filtering Race Out of GFR Calculation

Winfred Frazier, MD, MPH, and Yufei Ge, MD, MS

Use the new $eGFR_{cr-cys}$ equation (estimated glomerular filtration rate equation that incorporates both serum creatinine and serum cystatin C levels) to estimate the GFR for both Black and non-Black individuals because the equation has improved accuracy, minimizes differences in eGFR between race groups, and more accurately reflects chronic kidney disease (CKD) prognosis while eliminating the use of race in GFR estimating equations. (J Am Board Fam Med 2024;00:000–000.)

Keywords: Chronic Kidney Disease, Cystatin C, End-Stage Renal Disease, Glomerular Filtration Rate, Serum Creatinine

Strength of Recommendation: B

Retrospective cohort study.¹

Illustrative Case

Two patients with chronic kidney disease, identical demographics (except race), and lab data present to the nephrologist to discuss the possibility of kidney transplant. Based on the data shown below, the nephrologist recommends kidney transplant for Patient B, but not Patient A. You call the nephrologist to advocate for Patient A. How would you advocate for Patient A?

For adult patients who are not on dialysis, eGFR values must be less than or equal to 20 mL/min to start waiting time on the kidney transplant list. In the example above, the non-Black patient (Patient B) would qualify to access waiting time on the kidney transplant waiting list, while the Black patient (Patient A) would not. Using race in these equations

2009 CKD-EPI Creatinine Calculator²

Factors	Patient A	Patient B
Sex	Female	Female
Age (years)	55	55
Black Race	Yes	No
Serum Creatinine (mg/dL):	2.8	2.8
eGFR (mL/min/1.73m ²):	21	18

overestimates eGFR in Black patients, which could lead to delays in kidney transplant wait list times, treatment delays, more serious comorbidities, and increased mortality.³

Clinical Context

Black patients are 3 to 4 times more likely than White patients to progress to end-stage renal disease (ESRD) and require renal replacement therapy (RRT).⁴ Black patients are also less likely to be referred for kidney transplant, less likely to be wait-listed, and less likely to receive a kidney transplant.^{5,6}

Using race as a factor started with the 1999 Modification of Diet in Renal Disease (MDRD) study.⁷ The study concluded that Black patients had higher creatinine levels per given GFR, so a correction factor was placed in the MDRD estimating equation. In 2009, the Chronic Kidney Disease Epidemiologic Collaboration published the widely used CKD-EPI 2009 formula with a similar race-based correction factor.² Traditional eGFR equations used race as a factor to calculate eGFR based on the flawed belief that Black patients have a

This article was externally peer reviewed.

Submitted 23 January 2024; accepted 29 January 2024.

This is the Ahead of Print version of the article.

From the UPMC St. Margaret Family Medicine Residency Program, Pittsburgh, PA (WF, YG).

Funding: None.

Conflict of interest: None.

FPIN Editors: Carina Brown, MD, Cone Health Family Medicine, Greensboro, NC, and Greg Castelli, PharmD, University of Pittsburgh Family Medicine Residency, Pittsburgh, PA.

Corresponding editor: Winfred Frazier, MD, MPH, FAAFP, Department of Family Medicine, University of Pittsburgh School of Medicine, Schenley Place, 4420 Bayard Street, 5th Floor, Suite 520, Pittsburgh, PA 15260 (E-mail: frazierwt2@upmc.edu).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.

higher average muscle mass. Race is a social construct susceptible to significant bias with limited utility in addressing biologic variability. Race-based modifiers in clinical equations can negatively impact patient health and continue biases in populations where health disparities already exist.⁸

Serum cystatin C is a low-molecular-weight protein produced by all nucleated cells and filtered by the glomerulus that has been recently used as an alternative marker to evaluate kidney function that is less affected by race, muscle mass, gender, or age than creatinine.⁹ Studies have indicated that adding cystatin C to creatinine measurements to calculate eGFR improves the risk classification for death, cardiovascular disease, and end-stage renal disease without the need to include race-based adjustments.¹⁰

Methods

This article was identified as a potential PURL through the standard systematic methodology.¹¹ An additional literature search was conducted by searching UpToDate, DynaMed, and PubMed with the terms “GFR,” “CKD,” “cystatin C,” and “creatinine” to find additional literature to place this research into the context of current clinical practice.

Study Summary

This retrospective individual-level data analysis evaluated KFRT (kidney failure with replacement therapy) and death among Black and non-Black patients using different adjusted eGFR calculators using creatinine alone, cystatin c alone, and both creatinine and cystatin c. Five general population and 3 CKD US-based cohorts with serum creatinine and cystatin C were evaluated between 1988 and 2018. The main calculators used were the CKD-EPI (CKD Epidemiology Collaboration) equation with serum creatinine (eGFR_{cr} with and without race), cystatin C (eGFR_{cys} without race), or

both markers (eGFR_{cr-cys} without race) and are described in Table 1. Primary outcomes included KFRT, all-cause mortality, and cardiovascular (CV) mortality.

