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Q&A

Is It Time to Move On? Reexamining Race in Glomerular Filtration Rate Equations

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Glomerular filtration rate (GFR) is the best overall index of kidney function. Because GFR is difficult to measure accurately in clinical practice, it is commonly estimated using equations that incorporate serum creatinine, which is easier to measure and routinely available. Various equations for estimated GFR (eGFR) have been developed, with the Modification of Diet in Renal Disease (MDRD) Study and the more recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations being the most widely used. In addition to the serum creatinine concentration, both the MDRD and CKD-EPI equations also factor in the patient's age, sex, and—controversially—race. In the United States, the inclusion of race into the MDRD and CKD-EPI equations takes the form of a separate coefficient for African-American patients that is intended to provide a more accurate estimate of the measured GFR value. Outside the United States, some countries have developed their own equations that include a separate coefficient for race.

Because electronic medical records and laboratory information systems are typically not equipped to provide separate eGFR calculations based on a patient's race, some US laboratories have adopted the practice of reporting both the eGFR for Black and non–Black patients in tandem in the electronic medical record. Examining the history of how and why a separate coefficient has been applied for Black patients in the MDRD and CKD-EPI equations reveals that the developers of the equations noted that Black patients had higher mean serum creatinine values than non–Black (mostly White) patients for the same measured GFR. Historically, this higher mean serum creatinine at baseline in Black patients was attributed to mean higher muscle mass in Black individuals. However, when the evidence for the claimed higher muscle mass in Black patients is investigated, it becomes clear that strong evidence is lacking, and only 2 small, poorly designed studies underpin the basis of this explanation.

Regardless of the historical basis of the association between a higher baseline serum creatinine concentration in Black individuals, some data suggest that a separate equation for Black patients better reflects the gold standard measured GFR value. These data suggest that the use of a separate coefficient for Black patients is a well-intentioned act designed to improve the accuracy of the eGFR for a subset of the US population. Nevertheless, we cannot be blind to the reality that these data come with caveats. The first and most important of these caveats is the knowledge that race is a construct that is not biological but rather societal. One's race is a matter of self-identity. Placing all individuals with African descent into one group ignores differences within the group and those of mixed race.

Black Americans face inequities in access to health care and are often referred for specialty care at a later point than their non–Black counterparts. We also must acknowledge that simple categorization of Black vs non–Black (i.e., White) can further reinforce stereotypes that Black individuals' biology is inherently different from that of non–Black people.

To address the evolving discussion on the use of race in the MDRD and CKD-EPI equations, we invited a group of global experts in the fields of nephrology, laboratory medicine, and public health to share their perspectives on this topic of vital importance.

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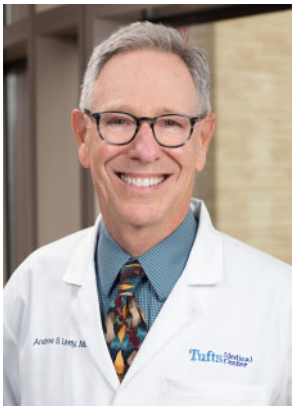
How do you currently calculate and report eGFR at your own institution? If you are currently reporting both non–African-American and African-American eGFR calculations, is there a move to eliminate separate reporting? If you are outside of the United States, do you report eGFR using a race- or population-specific coefficient?



Andrew S. Levey: At Tufts Medical Center, we follow the recommendations to clinical laboratories for GFR evaluation that are contained in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) Guideline for Evaluation and Management of Chronic Kidney Disease. We measure serum creatinine and cystatin C using measurement procedures traceable to international reference materials and procedures (cystatin C is a send-out test). We report eGFR from creatinine (eGFRcr) whenever serum creatinine is measured, using the 2009 CKD-EPI equation, and we report eGFR from cystatin C (eGFRcys) and the combined eGFR equation incorporating both creatinine and cystatin C (eGFRcr-cys) whenever serum cystatin C is measured, using the CKD-EPI 2012 equations. For eGFRcr and eGFRcr-cys, we report 2 values, one for African Americans and one for non–African Americans. For eGFRcys, we report a single value, since the estimate does not depend on race. We acknowledge the concerns about potential inaccuracy in the assignment of race and concerns regarding implementation and equity with the use of race in GFR estimation and anticipate that there may be suggestions for changes to current recommendations. We are awaiting recommendations from the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) Task Force before making changes to eGFR reporting.

