Does eGFR by Any Number Mean the Same?

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The development of a consensus strategy for classification and stratification of CKD was a major advance for clinicians managing individuals with CKD, for individuals with CKD under their care, and for those at CKD risk.[1] This strategy allowed for the development of CKD stage–guided practice guidelines governed by level of remaining GFR and degree, if any, of kidney injury determined by urine indices, such as albuminuria.[2] An individual's stage helped determine whether and if so, how clinicians would investigate them for the cause of reduced eGFR and/or underlying kidney injury. This staging system subsequently allowed investigators to help predict outcomes, including mortality,[3] according to stage and therefore, help guide the approach to individuals with CKD.

Our evolving understanding of the contributors to GFR as well as CKD and its progression prompts the kidney community to consider if we need to modify this comparatively recent classification and stratification system. For example, individual race/ethnicity factors into the eGFR calculation,[4] and some question the appropriateness of this inclusion.[5] Do different eGFRs derived for individuals with different race/ethnicity mean that the different derived eGFRs indicate different outcomes for individuals with identical parameters except for race/ethnicity? However, does the generally lower eGFR of individuals habitually eating a primarily vegetarian diet[6] predict the same outcome as the identical eGFR in individuals habitually eating a primarily meat-based diet? Relatedly, is progressive nephron loss of aging[7] a consequence of "healthy" aging or due, at least in part, to the comparatively high meat content of diets typical of developed societies? If progressive nephron loss is indeed a consequence of healthy aging, does the lower eGFR of a healthy aged individual indicate the same outcome(s) as the identical lower eGFR in a younger individual? These and possibly, other insights question whether our CKD classification system should evolve to help clinicians better assess the consequence(s) of a given lower eGFR through the lens of its cause and context.

In a perspectives article in this issue of *JASN*, Delanaye *et al.*[8] propose that "the CKD definition be amended to include age-specific thresholds for GFR." With respect to the association of lower eGFR with increased mortality,[3] the authors cite data showing that the predictive value of reduced eGFR differs in younger (18–54 and 55–64 years old) compared with older (>65 years old) individuals. These data show that, for individuals 18–54 and 55–64 years old, mortality increases at eGFR<75 and <60 ml/min per 1.73 m^2, respectively, compared with those in the general population of the same age range. In contrast, mortality did not increase in individuals >65 years old until eGFR decreased below 45 ml/min per 1.73 m^2. The authors cite data showing that age- and sex-standardized mortality rates for individuals >65 years old with G3a (eGFR=45–59 ml/min per 1.73 m^2)/A1 (no increased urine albumin excretion) classification were similar to those of the general population of the same age range. However, those classified as G3b (eGFR=30–44 ml/min per 1.73 m^2)/A1 and G4 (eGFR=15–29 ml/min per 1.73 m^2)/A1 had higher mortality. They cite data supporting that it is common for individuals >65 years old to have eGFR<60 ml/min per 1.73 m^2, the level at which individuals of any age are currently classified as having CKD,[1] yet those without signs of kidney injury seem to have similar mortality to those in the general population. They further state that the progressive eGFR decline after age 40 years old is not associated with kidney adaptations, like increased single-nephron GFR that accompanies GFR reductions due to kidney "disease," leading the authors to characterize this progressive eGFR decline after age 40 years old as part of healthy aging. They propose modifying the current CKD classification system to account for these evolving insights and recommend an age percentile strategy to do so. The authors suggest that advantages of such a modification include emphasizing the need to work up younger individuals with modestly reduced eGFR that could reflect indolent, underlying kidney disease and avoidance of expensive workups of aged individuals whose reduced eGFR is due to healthy aging. Their proposal deserves consideration.

Published online ahead of print. Publication date available at www.jasn.org.

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The authors base the need for their age-adjusted proposal primarily on data supporting the predictive value of eGFR on mortality and not on other eGFR-related considerations. This is an important caveat, because although clinicians might not consider a modestly reduced eGFR in an older individual to be CKD, clinicians must still be aware that even modest eGFR reductions increase risk for metabolic complications, such as metabolic acidosis.[9] Nevertheless, because clinicians desire to address factors that limit disease-free years of life for those under their care, an age-adjusted modification of the CKD classification system would focus investigative attention on younger individuals with modestly reduced eGFR and avoid potential complications, cost, and anxiety of possibly unnecessary workups of older individuals with modestly reduced eGFR due to healthy aging. Accordingly, clinicians might consider simply counseling individuals >65 years old with CKD stage G3a/A1 regarding strategies that reduce the risk of complications of reduced eGFR, like metabolic acidosis, rather than conveying that they have a "disease." However, those with unexplained signs of kidney injury, such as albuminuria, would still be candidates for workup. These considerations lend merit to the age-adjusted modification of the CKD classification system proposed by Delanaye *et al.*[8]

An additional benefit of the work of Delanaye *et al.*[8] is their suggested need to reassess what we in the kidney community consider to be "normal" eGFR and for us to more critically consider reference eGFR values when conducting epidemiologic studies. Studies that are more recent support a lower "normal" eGFR than 120 ml/min per 1.73 m^2 as reported in classic studies by Wesson.[10] The authors also suggest that the reference eGFR should be age adjusted.

This challenge to the nephrology community from Delanaye *et al.*[8] to consider evolving the structure of our strategy for our CKD classification and stratification system might facilitate the work of clinicians caring for those with CKD and improve the lives of those under their care.

ACKNOWLEDGMENTS

Dr. Wesson acknowledges the support of the Baylor Scott and White Health Center.

DISCLOSURES

Dr. Wesson has portions of his salary paid through his employer for consultation provided to Tricida, Inc. (San Francisco) and from National Institutes of Health grant R21DK113440.

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See related review, "CKD: A Call for an Age-Adapted Definition," on pages XXX–XXX.