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Spotlight

Race, ancestry, and genetic risk for kidney failure

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In a retrospective analysis of over 62,000 Black and non-Black participants from eight United States cohorts, Gutiérrez et al.[1] examined estimated glomerular filtration rate (eGFR) equations to assess racial differences in kidney failure requiring replacement therapy and in mortality across different equations.

Chronic kidney disease (CKD) is a major global health problem that disproportionately affects racial and ethnic minority communities within a given nation.[2] Equations to estimate glomerular filtration rate are commonly used to determine kidney function. They have been used for both clinical care and for research, such as identifying racial differences in CKD prevalence and racial differences in the association of low estimated glomerular filtration rate (eGFR) and the risk of both kidney failure requiring replacement therapy (KFRT) and mortality.[3] In 1999, in an attempt to better address CKD disparities, a race variable was added to the eGFR equation.[4] In 2020, medical students[5] and activated faculty[6] led calls to remove race as an individual-level modifier from medical formulas fueled by a better understanding of existing racial and ethnic disparities in CKD, CKD risk factor, and rates of CKD progression as well as growing theoretical and empirical knowledge demonstrating the flaws in biological determinism. The premise of using race as a modifier in an individual-level formula has been challenged given that man-made racial and ethnic groupings are socio-political constructs that have no direct relation to any medical or physiologic process outside of phenotype. While race and ethnicity have value for identifying group level differences, these groupings have a high degree of genetic and biologic heterogeneity within and across them making it futile for ascribing group-level findings to individual patients.[7] The re-assessment of the eGFR formula using larger and more diverse cohorts ultimately led to the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equation, free of race in its development or reporting. This new race-free equation with combined creatinine and cystatin C did not differ greatly between Black and non-Black patients compared with the race-free equation with either creatinine or cystatin C alone.[8]

Given the large confidence interval of the eGFR estimate, the new formula probably has no significant impact at the level of individual patient care, but at a group level, it could lead to differing racial estimates in the prevalence of CKD and CKD complications.

Gutiérrez et al.[1] recognized that when assessing population-level disease prevalence of CKD, the elimination of the race modifier from the eGFR equation increased the estimated prevalence of CKD in the Black population by 2% and lowered the estimated prevalence of CKD in non-Black population by 1.5% compared with earlier 2009 CKD-EPI eGFR equations that included race.[4] However, whether the race-free formula alters the relation of reduced eGFR values with the rates of KFRT and mortality within and between racial groups was unclear, leading them to undertake this study. They analyzed over 62,000 Black and non-Black participants from five general population and three CKD United States cohorts to compare creatinine- and race-based eGFR equations without cystatin C, to the race-free eGFR equation that included creatinine, cystatin C, or both for predicting population level differences in the risk of KFRT and mortality across racial groups.

Making White patients with an eGFR of 80 mL/min/1.73 m^2 using the 2009 CKD-EPI race and creatinine based eGFR formula[4] the referent for KFRT risk, they found that the race-free 2021 CKD-EPI eGFR equation that included both creatinine and cystatin C appeared preferable to the eGFR equation that included creatinine without race or cystatin C for predicting population-level differences in the risk of KFRT and mortality across racial groups.

The racial differences in risk of KFRT using the 2021 CKD-EPI $eGFR_{cr\text{-}cys}$ equation most closely resembled that of the race and creatinine based eGFR equation, suggesting it may be the preferred race-free eGFR equation to assess group-level risk of KFRT and mortality associated with low eGFR.

Key limitations in this study included low enrollment of racial and ethnic groups other than Black and non-Hispanic White, potential heterogeneity in the methods of measurement across different cohorts and different time periods, and the lack of information on the many structural drivers of health, which are inequitably distributed across racial groups and may mediate much of the observed race-based associations. The work by Gutiérrez et al.[1] has identified important differences between various eGFR formulas for assessing racial group risk of KFRT and mortality, which could have important public health implications. Conventional approaches to studying KFRT and mortality have relied uncritically on biological determinism. The 2021 challenge to this approach[8] is providing opportunities to develop alternative approaches. This study begins to demonstrate the feasibility of applying rigorous, responsible methods to address this persistent health inequity. As the nephrology community moves forward, it will be important to look closely at the many eGFR formulas and to re-assess

whether or not the prior race- and creatinine-based eGFR formulas should be used as reference values. As noted above, to generate and assign race-based modifiers to individual patients is methodologically flawed.[7,9] Doing so (1) ignores genetic and social heterogeneity within groups, (2) obscures the mechanisms linking racism to health disparities, (3) reinforces race essentialism (innate group differences outside of phenotype), and (4) generally lacks scientific rigor (e.g., ecologic fallacy). Thus, in the future, medicine should pay closer attention not to perpetuate well-intentioned, but methodologically flawed practices. Rather, it should recognize that the transition to race-free formulas needs to occur with the careful assessment of its derivation and impact to ensure its introduction does not further exacerbate disparities.

The work by Gutiérrez et al.[1] is a step in the right direction toward a better understanding of these different equations with an intent to ensure equitable allocation of population health efforts to target risk reduction strategies for those groups in greatest need.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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