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Q&A

International Perspectives on GFR Estimation and Race-Based Adjustments

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In 2021, the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease called for the discontinuation of race-based glomerular filtration rate (GFR) estimation in the United States, and issued recommendations for immediate implementation of the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, and increased use of cystatin C. In response, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) published a position statement in 2022 expressing concern about the accuracy of the 2021 race-free CKD-EPI creatinine equation in European populations, and recommended that European laboratories keep utilizing the 2009 CKD-EPI creatinine equation without using the race correction factor, along with reconsideration of other GFR estimating equations such as the revised Lund–Malmö equation or the European Kidney Function Consortium (EKFC) equation. These recent developments raise questions about the global applicability of the new race-free CKD-EPI creatinine equations and NKF/ASN recommendations, as well as questions as to whether global consensus on a single standardized GFR estimation approach is an achievable goal.

For this Q&A, we invited a group of experts from across the globe to share their current practices for GFR estimation, their insights into race correction coefficients, and their thoughts on the future of GFR estimation.

What GFR estimating equation(s) are you currently using for your population, and why?

Etienne Cavalier: The EKFC equation has recently been implemented in our laboratory in Belgium. This equation, published in the Annals of Internal Medicine journal in 2021, has been developed in a large cohort of European subjects and validated in both European subjects and African subjects living in Europe or Africa. It performs very well in these 2 populations. It also has the great advantage of being suitable for use in children. This is particularly practical because very few other equations allow direct reporting of estimated GFR (eGFR) in test protocols when a creatinine determination is requested in a child. Of

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importance, it also avoids the "jumps" that can be observed in the follow-up of the patient, when switching from a paediatric equation to an adult one.

Robert Kalyesubula: In my practice in Uganda, we are currently using the 2009 CKD-EPI creatinine equation without race for routine care of patients. This is because it is readily available and can easily be calculated using the apps available online. We conducted a multi-country study in over 2500 people from sub-Saharan Africa and demonstrated that the 2009 CKD-EPI creatinine without race performed well in this population. The only equation that performed better than this was the 2012 CKD-EPI cystatin C-based equation, but cystatin C is not routinely available in most of my practice; it is also about 5 times more expensive than creatinine measurement.

For cases where I need a more accurate measurement of the eGFR, I use the 2012 CKD-EPI cystatin C equation due to its superior performance in our population.

Boon Wee Teo: In my practice in Singapore, we are using the 2009 CKD-EPI creatinine equation without race adjustment. The original MDRD study equation was evaluated by Chinese and Japanese investigators resulting in a greater than 40% difference in estimates with adjustments in opposite directions. The criticisms at that time were that the MDRD study equation was limited to chronic kidney disease (CKD) patients and the proposed Asian (Chinese or Japanese) race coefficients added more confusion and uncertainty to GFR estimations. Moreover, race-based adjustments were practically problematic for global or metropolitan cities with multi-racial populations and mixed offspring. Our group set out to validate the Asian coefficients and also the then newly introduced 2009 CKD-EPI creatinine equation. Our data suggested that the race coefficient was much smaller once serum creatinine standardization was included in the CKD-EPI equations and, for the purposes of clinical practice and usual epidemiologic studies, the magnitude of the coefficient was within the realm of normal intra-individual variability and did not differ much (less than 10%) between the main Asian ethnicities of Chinese, Indians, and Malays. Therefore, there was no need to adjust for race in a multi-racial population. Moreover, when we evaluated GFR estimation using both serum creatinine and cystatin C, the racial coefficient was deemed unnecessary. Therefore, we concluded that using both markers in GFR estimation equations can avoid racial coefficients. However, for the purpose of GFR estimation and cost-effectiveness in regular clinical practice, we rely on the serum creatinine-only 2009 CKD-EPI equation.

Verônica T. Costa e Silva: I work at the University of São Paulo, an academic center in Brazil, and I'm currently using the 2021 race-free creatinine-based CKD-EPI equation because the CKD-EPI equation is a robust model, and in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines they recommended use of the 2009 CKD-EPI creatinine equation. We have updated to the 2021 race-free CKD-EPI creatinine equation as I believe the race-free version is more appropriate for the Brazilian population.