The study included 62,011 participants who had a mean age of 63 years, 53% were women, and 33% identified as Black. The age- and sex-adjusted hazard ratios for KFRT comparing Black with non-Black participants at eGFR of 60 mL/min/1.73 m² were 2.8 (95% CI, 1.6-4.9) for eGFR_{cr} with race, 3.0 (95% CI, 1.5-5.8) for eGFR_{cys}, 2.8 (95% CI, 1.4 to 5.4) for eGFR_{cr-cys} and 1.3 (95% CI, 0.8-2.1) for eGFR_{cr} without race.

At an eGFR of 60 mL/min/1.73 m², the 5-year absolute risk difference of KFRT among Black vs non-Black patients was 1.3% (95% CI; 0% to 2.6%) using race-free eGFR_{cr-cys} compared with 0.37% (95% CI, -0.32% to 1.05%) using race-free eGFR_{cr}. The hazard ratios for all-cause mortality comparing Black with non-Black participants were 1.2 (95% CI; 1.1 to 1.4) for eGFR_{cys} and 1.0 (95% CI, 0.9-1.1) for eGFR_{cr} without race. The C-statistic was calculated from a single model that includes age, sex, race, and eGFR. The C-statistic was greater than 0.78 for all eGFR equations within race groups for KFRT and greater than 0.716 for all-cause mortality, indicating greater accuracy.

What Is New

The new 2021 eGFR_{cr-cys} equation is a more accurate measure of eGFR than equations with either the creatinine or cystatin C level alone compared with previous equations that included race. This new equation more accurately predicts KFRT and mortality risk among Black participants compared with the previously used eGFR equations. The equation also appropriately quantifies racial disparities in kidney disease risk and mortality across the spectrum of kidney dysfunction, a crucial prerequisite for efforts to intervene on and track improvements in kidney health equity.

Table 1. eGFR Equations

Equation	Year Developed	Filtration Markers	Demographic Variables
eGFR _{cr} [ASR]	2009	creatinine	age, sex, race
eGFR _{cr} [AS]	2021	creatinine	age, sex
eGFR _{cys} [AS]	2012	cystatin c	age, sex
eGFR _{cr-cys} [AS]	2021	creatinine, cystatin c	age, sex

Caveats

The $eGFR_{cr-cys}$ could underestimate $eGFR$ (positive bias) and have the unintended consequence of over-diagnosis of CKD which could lead to unnecessary initiation of RRT. Physicians decide the need for KFRT based on serum creatinine, $eGFR$, and other factors that may have differed among cohorts. The data on measured GFR and KFRT were not available in all cohorts.

The study categorizes participants into 2 distinct groups (Black and non-Black), which precludes comparing outcomes across other race and ethnic groups.

Challenges to Implementation

The National Kidney Foundation (NKF) and the American Society of Nephrology's (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease recommends all laboratories adopt the new $eGFR_{cr}$ calculation.¹² Adjusting the equations is relatively easy for health systems but may still take months to years for hospital-affiliated and national referral laboratories to implement in coordination with IT departments. Additional challenges include health care professional cystatin C education and fluency compared with creatinine. Widespread adoption of cystatin C testing will require increased availability and lower cost testing in clinical laboratories.

To see this article online, please go to: <http://jabfm.org/content/00/00/000.full>.

References

- Gutiérrez OM, Sang Y, Grams ME, Chronic Kidney Disease Prognosis Consortium, et al. Association of estimated GFR calculated using race-free equations with kidney failure and mortality by Black vs non-Black race. *JAMA* 2022;327:2306–16.
- Levey AS, Stevens LA, Schmid CH, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
- Ahmed S, Nutt CT, Eneanya ND, et al. Examining the potential impact of race multiplier utilization in estimated glomerular filtration rate calculation on African American care outcomes. *J Gen Intern Med* 2020;36:464–71.
- USRDS. United States Renal Data System. 2015 *USRDS annual data report: Epidemiology of kidney disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2015. 2015.
- Sood A, Abdullah NM, Abdollah F, et al. Rates of kidney transplantation from living and deceased donors for Blacks and Whites in the United States, 1998 to 2011. *JAMA Intern Med* 2015;175:1716–8.
- Purnell TS, Luo X, Cooper LA, et al. Association of race and ethnicity with live donor kidney transplantation in the United States From 1995 to 2014. *JAMA* 2018;319:49–61.
- Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. *J Am Soc Nephrol* 1999;10:2426–39.
- Jain A, Brooks JR, Alford CC, et al. Awareness of racial and ethnic bias and potential solutions to address bias with use of health care algorithms. *JAMA Health Forum* 2023;4:e231197.
- Shlipak MG, Matsushita K, Ärnlöv J, CKD Prognosis Consortium, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013;369:932–43.
- Peralta CA, Shlipak MG, Judd S, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* 2011;305:1545–52.
- National Kidney Foundation, American Society of Nephrology. Removing race from estimates of kidney function. March 9, 2021 (https://www.asn-online.org/about/press/releases/ASN_PR_20210309_Press_release_NKF_A.pdf. opens in new tab).
- Smith P, Castelli G. The Priority Updates from the Research Literature (PURLs) Methodology. *J Am Board Fam Med* 2024;37:799–802.