Graham Jones: In Australia, eGFR using the CKD-EPI creatinine equation is routinely reported by all laboratories, and a race coefficient is not used, in keeping with national guidelines. Like many countries, Australia is a multicultural country with individuals from many racial backgrounds and various different times of adopting Australian dietary and lifestyle habits, although the

number of people of African American origin is very small indeed. The appropriateness of the eGFR formula developed in the United States and internationally for use in Aboriginal and Torres Straight Islander people was initially questioned; however, specific research in this area demonstrated satisfactory performance of the CKD-EPI equation in these populations without a race-based modification.

Nwamaka Eneanya: At hospitals affiliated with the University of Pennsylvania, we currently report eGFR using the MDRD equation. There are 2 eGFR values that are reported—one for African-American and one for non–African-American individuals. If desired, clinicians can also order cystatin C with reflex eGFRcys using the CKD-EPI equation—one eGFR value (without race) is reported with this option. We are in the process of changing our default creatinine eGFR equation to CKD-EPI. The institutional leadership is awaiting formal recommendations from the joint ASN-NKF and eGFR Task Force to help guide next steps. I am currently a member of this task force and am honored to serve with others to develop recommendations that will revolutionize clinical practice.

John C. Lieske: At all Mayo Clinic sites, we currently report an eGFR on all adults using the CKD-EPI equation for serum creatinine. In all cases, we report 2 values labeled "Black" and "non-Black." We also report an eGFR using the CKD-EPI cystatin C equation for all adults when this test is ordered. For cystatin C, only a single value is provided, since there is not a race term in

this equation. Over the past 4 months, active discussions involving various stakeholder groups have occurred throughout Mayo Clinic about whether we should continue to report 2 numbers for the creatinine-based eGFR. We plan to continue these discussions while we eagerly await results of the ASN-NKF work group formed to consider this topic.

Vivek Jha: Routine eGFR reporting is not mandatory and thus not the norm in most laboratories in low- and lower-middle-income countries including those in India. In fact, even the serum creatinine assays are often not standardized, and many laboratories do not use assays calibrated to standard reference material with isotope dilution mass spectrometry–traceable creatinine values. Among the laboratories that report eGFR, most use the 2009 CKD-EPI equation, without race-specific coefficients.

After the original equation was developed, researchers in different parts of the world, including China, Japan, Korea, Thailand, Pakistan, India, and Africa, examined the accuracy of the MDRD and CKD-EPI equations for their populations and almost uniformly found them to be inaccurate in predicting the GFR measured using gold standard methodology in their populations. We found that both CKD-EPI and MDRD equations systematically overestimate GFR in the Indian populations. Chinese and Japanese researchers have developed specific alterations to the CKD-EPI equation for their ethnically homogeneous populations.

What are some of the pros and cons of including a race-specific coefficient when calculating eGFR from a biological or medical standpoint?

Andrew S. Levey: Pro—all endogenous filtration markers are affected by non-GFR determinants (factors other than GFR that affect the serum concentration). For creatinine, the non-GFR determinants include its generation (by muscle or diet), tubular secretion, and extrarenal elimination. The higher observed serum creatinine concentration at the same level of measured GFR in African Americans than non–African Americans in the CKD-EPI study population indicates a difference in the totality of non-GFR determinants between them. The use of the African-American race coefficient in eGFRcr and eGFRcr-cys is based on this observed difference in non-GFR determinants and allows greater accuracy in both races for study populations similar to CKD-EPI (Blacks and Whites in North American, Europe, and Australia). Con—the cause for the observed differences in non-GFR determinants is not known and likely multifactorial and only partly related to ancestry. Although race is related to ancestry, this relationship varies substantially across regions and is not fully characterized by a binary categorical variable. For example, the African-American race coefficient is not applicable in other regions (South America, Asia, Africa) and in races other than Black or White in North American, Europe, and Australia.

Graham Jones: A race-based factor is of great fundamental difficulty for a wide range of reasons. These include whether the difference is due to genetics or to lifestyle factors, the difficulty of assigning a racial category when populations have mingled over time, and the assignment of a racial classification both at the time of the initial research and for routine practice. On this basis, the use of race as an input has inherent difficulties and should probably be avoided if possible.