Lesley A. Inker: In my practice in the United States, we are using the 2021 CKD-EPI creatinine equation, 2012 CKD-EPI cystatin C equation, and 2021 CKD-EPI creatinine-cystatin C equation that are recommended by the national kidney societies in the United States. I was the lead investigator in the development of the 2021 creatinine equation and was on the NKF/ASN Task Force which recommended its use. As such, I was an early adopter and worked with our clinical laboratory to make the change early after the equation was published and the recommendations were released.

Being so intimately connected to the analyses, I am aware of all of the strengths and weaknesses of the new equation. The main limitation is that the 2021 CKD-EPI creatinine equation gives a small underestimation of measured GFR in the Black race group, and small overestimation in the non-Black race group.

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With this approach, the error is shared by both race groups instead of having all of the error in the one group, as occurs when using the approach of ignoring the race coefficient in the 2009 CKD-EPI creatinine equation that was proposed as an alternative method to remove race from computation of GFR.

What is your region's perspective on race-based GFR estimation? Have the recent US-based NKF/ASN recommendations changed your regional perspective on this issue?

Etienne Cavalier: In previous research, we have demonstrated that a race/ethnicity correction factor should not be used for Africans living in Africa or for people of African origin living in Europe. In our laboratory, we have thus avoided using any race/ethnicity factors. Additionally, a survey conducted by the EFLM Task Group on CKD (with results not yet published) indicates that European laboratories do not rely heavily on adjustment for race/ethnicity in their clinical practice. About 20% of respondents chose to use the new "race-free" equation. It's worth noting that this survey was conducted before the EFLM and European Renal association (ERA) provided guidance to continue using the 2009 CKD-EPI creatinine equation (without correction factor) or the EKFC one. It would be interesting to repeat this survey in a year or two to see if there have been any changes in laboratory practices following the release of this new guidance.

Robert Kalyesubula: I come from sub-Saharan Africa. Until 2021, we had little evidence on how race-based equations were performing among the African population. We had preliminary evidence that people from Africa were quite different from African Americans, but we really did not have enough evidence to abandon use of the race factor. In the wake of the race-based discussions and new evidence coming out of Africa, most African countries have abandoned use of race factors and use either the 2009 CKD-EPI creatinine equation without race adjustment or have switched to the 2021 race-free CKD-EPI equation. Most scientists from Africa felt that race-based eGFR estimations were discriminatory and largely disadvantaged people of Black color but did not have big studies to back this up until recently. We currently do not have an independent guidelines' body in Africa and tend to adopt the prevailing recommendations with most evidence from America or Europe. However, we certainly now know that Africans are not the same as African Americans when it comes to eGFR estimation.

Boon Wee Teo: I cannot speak for the region, but at the moment I have to think about the pros and cons of using the race-free 2021 CKD-EPI equations. As I alluded to earlier, the race coefficient for Black race persisted in the serum creatinine-only 2009 CKD-EPI equation but is reduced significantly in the 2012 combined serum creatinine and cystatin C equation, and both performed very well when applied to our multi-racial population without race adjustment. While the CKD-EPI equations are more accurate for GFR estimation with race adjustment, is it clinically important for CKD patients to have an accurate GFR estimate or are we happy to accept a systematic "error" in an estimate of GFR which is consistent on a longitudinal basis? In practice, we are usually interested in GFR slopes (rate of decline per year) for the clinical management of CKD. The main concern would be that any marginal inaccuracy may magnify inaccuracies in the detection of CKD in population studies or during health screening (some also argue that the diagnosis of CKD based on the paradigm of reduced GFR and elevated albuminuria is to some extent flawed). Our studies, along with those from other groups on this matter, also showed that there is no perfect equation for GFR estimation for every clinical scenario. A wider range of GFR covered by the estimation equations affects the accuracy at the upper or lower bounds, which has been considered in the underpinning maths and design of the CKD-EPI equations.

Verônica T. Costa e Silva: There has always been some discomfort and disbelief in using the race-based GFR equation by the nephrology community in Brazil, a country with a mixed-race population where race ascertainment is challenging to establish. Mixed-race people make up to 60% of the Brazilian population, depending on the geographic area, with a steady increase in this proportion over several decades. This group may self-report as White or Black depending on social, environmental, and cultural background, which play a greater role when racial barriers are not so clearly established. Also, the number of people self-declaring as Black in Brazil doubled in the last 10 years, with a projection of continued expansion. In this scenario, race stands closer to a social/cultural construct than a biological variable determining GFR estimation, such as age and sex. For these reasons, although we do not have a formal statement from the Brazilian Society of Nephrology, my colleagues and I quickly incorporated the 2021 race-free equations as soon as they were published. With the NKF/ASN recommendations, I expect a quick and widespread use of the race-free equations in our country.

