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.

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REFERENCES

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al.: National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 139: 137–147, 2003
2. Chapter 3: Management of progression and complications of CKD. *Kidney Int Suppl (2011)* 3: 73–90, 2013
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
4. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al.: CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012
5. Eneanya ND, Yang W, Reese PP: Reconsidering the consequences of using race to estimate kidney function. *JAMA* 322: 113–114, 2019
6. Wiseman MJ, Hunt R, Goodwin A, Gross JL, Keen H, Viberti GC: Dietary composition and renal function in healthy subjects. *Nephron* 46: 37–42, 1987
7. Denic A, Lieske JC, Chakkera HA, Poggio ED, Alexander MP, Singh P, et al.: The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 28: 313–320, 2017
8. Delanaye P, Jager KJ, Bokenkamp A, Christensson A, Dubourg L, Eriksen BO, et al.: Chronic kidney disease: Call for an age-adapted definition. *J Am Soc Nephrol* 30: 1785–1805, 2019
9. Adeva MM, Souto G: Diet-induced metabolic acidosis. *Clin Nutr* 30: 416–421, 2011
10. Wesson LG: Renal hemodynamics in physiologic states. In: *Physiology of the Human Kidney*, edited by Wesson LG, New York, Grune & Stratton, 1969, pp 96–108

See related review, "CKD: A Call for an Age-Adapted Definition," and perspective, "Modification of eGFR-Based CKD Definitions: Perfect, or Enemy of the Good?," on pages 1785–1805 and 1807–1809, respectively.

Modification of eGFR-Based CKD Definitions: Perfect, or Enemy of the Good?

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In this issue of the *Journal*, Delanaye *et al.*[1] propose a modification to the traditional eGFR-based definition and classification of CKD. The authors argue that the eGFR thresholds at which CKD is designated should be age specific, including lower eGFR thresholds for older relative to younger persons. The authors suggest that older persons with mildly reduced eGFR may not be compromised, as they

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simply exhibit renal senescence (although we find it difficult to reconcile a 40%–50% decline in function as attributable to healthy aging). The authors support their proposal with evidence synthesized by the CKD Prognosis Consortium along with a summary of 20 additional studies from the general population. They highlight the observation that relative mortality hazards in persons over 65 with an eGFR of 45–59 ml/min per 1.73 m^2 are not consistently increased relative to referent groups across studies. In other words, theirs is an evidence-based definition of CKD, with mortality as the sole outcome of interest.

As the authors note, the current criterion standard for CKD classification was put forth in the Kidney Disease Improving Global Outcomes (KDIGO) report on evaluation and management of CKD published in 2013,[2] a comprehensive update to the original Kidney Disease Outcomes Quality Initiative (K/DOQI) report on evaluation, classification, and stratification of CKD published in 2002.[3] Several of us remember a world without eGFR: one informed by BUN, serum creatinine, and occasionally timed (24-hour) urine collections. Before publication of the K/DOQI guidelines, many persons with mild-to-moderate (and some with moderate-to-advanced) CKD were not recognized because the serum creatinine concentrations fell below the "radar screen" range of 1.5–2.0 mg/dl. The K/DOQI guidelines prompted nephrologists and other providers to pay more attention to persons with modest elevations in serum creatinine that typically fell within the population reference range (in fact, these persons were often elderly) rather than consider them "normal." The K/DOQI guidelines were good —damn good—and the KDIGO guidelines were even better, distinguishing individuals not only by categories of eGFR (formally denoting stages 3a and 3b) but by categories of albuminuria, highlighting the heightened risks of cardiovascular disease associated with the presence and degree of albuminuria. Can we improve upon the current criterion standard?

The data presented by Delanaye *et al.* are not in dispute. Indeed, the relative mortality hazards for older persons with an eGFR of 45–59 ml/min per 1.73 m^2 are attenuated relative to lower eGFR among persons in the same age range, and relative to the same level of eGFR in persons of younger age. However, we should consider several facts. First, the widely used GFR-estimating equations, derived largely in populations with impaired kidney function, yield more misclassification of eGFR when the true GFR extends beyond the range within which the equation was derived. Thus, assuming a direct relation between GFR and survival, one would expect mortality rates to be attenuated, not only because persons with CKD stage 3a have less severe disease than persons with CKD stage 3b or 4, but also because some (perhaps many) persons with normal or near-normal kidney function are misclassified as having CKD stage 3a. In other words, it might not be prudent to steadfastly rely on the association given uncertainty in the exposure. Second, the relative mortality hazard associated with CKD stage 3a in older persons (relative to persons with normal or near-normal kidney function) may be lower than that in younger persons because the baseline mortality hazard is higher in older persons—not a reason to dismiss CKD stage 3a in the elderly. Third, although the relative mortality hazard associated with eGFR is lower with stage 3a CKD than with stage 3b CKD, the burden of CKD to the population is comparable because of differences in population prevalence. For example, in the population-based study by Go *et al.*,[4] CKD stage 3a was roughly fourfold more common than CKD stage 3b, whereas the corresponding risks of death were 20% and 80% higher than among persons with normal or near-normal kidney function at baseline. Therefore, from a public health perspective, heightened risks of death, even if marginal, in larger populations should not be ignored. Finally, we disagree with the authors' contention that studies of other clinical complications (including frailty, fracture, physical function, cognitive function, and health-related quality of life) are "of little utility in informing. . .the age-adapted threshold." Although it is true that these and other conditions have not been uniformly studied (*e.g.*, performance-based versus self-reported assessments), they matter to patients and their loved ones.

Finally, we are puzzled by the authors' statement that lowering the eGFR threshold for older persons would "(reduce) inappropriate care and its associated adverse effects." We are not aware of circumstances where older persons receive unnecessary care if they carry a diagnosis of mild-to-moderate CKD. It is extremely unlikely that persons with CKD stage 3a would be referred for pre-emptive (and arguably unnecessary) hemodialysis vascular access. In fact, persons diagnosed with CKD may be *less likely* to receive *clinically indicated* care for ischemic heart disease and other conditions requiring radiocontrast-enhanced imaging due to an exaggerated fear of radiocontrast exposure, a phenomenon we previously referred to as "renalism."[5]

In sum, Delanaye *et al.* should be congratulated for presenting a cogent argument in favor of age-specific CKD definitions, and clearly summarizing what has been a festering debate in the nephrology community for some time. Much good has come from the two decades of arduous effort undertaken by the authors (the European Kidney Function Consortium), the CKD Prognosis Consortium, and other groups. For the meantime, whether the next generation of GFR-estimating equations are age specific or not, we should consider the clinical context (*vis-à-vis* age, body composition, donor status, and other factors) when considering the diagnosis of CKD. Less misclassification and a more comprehensive assessment of kidney function (beyond GFR and albuminuria) would help, although perfection may not be forthcoming.

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REFERENCES

1. Delanaye P, Jager KJ, Bökenkamp A, Christensson A, Dubourg L, Eriksen BO et al.: CKD: Call for an age-adapted definition. *J Am Soc Nephrol* 30: 1785–1805, 2019
2. KDIGO: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 3: 1–150, 2013
3. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39[Suppl 1]: S1–S266, 2002
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
5. Chertow GM, Normand SL, McNeil BJ: "Renalism": Inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. *J Am Soc Nephrol* 15: 2462–2468, 2004

See related review, "CKD: A Call for an Age-Adapted Definition," and perspective, "Does eGFR by Any Number Mean the Same?" on pages 1785–1805 and 1806–1807, respectively.