Nwamaka Eneanya: Current eGFR equations are statistically accurate in quantifying kidney function among certain individuals. This is helpful to make quick decisions, such as specifying the dose of critical medications like chemotherapy or antibiotics. However, race is a social construct and the Human Genome Project taught us that we are genetically more similar between racial groups as opposed to within. Therefore, the race coefficient that is currently used with creatinine-based formulas likely represents characteristics that were specific to Black individuals who were included in eGFR studies—rather than the entire Black population in the United States. We know that genetics, diet, muscle mass, and certain medications can affect serum creatinine concentrations, and these were not directly measured or accounted for in any of the original eGFR studies. The downside of uniformly applying a Black race–specific coefficient is that it reinforces racist notions that Black bodies are inherently different than others. Given that race-adjusted eGFR is commonly used by clinicians to determine when patients should be referred for general and specialty nephrology care, Black individuals may

experience delays in receiving optimal preventative nephrology care and also evaluations for kidney transplantation. Delay in clinical referrals only compounds existing racial disparities in nephrology care for Black individuals in the United States. Furthermore, there is currently no accommodation for individuals who identify with more than one race. We also risk introducing implicit bias into the clinical encounter by assuming certain false characteristics about Black individuals (e.g., having higher muscle mass compared with other races). Implicit bias has been associated with a multitude of poor outcomes among Black individuals in the United States. Last, we are not transparent with our patients about the use of race with eGFR equations, which violates the central principles of shared decision-making. As previously demonstrated, we should only use race in medical decision-making if race confers a substantial benefit, if the benefit cannot be achieved through other feasible approaches, if patients who reject race categorization are accommodated fairly, and if the use of race is transparent.

John C. Lieske: The data used to develop both the MDRD and CKD-EPI creatinine-based eGFR equations were robust and included large populations of Black and non-Black individuals. These studies demonstrated a significant difference in the relationship of serum creatinine and measured GFR between these 2 groups, and the results supported use of a race factor in both equations. It has been assumed that this apparent need for a race factor relates to differences in muscle mass and/or creatinine production, but data on the underlying cause(s) are sparse. Furthermore, there are many other clinical factors that can introduce comparable amounts of bias into the performance of eGFR equations, including whether or not the individual is chronically ill or even if they have CKD! It is also not clear if these same race factors would be applicable for all individuals with African ancestry who are currently living in the United States. In the end, clinical judgment must be used when interpreting any estimated GFR value, specifically whether or not the eGFR might be confounded in a given individual. A key question for the medical community is whether or not a potentially more accurate eGFR value obtained using a race factor is clinically meaningful, considering all the other potential confounders and the relatively few times that a highly precise and/or accurate eGFR number is needed for clinical decision-making.

Vivek Jha: Accurate GFR estimation, by providing more precise correlation with the measured GFR, reduces variabilities in reporting, allows more accurate calculation of burden of kidney disease (relevant for epidemiologists), and helps clinical decision-making in situations where accuracy is important, such as in selection of living kidney donors. On the other hand, populations in many countries are not ethnically or racially homogeneous. For example, people living in India represent a large mix of ethnicities from a diverse ancestry. In fact, the diversity among Indian populations is second only to that seen in Africa, thus it does not make sense to develop race-specific coefficients for these populations. [Furthermore], equations that use ethnicity-specific coefficients cannot be used for GFR estimation in clinical trials, since regulatory agencies and many journals recognize only the original CKD-EPI equations.

As is often pointed out, race is a societal construct and not a biological one. Given this limitation, is there another way in which you would recommend reporting out values from creatinine-based eGFR equations? What are the limitations of that strategy?

Andrew S. Levey: We agree that it would be preferable to omit race in GFR estimation, but given the frequency of serum creatinine measurement (hundreds of millions of times per year in the United States) and the magnitude of the African-American race coefficient (16% in the 2009 CKD-EPI equation), any change in current practice is likely to have large implications, with potential benefits and harms for specific populations according to clinical settings. It would be preferable that any change be based on evidence regarding the balance of benefits and harms to representative populations to maintain transparency and fairness and be implemented uniformly across the country to maintain consistency. We do not recommend ad hoc changes by individual medical centers or clinical laboratories in eGFR reporting.