Lesley A. Inker: Inclusion of the term for Black race leads to improvement in statistical performance of eGFR by creatinine (eGFRcr) compared to measured GFR. However, because race is a social construct with greater biological variability between individuals within

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racial groups than between racial groups, and with definitions that change over time and geography, the NKF and ASN did not support its ongoing use in GFR estimation. The NKF/ASN task force subsequently recommended the 2021 CKD-EPI equation because it was "developed in a diverse population that included Black and non-Black individuals; it does not include a term for Black race; had acceptable performance characteristics in all groups; and potential consequences that do not disproportionately affect any one group of individuals." An analysis of the 2022 College of American Pathologists (CAP) general chemistry proficiency testing survey in the US reported that 40% of laboratories have or planned to report eGFR using the 2021 CKD-EPI creatinine-based eGFR by the end of 2023.

Are you currently using cystatin C for GFR estimation, and do you project increased use of this biomarker regionally?

Etienne Cavalier: Although the cystatin C test is available in our laboratory, it is only reimbursed in Belgium under very specific conditions (such as for children and renal transplant patients), which limits the number of requests we receive. This pattern is consistent across most European countries, with the notable exception of Sweden. One significant advantage of cystatin C, particularly when used in conjunction with the EKFC equation, is that it is "sex and gender-free," which makes it a valuable tool for monitoring sex and gender diverse patients. Additionally, it could be useful in cosmopolitan European cities where the population is diverse, as it is independent of ethnicity. However, the primary drawback of cystatin C remains its cost. Considering all factors, I don't foresee cystatin C replacing creatinine in most European countries anytime soon. Nevertheless, I believe it is the marker of choice for certain clinical scenarios, such as in frail patients. Overall, cystatin C has great potential for specific applications and could be a valuable addition to our diagnostic tools in certain situations.

Robert Kalyesubula: Yes, I occasionally use cystatin C for GFR estimation when it is critical for me to know the most accurate eGFR. For example, it is useful in patients with liver cirrhosis, those who have amputations, and those who are going to be referred for kidney transplants (we currently are not able to do kidney transplants in my country). Based on the current literature and the studies we have conducted ourselves, cystatin C is definitely going to be the go-to marker. It just needs the nephrologists to overcome the inertia and use the evidence available. The argument of cost, is really about numbers! Once more doctors order this test, the costs will come down. I often relate this to what happened in the field of HIV-AIDS where we have moved from using T-lymphocyte counts, to CD4 counts and currently to the HIV-viral loads because they are more accurate though up to 4 times more expensive than CD4 counts. There will definitely be more use of the cystatin C biomarker.

Boon Wee Teo: We are not using cystatin C on a regular basis. However, in an era of precision medicine, where clinical trial outcomes are based on eGFR (fairly short-term of 3 years or so), and "pay for performance" by health systems using monitoring with electronic health records, more accurate GFR estimations are needed to improve clinical assessments. I had, in fact, contemplated updating clinical practice guidance and comments to recommend that nephrology specialty clinics should perform GFR estimations using both serum creatinine and cystatin C once a year. Moreover, in clinical trials, where practicable, GFR should be measured by a reference method especially if critical decisions are made on expensive or potentially toxic treatments. Currently, when there is clinical uncertainty or situations like kidney transplantation, we measure GFR using a radioisotope method.

Verônica T. Costa e Silva: No, I am not currently using cystatin C for GFR estimation in my routine clinical practice because we are a public institution, and the Brazilian health system does not fund cystatin C. Considering that 80% to 90% of the Brazilian population (220 million people) depends on public healthcare, I do not envision an increased use of cystatin C in our country in the short term until we can cover the cost. Hopefully, more affordable assays will help to reverse this scenario.

