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In Search of a Better Equation — Performance and Equity in Estimates of Kidney Function

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Grassroots activism and the resurgent focus on racism in the United States have led medical centers to revisit their approaches to estimating and reporting kidney function. Although many experts agree that we should reconsider the use of race in equations for estimated glomerular filtration rate (eGFR) and in medicine more generally,[1,2] precisely how eGFR equations should remove race remains unclear. In August 2020, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) formed a joint task force to provide recommendations. Various changes to eGFR reporting have already materialized, with diverse implications for Black patients, including new diagnoses and reclassifications of chronic kidney disease (CKD), contraindications and dose reductions for prescription drugs, increased eligibility for specialist care and kidney transplantation, and decreased eligibility for kidney donation and clinical trials.[2] Some observers argue that applying clinical judgment while bearing in mind the imprecision of the eGFR may lessen these effects. Still, the magnitude of changes generated by using current coefficients (16 to 21%) suggests that removing race may substantively affect care.[2]

Earlier equations for kidney function were derived exclusively from White people and did not consider race. The finding of decreased accuracy in Black Americans later prompted researchers to introduce race-based factors statistically derived from diverse populations. For example, the factor of 15.9% in the eGFR equation developed by the CKD Epidemiology Collaboration (CKD-EPI) was derived from the observation that measured GFR (mGFR) for Black Americans was, on average, 15.9% higher than that for non-Black persons with the same serum creatinine level, sex, and age.[3] Adjusting for this difference made statistically unbiased GFR estimates possible in both groups. Observed differences are attributable to non-GFR determinants, including tubular secretion and creatinine generation. Although it was initially hypothesized that differences in body size or muscle mass were explanatory factors, they have not been shown to explain observed differences. Researchers should

continue to investigate underlying causes and replace race with factors measurable by clinicians.

Today, nearly all laboratories estimate GFR using race, but multiple academic medical centers have recently removed the race coefficient for Black patients out of concern about differential access to kidney transplantation and specialist care, as well as broad misuses of race as a biologic category.[1,2] However, no reports have systematically evaluated all options for computing and reporting eGFR. We documented race-free alternatives with respect to validation, overall and within-group accuracy, availability of assays and equation parameters, representation of Black patients in development data, and use of race (see table). The potential implications for millions of patients necessitate a thorough consideration of these factors in the search for a better equation.

Alternatives are typically proposed as modifications of the CKD-EPI equations. These equations — eGFR computed from serum creatinine (eGFRcr), cystatin C (eGFRcys), and both (eGFRcr-cys) — are recommended by authoritative guidelines such as “Kidney Disease: Improving Global Outcomes” (KDIGO). Validation of the equations revealed no substantial bias (defined as eGFR minus mGFR) in either Black Americans or the general population. The 2009 eGFRcr and 2012 eGFRcys and eGFRcr-cys equations were derived from populations containing approximately three times the proportion of Black people as in the overall U.S. adult population (31.5% and 40.0%, respectively, vs. 11.7%). The eGFRcr and eGFRcr-cys require race, whereas eGFRcys does not.

eGFRcys is a validated race-free equation with minimal bias. Although assays for cystatin C are now standardized, some argue that eGFRcys and eGFRcr-cys present problems of limited assay availability, longer turnaround times, and imprecisely understood associations with smoking, fat mass, and inflammation. These challenges are surmountable with efforts to increase assay availability and further investigate non-GFR determinants of serum cystatin C concentrations.

Among the first alternatives implemented for removing race from the eGFRcr involved relabeling its two outputs (“if Black” and “if White/Other”). One approach relabels race-specific outputs as the high and low ends for a range of plausible eGFR values (“Black” becomes “high estimate” and “White/Other” becomes “low estimate”). These ranges misrepresent the true variability of GFR estimates and would be biased downward for Black patients and upward for non-Black patients. Another approach relabels race-specific outputs as differences in muscle mass (“Black” becomes “high muscle mass” and “White/Other” becomes “low muscle mass”). This approach lacks evidentiary support.

Subsequent proposals have included, first, simply using eGFRcr with the race coefficient removed — effectively using the White/Other output for all patients; this approach preserves accuracy for White patients while concentrating errors in Black patients. A second proposal was refitting eGFRcr without race — a more statistically valid approach that distributes errors more evenly, although Black patients remain disproportionately affected. A third was refitting eGFRcr with height and weight replacing race, based on the now-unsupported hypothesis that body measurements may account for observed racial GFR differences.

Evaluation of these alternatives using the CKD-EPI development data showed decreased accuracy and increased bias relative to race-based eGFRcr and race-free eGFRcys, especially in Black patients (see table). None of these alternatives requires race input, but only the first one has been implemented.

Other race-free approaches include blended equations and equations based on filtration markers other than creatinine or cystatin. Blending combines race-specific outputs using weights based on population proportions (e.g., 11.7% for Black and 88.3% for White/Other) and can be applied to either eGFRcr or eGFRcrcys. Blended equations would not require refitting or additional assays and would distribute errors more evenly than direct removal. In theory, each institution could assign weights according to its patient demographics or those of the U.S. population; however, non-uniform weights may confuse patients, clinicians, and trainees who travel among organizations. Finally, multiple-filtration-marker panels such as eGFRmet (metabolite) and eGFR-LMWP (low-molecular-weight proteins) have been shown to have accuracy and bias equivalent to those of KDIGO-recommended equations even without using race. Though they are promising, their feasibility for wide-spread adoption is unclear.