Graham Jones: While this has not been an issue in Australia, since only eGFR results without the African-American factors are reported, it raises the question as to whether there may be a better way to address this question. With regard to the estimation of GFR with the use of serum creatinine measurements, the question becomes whether it is an issue of muscularity (i.e., rate of creatinine production) or whether there are other factors. These could include differences in the rate of creatine conversion to creatinine, tubular handling of creatinine, or extrarenal handling of creatinine. If any identified difference is shown to be largely due to differences in relative muscularity, the approach may be to identify factors that directly relate to muscularity without using race as a surrogate. Unfortunately, studies using this approach have been disappointing in improving the accuracy of GFR estimation.

Nwamaka Eneanya: I recommend that institutions report 1 creatinine-based eGFR value that is accompanied by an annotation to help clinicians understand the limitations of this test. This annotation could briefly describe eGFR precision error and also note that some studies have shown variable performance of eGFR among patients who are frail, critically ill, muscular, and of certain race and/or ethnicity. The limitation of this strategy is that many clinicians outside of the field of nephrology may not fully understand how to access or interpret alternative methods of GFR measurement and estimation.

John C. Lieske: One possibility under consideration is not reporting a single eGFR number but rather a range of eGFR that corresponds with a given serum creatinine in a given person. Although this might represent a scientifically valid approach, it also might be more confusing to those not well versed in the underlying reasons for this range. It is also important to consider how reporting a range (rather than a specific number) would impact established clinical cut points that have been set at specific eGFR/GFR values (e.g., CKD stages, eligibility for kidney transplant donation, listing for kidney transplant recipients). In addition, careful consideration would need to be given when deciding how big this range should be (middle 30%, middle 50%, etc.) and what populations should be used to derive these ranges. Ideally, the population used to derive the range would be representative of the population it would be applied to.

Vivek Jha: It is important to understand the goal of eGFR reporting in clinical practice. Epidemiologists use single values for classification purposes. In clinical practice, unless clearly abnormal, single eGFR values are not as important as temporal trends using the same methodology and application within the patient's clinical context. Therefore, for low- and lower-middle-income countries, the equation to estimate GFR is less important than ensuring use of consistent assay methodology. Equations and their accuracy do not matter if the assay methodology is flawed. A limitation of this approach is the inability to perform immediate disease classification, which is of value for epidemiological purposes but not so much for patient care.

It has been suggested that a move away from serum creatinine–based eGFR calculations to a race-neutral cystatin C eGFR value could eliminate the controversy of reporting out separate eGFR results for African Americans and non-African Americans. What do you see as the challenges associated with making this transition?

Andrew S. Levey: We do not support moving away from eGFRcr because of its widespread use. We strongly agree with more frequent measurement of cystatin C and use of eGFRcys and eGFRcr-cys, in addition to eGFRcr, for GFR evaluation. All clinicians, not only nephrologists, should understand indications for measurement of serum cystatin C. Clinical laboratories can facilitate greater use of cystatin C by lowering cost, shortening turnaround time, reporting eGFRcys (and eGFRcr-cys) rather than serum cystatin C alone, and working with nephrologists to develop clinical indications for use.

Graham Jones: This is largely a matter of cost due to the substantially higher costs of cystatin C measurements, but there are a range of other factors related to making this kind of testing available. Creatinine testing is available on all laboratory analyzers and some point-of-care systems and is well understood by medical personnel. It has also provided the basis of all advice for drug-dosing decisions in reduced renal function. If such a recommendation were made, the implementation phase would involve considerable time, cost, and effort, which need to be balanced against the likely benefits.

Nwamaka Eneanya: Cystatin C is not readily available and also has not been standardized across many clinical laboratories in the United States. Consequently, clinicians may not feel proficient in ordering or interpreting cystatin C results. Implementation of this test may also take time, which could result in wide variability in how kidney function is assessed and how kidney disease is managed. However, I strongly advocate for health policies and clinical practice guidelines that improve widespread access to cystatin C, given the enormous health equity concerns that are associated with creatinine eGFR equations.