Lesley A. Inker: We are using cystatin C for GFR estimation for patients in whom we question the accuracy of eGFRcr and to support the level of GFR when it impacts medical decisions. Initially, cystatin C was sent out to a reference lab for measurement. Our close collaboration with our clinical chemistry colleagues in my hospital helped pave the way for bringing the assay "in-house" so that it's now available within hours. This has allowed cystatin C-based GFR estimates (eGFRcys) to be easily incorporated into our clinical decision-making. If we measure cystatin C, we prefer creatinine to be also measured. Recent papers have shown that when there is a large discordance between eGFRcr and eGFRcys, the combined eGFRcr-cys is the most accurate, suggesting need for continued measurement of cystatin C. In contrast, when there is concordance, all 3 provide a similar level of accuracy, suggesting eGFRcr is reasonable to use unless there is a change in health status.

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I do project increased use of cystatin C in the United States. Attention to the GFR, through the high-profile discussion about use of race in GFR estimating equations, has increased the recognition of the importance of accurate eGFR. Greater education is required to increase utilization especially in non-nephrology practices, such as cancer or infectious diseases, where more accurate GFR estimates could improve care and outcomes for our patients.

What is your opinion on global agreement to use a single equation for GFR estimation, and do you think it is necessary to validate an equation for use in different populations?

Etienne Cavalier: When it comes to estimating kidney function in Europe, I believe that the 2009 CKD-EPI creatinine equation (without the "race" factor), and still more the EKFC and Lund–Malmö Revised (LMR) equations, are reliable options. Compared to the newer "race-free" equation, these European equations appear to provide more accurate results. Notably, they are suitable for people of all ages, including children above 2 years old and the elderly. Additionally, the EKFC cystatin C equation is not influenced by sex and could thus be used universally, although it may incur higher costs.

Robert Kalyesubula: I believe it is a good dream to think about using a single GFR equation across the globe. However, it should be appreciated that there are several differences that may preclude this from happening. The non-GFR determinants of markers vary across individuals as well as regions and it is certainly going to be difficult to have a single equation in use. I also believe that creatinine is such an inaccurate marker of kidney function and, as long as it continues to be the backbone of GFR estimation, uniformity across the globe cannot possibly be achieved. In the African Research on Kidney (ARK) study we actually tried to develop an African-specific equation but were let down by creatinine. I believe it is important to validate equations in different regions because of the underlying differences in people. It is also important to know to what extent different populations conform to the internationally acceptable equations so that they make the necessary adjustments and perhaps also pave way for newer and more universal markers.

Boon Wee Teo: I think there is a need to have a global agreement on a single equation for GFR estimation for the purposes of consistency in reproducing results from clinical trials for translation into usual clinical practice. A standard equation allows comparison between regions of the world for the study of kidney disease epidemiology. Taking all the studies on GFR measurement and validation into consideration, there is no perfect equation for all scenarios. I believe we have sufficiently assessed the merits of the 2009 CKD-EPI creatinine equation and also the combination serum creatinine and cystatin C equation; there probably is no need to spend more time and resources on developing newer GFR estimation equations.

Verônica T. Costa e Silva: I think that a single equation for use in different populations worldwide is likely to improve the care of patients with CKD, bringing benefits in terms of clinical practice: providing an instrument that can be globally used to define and stage CKD, and identify risk factors for CKD onset and progression; research: allowing the incorporation of standard eligibility criteria and end points for clinical trials of kidney disease progression which will facilitate the incorporation of study results into clinical practice worldwide, particularly low- and middle-income countries, that are not where large clinical trials are usually done; and public health: informing strategies to improve health outcomes related to kidney disease. However, I acknowledge that local aspects can impact the serum level of creatinine (race composition and diet patterns) and cystatin C (smoking habits), challenging conclusions based on direct comparisons. There is still work to be done to validate the GFR estimating equations in different areas of the globe.

Lesley A. Inker: In the past 20 years I have seen a strengthening of kidney care globally. I can still remember when KDIGO, our international guideline group, was formed. I have witnessed the impact of our united voice, using the same language, on the public health of CKD. While having different estimating equations does not necessarily result in different terminology, I am concerned that the current focus on differences between equations will halt progress on the public health challenge of CKD, perhaps even leading to its regression.

It is appropriate to evaluate GFR estimating equations in different populations. For eGFRcr, variation may be related to biological differences in tubular handing of creatinine, or in protein intake or muscle mass compared to the populations in which the equations were developed. Regional equations, often formulated as modification of the original equation, can capture the average difference in the totality of these factors. There is less variation for cystatin among regions and eGFRcr-cys appears to be more robust to regional differences.

