Filtering Race Out of GFR Calculation

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Use the new $eGFR_{cr\text{-}cys}$ 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;37:1146–1148.)

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 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]

2009 CKD-EPI Creatinine Calculator[2]

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

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 higher average muscle mass. Race is a social

This article was externally peer reviewed.
Submitted 23 January 2024; accepted 29 January 2024.
From the UPMC St. Margaret Family Medicine Residency Program, Pittsburgh, PA (WF, YG).
Funding: None.
Conflict of interest: None.
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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 ($eGFR_{cr\text{-}cys}$ 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 m^2 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 $eGFR_{cr\text{-}cys}$ and 1.3 (95% CI, 0.8-2.1) for $eGFR_{cr}$ without race.

At an eGFR of 60 mL/min/1.73 m^2, 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 $eGFR_{cr\text{-}cys}$ 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 $eGFR_{cr\text{-}cys}$ 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
eGFRcr[ASR]	2009	creatinine	age, sex, race
eGFRcr[AS]	2021	creatinine	age, sex
eGFRcys[AS]	2012	cystatin c	age, sex
eGFRcr-cys[AS]	2021	creatinine, cystatin c	age, sex

Caveats

The $eGFR_{cr\text{-}cys}$ could underestimate eGFR (positive bias) and have the unintended consequence of overdiagnosis 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/37/6/1146.full.

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