Race is a social construct that has been used to divide people in ways that harm human health; removal of race from clinical algorithms is therefore needed. It is not appropriate, however, to ignore race or the pervasive effects of structural racism. Race-blind approaches can benefit minorities by increasing access to specialist care and kidney transplantation,[2] but can also result in biases.[4] For example, observational retrospective data suggest that transitioning from thresholds based on race-blind serum creatinine measures to those based on race-adjusted eGFR reduced disparities in metformin access by accounting for higher serum creatinine levels in Black patients.[5] As hospitals move from race-based equations, we must remain vigilant in reassessing data and algorithms for bias.

The national conversation has rightly focused on equity concerns for Black people, who are the most affected by disparities in kidney outcomes and are the only group for whom race adjustment is recommended in the United States. Non-Black minority populations are also affected. Although non-Hispanic Black and White patients were well-represented in the data used to develop the eGFRcr (31.3% and 61.7%, respectively), neither Hispanic (1.5%) nor Asian (1.2%) patients were. Increased representation of non-White and non-Black persons is desirable.

Furthermore, there are concerns that race may be assigned by investigators or clinicians in developing or using eGFR equations. In clinical and research settings where race or other identity characteristics will be considered, patients should define their own identity. Further discussion with patients is especially important when their identity is not well described by existing inputs to eGFR equations or when patient values affect the risk–benefit balance. It is thus vital to maintain transparency and shared decision making.

While we await guidance from the NKF-ASN task force in the next several months, the search for a better equation remains a highly complex process with no universally accepted outcome. Broad consensus is important; a uniform method for computing and reporting the

eGFR would facilitate communication and development of best practices. The ideal race-free solution will prioritize accuracy to avoid generating, maintaining, or worsening disparities. Future kidney-function estimation should be shaped by evidence from clinical researchers, social context from activists and historians, and ultimately, consideration of patient care and preferences.

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Alternatives for Computing or Reporting eGFR from Serum Markers. *

Method	Input Variables	KDIGO Recommended	External Validation	Coefficient for Black Race (value)	Development Data Representation	Overall Accuracy vs. eGFRcr	Median Bias	Availability (Reason)
					no. of persons (% Black)		*ml/min/11.73 m²*	
eGFRcr	Creatinine, age, sex, race	Yes	Yes	Yes (1.159)	8254 (31.5)	(Baseline)	Black: 0.0; White/ Other: −0.5	Yes (implemented in nearly all hospitals)
eGFRcr-cys	Creatinine, cystatin, age, sex, race	Yes	Yes	Yes (1.080)	5352 (40.0)	Higher	Black: −0.3; White/ Other: 0.0	Yes; limited (cystatin C assay currently not widely accessible)
eGFRcys	Cystatin, age, sex	Yes	Yes	No	5352 (40.0)	Equal	Black: 0.0; White/ Other: −0.5	Yes; limited (cystatin C assay currently not widely accessible)
eGFRcr with “Black” and “White/Other” relabeled as the high and low ends of an eGFR range	Creatinine, age, sex	No	No	No	Not fitted from Data (NA)	Unknown, most likely lower	Unknown	Yes (implemented in some hospitals)
eGFRcr with “Black” relabeled as “high muscle mass” and “White/Other” as “low muscle mass”	Creatinine, age, sex	No	No	No	Not fitted from Data (NA)	Unknown, most likely lower	Unknown	Yes (implemented in some hospitals)
eGFRcr with race coefficient removed	Creatinine, age, sex	No	No	No	8254 (31.5)	Lower	Black: −6.1; White/ Other: −0.5	Yes (implemented in some hospitals)
eGFRcr refitted without race variable	Creatinine, age, sex	No	No	No	8254 (31.5)	Lower	Black: −4.0; White/ Other: 1.4	No (equation parameters not available)
eGFRcr refitted with height and weight replacing race	Creatinine, age, sex, height, weight	No	No	No	8254 (31.5)	Lower	Black: −3.7; White/ Other: 1.3	No (equation parameters not available)
Blended eGFRcr (weighted combination of race-specific outputs)	Creatinine, age, sex	No	No	No	8254 (31.5)	Unknown, most likely lower	Unknown likely negative for Black and positive for White	Yes (multiple options for weighting)
eGFRmet	Acetylthreonine, phenyl-acetylglutamine, tryp-tophan, pseudouridine	No	No	No	2424 (51.8)	Higher	Black: −1.4; White/ Other: 1.3	No (assays not available)
eGFR-LMWPs	Creatinine, cystatin C, B2M, BTP, age, sex	No	Yes	No	5017 (38.5)	Higher	Black: −1.1; White/ Other: 0.4	No (assays not widely available)

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*Accuracy is defined relative to the baseline of eGFRcr on the basis of a statistically significant difference ($P<0.05$) in either the root mean squared error of eGFR relative to mGFR (log-log scale) or 1 minus P_{30}% (defined as <30% difference from mGFR). All data sets had a mean mGFR of 68 ml/min/1.73 m^2, except eGFRmet (55 ml per minute per 1.73 m^2 of body-surface area) and eGFR-LMWP (58 ml per minute per 1.73 m^2). The median bias is the median difference between eGFR and mGFR in the development data. Some previous CKD-EPI studies reported bias differently, as mGFR minus eGFR. The mean bias is expected to be zero in development data sets overall and in race subgroups if there is a race coefficient. B2M denotes beta-2-microglobulin, BTP beta-trace protein, eGFR estimated glomerular filtration rate, KDIGO Kidney Disease: Improving Global Outcomes, LMWPs low-molecular-weight proteins, mGFR measured glomerular filtration rate, and NA not applicable.