Alternative creatinine-based GFR estimates in United States populations—similar performance, same gaps—is it time to move on?

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This study evaluated performance of the European Kidney Function Consortium (EKFC) equation in a US cohort, comparing population-specific (EKFCPS) with race-free (EKFCRF) Q values (median normal creatinine). Both EKFCPS and EKFCRF equations showed less bias than the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation. The percentage of estimated glomerular filtration rate (GFR) within 30% of measured GFR was similar for CKD-EPI 2021 (79.2% [range, 78.5%–79.9%]) and EKFCRF (80.1% [range, 79.4%–80.7%]) equations but improved with the EKFCPS equation (81.1% [range, 80.5%–81.8%]), confirming utility of the EKFC equation in US populations.

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Across the globe, evaluating kidney function is a critical component of everyday clinical and laboratory practice, informing diagnoses of kidney disease, specialist nephrology referrals, and dosing regimens for nephrotoxic drugs. Although measured glomerular filtration rate (GFR) is considered the reference, it is invasive, time-consuming, and more expensive relative to creatinine-based estimates of GFR (eGFR).[1] Currently, all the available eGFR equations have been developed and validated in predominantly European and North American White populations, with surprisingly little validation in continental Africa, the American and European African diaspora, Latin America, India, and Asia. The era of race-based adjustments of eGFR was introduced in 1999 with the Modification of Diet in Renal Disease equation and further perpetuated in the modeling of the first Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in 2009.[2,3] It is noteworthy that such adjustments were based on a relatively small proportion of Black US study participants with established CKD, with most observed population-based differences in men rather than women.

Recently, race-based adjustments of GFR estimates have come under the spotlight, heavily criticized in Black Lives Matter for perpetuating inequalities in the US health system, especially in the provision of nephrology services. Such services include timeous specialist referral, initiation of directed treatment for prevention of CKD progression, and, for those with end-stage kidney disease, access to chronic dialysis and listing for transplantation. Overestimating GFR as an artefactual consequence of race-based adjustments especially impacts women, younger people, and those with better-preserved kidney function, with similar findings replicated in non-US populations.[4] Despite the ensuing debate that polarized the nephrology community, there was a collective sigh of relief when the National Kidney Foundation–American Society of Nephrology Task Force called for a reappraisal of race coefficients in GFR equations, resulting in the modeling of a race-free CKD-EPI equation that only includes age and sex as variables.[5] Likewise, in the United Kingdom, we took another step forward when the revised National Institute for Health and Care guidelines were published, recommending the omission of race-based GFR estimates from clinical practice.[6]

In this edition of *Kidney International*, acknowledging the utility of the new creatinine-based European Kidney Function Consortium (EKFC) equation remained confined to mainly European populations, Delanaye *et al.* elegantly demonstrate its equivalent performance to that of the race-free CKD-EPI equation in a large pooled US cohort.[7] The EKFC equation is based on rescaling creatinine using the Q value, which is defined as the median normal creatinine for a given population. Two options for the EKFC are subsequently proposed: the first is defined as population specific (which is race based), and the second is race free. Overall, for both forms of the EKFC equation, their respective bias, accuracy, and precision have such small differences they can be considered comparable with each other, and with the race-free CKD-EPI equation. The strength of the study lies in the large number of participants sourced from multiple US-based studies with a broad range of GFR; however, the representation of those who were self-identified as Black remained relatively small (21%).

We could argue that the missed opportunities lie in the absence of an

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evaluation of EKFC in children and adolescents, as we know a focus on improving the detection of kidney disease in this group would be of immense value because of their burgeoning risk of CKD. Also, the absence of an evaluation of cystatin C as a biomarker for eGFR, either in combination with creatinine, or as cystatin C alone, is disappointing. We know that cystatin C improves the accuracy of eGFR equations and is a prognostic indicator of outcome; thus, the more evidence we have accumulated in multiple studies, the more informed our approaches can be to defining its role in eGFR testing going forward.

A few aspects of this study provide opportunity for reflection, especially if we want to practice nephrology that is truly global. As there was little difference between the population-specific and race-free versions of the new EKFC equation, we could ask ourselves why we continue to perform race-based analyses in GFR estimates. Although one could justify there is some heritability relating to creatinine and that self-reported race may be a proxy for heritability, which varies considerably in African American populations, the data presented do not justify this differentiation. Furthermore, the European-American comparison in this work reflects the dominant narrative in nephrology, which remains that of the Global North. Thus, this study contributes relevant information to an already well-studied population. Although this is not a phenomenon specific to nephrology, as most research is done in well-resourced environments, mostly from high-income countries, the (unintentional) fallout is obvious. The voices of many populations from low- and middle-income countries in the Global South remain silent or are silenced.

Finally, the authors state in their discussion that the ambition of the EKFC equation is for it to be applicable to different populations. There have been numerous ongoing debates about which GFR estimating equation is better, and in the case of creatinine-based performance—most accept there are limitations that no amount of modeling will overcome, and alternative biomarkers must be sought. The notion of a "one-size fits all" equation for global use is an oversimplification with the potential to compromise individual-level care and population-based policy for the management of kidney disease. Incorrectly estimating GFR (as seen in Africa and Asia)—mostly overestimating true GFR—has devastating consequences in resource-limited settings with restricted access to kidney replacement therapy. The missed diagnosis of early-stage CKD is a death sentence.

DISCLOSURE

The author declared no competing interests.

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