John C. Lieske: Currently, at Mayo Clinic, we offer rapid-turnaround in-house cystatin C testing in adults combined with eGFR reporting using the CKD-EPI cystatin C equation. Turnaround time is comparable to serum creatinine. Our inpatient and outpatient practices find this test helpful for managing multiple clinical scenarios as an independent biomarker of GFR. Clinicians must always interpret discrepant results between creatinine- and cystatin C–based eGFR in light of clinical factors that can bias one biomarker vs the other. Given that cystatin C is analyzed using an immunoturbidometric assay run on a standard chemistry autoanalyzer, from a laboratory perspective, we do not find it a more difficult test to maintain than most other tests we offer. In the United States, the biggest barrier to more widespread use of cystatin C is that many laboratories do not offer it as a rapid-turnaround test, and thus implementing it into clinical practice becomes more challenging. In my opinion, all nephrologists should ask their local laboratories to offer cystatin C in support of their clinical practice.

Vivek Jha: Moving away from serum creatinine–based GFR estimation is not practical for most of the developing world, except in specialized settings. Any new marker, including cystatin C, will first need to be tested for accuracy in diverse populations around the world. Next, there would be huge challenges in getting the test laboratories to replace the existing hardware to incorporate new technology in resource-poor countries (especially in primary care settings). Second, the new test is likely to be substantially more expensive than creatinine tests, and the opportunity costs from the gains made in accuracy in terms of change in clinical practice are hard to justify.

What action do you recommend clinical laboratories and clinicians take to improve their reporting, interpretation, and communication of eGFR values?

Andrew S. Levey: One of the great accomplishments of the collaboration between clinical laboratory and nephrology specialists is the standardization of measurement procedures and reporting for creatinine, cystatin C, and estimated GFR, which [form] the basis for the KDIGO guideline recommendations. Clinical laboratories should follow KDIGO recommendations for measurement and reporting, specifically, use of standardized assays for creatinine and cystatin C and reporting eGFR using the CKD-EPI equations. Clinicians should also follow the KDIGO guidelines for GFR evaluation, specifically, using eGFRcr as the initial test; understanding the accuracy of eGFRcr and recognizing causes for inaccuracy (under the best of circumstances, 15%–20% of eGFRs are likely to differ by >30% from measured GFR); and using confirmatory tests in clinical settings in which more accurate assessment of GFR will affect clinical decision-making (confirmatory tests include eGFRcys, eGFRcr-cys, measured creatinine clearance using a timed urine collection, or measured GFR using an exogenous filtration marker). When there is uncertainty whether or not eGFRcr is sufficiently accurate for clinical-decision making or how to interpret eGFR, we recommend consultation with a nephrologist.

Graham Jones: An eGFR result is only one of the aspects of diagnosing and staging chronic kidney disease. The addition of supportive comments to note the presence of the change over time (e.g., >3 months, making a diagnosis of CKD) and including reference to any urinary albumin creatinine ratio result to allow CKD staging could improve understanding of the results.

Nwamaka Eneanya: Clinical laboratories should review their reporting structures and ensure the same equation is used to report eGFR across their affiliated institutions. Clinical laboratories should also not automatically adjust eGFR values based on race. To promote personalized medicine, clinicians should transparently discuss trends in eGFR values as well as the limitations of eGFR equations with their patients and use these discussions to guide referral, medication dosing, and other management decisions.

John C. Lieske: Much progress has been made over the past 20 years standardizing serum creatinine measurement and eGFR reporting. Overall, these combined efforts by the laboratory and nephrology communities have greatly improved our ability to diagnose and monitor kidney function across medical centers and, indeed, across the world. That being said, all processes and systems can be improved, and at this point, it seems appropriate to reassess our previous assumptions, based on good science, that including a race term significantly improves the assessment of kidney function and, ultimately, patient management. On the other hand, simply eliminating the race term without carefully considering the resulting intended and unintended consequences could create more harm than good. Thus, it seems prudent to take a careful look at all options and proceed as a national laboratory community once the task force recommendations come out in the next months, in order to preserve the great advances that have been made to date. Chronic kidney disease remains underdiagnosed and undertreated and affects minority communities disproportionately. We do not want to make those issues worse rather than better.

Vivek Jha: For resource-limited settings (e.g., existing in large parts of India), it is important that laboratories standardize the creatinine assay technology, use the KDIGO recommended equation to report eGFR, and mention the assay methodology as well as the equation used. Next, we need to contextualize how clinicians should use eGFR values. In most cases, clinical practice does not change based on a single eGFR value unless grossly abnormal. It is eGFR trend over time that informs the impact of kidney function on health, permitting the clinician to assess and communicate long-term risk to the patient and plan management. For clinical practice, it is important to emphasize reducing reliance on a single value (no matter how accurate) for care of a usual patient with kidney disease but to focus on trends. Clinicians should clearly communicate the uncertainties of the existing equation and emphasize the value of serial testing for clinical decision-making. Any equation, applied consistently, will allow evaluation of trends. GFR should be measured where accuracy is critical—for example, in evaluating a kidney donor with borderline eGFR values. Finally, research should continue on finding a race-neutral marker and developing affordable assay technologies that increase the likelihood of uptake in resource-poor regions.

Given the lessons learned here, are there other areas of laboratory medicine that would benefit from a similar review of the validity of the use of race in clinical decision-making?

Andrew S. Levey: Race is frequently used in algorithms in clinical practice. We would suggest development of general principles for use of race in diagnostic and prognostic algorithms, as well as reevaluation of current algorithms to ensure that current practices are consistent with general principles. Clinical laboratory specialists should be participating in both efforts.

Graham Jones: The issue has raised the question of whether race does play a role in performing and interpreting laboratory tests. While there is awareness of some analytes that may be different based on race—for example, creatine kinase and prostate-specific antigen—these differences have generally not been systematically explored for different analytes in different races. Before commencing any such investigation, important questions about the definitions of race to be used, the different inputs of "nature vs nurture," likely mechanisms of differences should be carefully considered. I suspect that these difficulties make appropriate and comprehensive investigation of racial effects highly difficult.

The use of race as a differentiator in the MDRD and, later, the CKD-EPI equations has led to important research to try and identify whether changes in GFR estimating equations are needed in other races or, more usually, in countries with a racial makeup different from that included in the CKD-EPI study. This is appropriate with a country or region seeking the most appropriate equation for the majority of their population, but it should be recognized that the results may not be transferable to populations in other countries. On a historical note, it is interesting that the Cockcroft and Gault equation has been used in many locations and many populations despite being based on the limited data set of 249 Canadians from 1976 and remains recommended for some purposes despite changes in creatinine assays since that time.

Nwamaka Eneanya: Other disciplines of medicine that automatically adjust clinical algorithms for race should carefully review the evidence that has contributed to the development and perpetuation of race-based medicine and associated health inequities. These include race-adjusted pulmonary function tests and a number of cardiovascular, obstetric, urology, oncology, and endocrinology risk scores that guide disease screening and management. Clinical algorithms that are not supported by robust evidence and/or cause harm to marginalized patient populations should not be used in practice.

John C. Lieske: The issues regarding the inclusion of a race factor in the eGFR equations are perhaps somewhat unique among the many medical calculators that have recently received attention. In the case of eGFR, demographics are being used to predict a measured variable GFR. In many other cases, the outcome of the calculator is a clinical one (e.g., risk of mortality), and race may be serving as a proxy for other underlying factors. Ultimately, the medical community will need to determine whether or not the improved accuracy of an eGFR obtained by including a race factor is clinically meaningful or if other alternative methods can be developed to avoid using it altogether.

Vivek Jha: I am not aware of any other widely used routine laboratory test that uses a racial coefficient. The US version of the Fracture Risk Assessment Tool for osteoporosis and the pooled cohort equation used for quantitative atherosclerotic cardiovascular disease risk assessment use ethnicity-specific factors. These risk equations would benefit from a review of their performance in a global context to enable meaningful use in multiethnic populations.

Nonstandard Abbreviations: GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; KDIGO, Kidney Disease Improving Global Outcomes; eGFRcr, estimated glomerular filtration rate from creatinine; eGFRcys, estimated glomerular filtration rate from cystatin C; eGFRcr-cys, estimated glomerular filtration rate from creatinine and cystatin C; NKF, National Kidney Foundation; ASN, American Society of Nephrology.

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