Labeling the report as eGFR with specification of the filtration marker, naming the equation only in the notes, and using the same equation across a large region (i.e., a country) will help retain our focus on our common public health goals for CKD.

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What should be the future goals for improving GFR estimation, and what is needed to achieve those goals?

Etienne Cavalier: It is important to recognize that estimating GFR is always an approximation, even with a new equation that would be completely free of bias based on race/ethnicity, age, or sex. This means that there is always a possibility of inaccuracy. To address this issue, I believe that we need to focus on promoting the measurement of GFR in routine clinical practice. Unfortunately, very few laboratories are currently equipped to perform this reference measurement (such as through plasma iohexol clearance), and even fewer nephrologists request or utilize this test in their clinical practice. This presents a significant challenge, as we must train nephrologists and laboratory physicians to use this reference technique, which has often been wrongly classified as "cumbersome." While determining plasma iohexol clearance does require some basic skills in liquid chromatography coupled with a UV detector or a mass spectrometer, it is one of the few reference methods that can be performed by clinical chemistry laboratories, and its cost is generally lower than other reference techniques used in everyday medicine. By prioritizing the use of plasma iohexol clearance and improving training opportunities, we can work towards more accurate and comprehensive kidney function assessments for our patients.

Robert Kalyesubula: The future goals of improving GFR estimation should encompass both diagnostic and outcome predictive models. It may be wise to focus on sets of patients/populations with defined characteristics rather than one size fits all. For example, creatinine could be used for screening and cystatin C as a confirmatory test guided by clear algorithms. The search for newer and more accurate markers of kidney function should continue and the price of more accurate markers like cystatin C should be brought down. People from low- and lower middle-income countries should be included in the development of newer equations because they have unique characteristics from those of high-income countries. We also need to harness artificial intelligence (AI) in this area of GFR estimation, with a caution that low-income countries are not left out as has been the case for earlier equations. We need to have more inclusive consortia and regular learning and re-learning with an open mind to using multiple markers for GFR estimation.

Boon Wee Teo: I think we should move beyond GFR estimation and develop simple, safe, fast, and accurate GFR measurement methods. In GFR estimation, we usually report greater than 90 mL/min for patients in the high end. One of the criticisms of the current CKD identification and staging, and GFR estimation, is the failure to consider hyperfiltration as an even earlier stage of kidney disease. We would expect this in diabetes, hypertension, or obesity. Without an ability to accurately measure GFR, we are unable to start the essential clinical trials for truly preventive nephrology. In cancer treatment, repeat scans like magnetic resonance imaging (MRI) or positron emission tomography - computed tomography (PET-CT) are used to ascertain clinical response, and yet the time and cost of these assessments are usually not questioned. In nephrology, the outcomes of some CKD patients are worse than cancer and there is a need to be more precise and serious about the assessment of kidney function. Even then we are currently only measuring filtration function and not the other many functions of the kidney. As a start, we should consider developing transcutaneous monitoring of injected markers for GFR measurement in the nephrology specialty clinic, and move on to further develop a diagnostic nephrology laboratory repertoire to better evaluate the kidney in all its functional domains. With the onset of a revolution in genetic analyses, a broadened and standardized nephrology specialty diagnostic suite would push kidney disease management into the new era of precision medicine.

Verônica T. Costa e Silva: Variation in the non-GFR determinants of serum concentrations of endogenous filtration markers is likely the most critical limitation to the accuracy of GFR estimating equations. Thus, GFR estimation might be improved by use of a panel of endogenous filtration markers (low-molecular-weight proteins such as β2-microgobulin and metabolites such as pseudouridine, acetylthreonine, and tryptophan) to minimize the impact of non-GFR determinants of each marker and lessen the need to use demographics and clinical characteristics in GFR equations. The panel would be particularly helpful in clinical settings where the estimate based on any single filtration marker is inaccurate, such as serum creatinine-based estimation in patients with sarcopenia. Also, it's likely that novel statistical methods such as machine learning may generate highly accurate personalized estimates based on the panel, combined with statistical approaches that consider the error of measured GFR in estimating actual GFR, to further improve the accuracy of GFR estimating equations. It is fundamental that these GFR models be validated in different populations worldwide and that filtration markers are made available at an affordable cost.

Lesley A. Inker: Current equations maximize the information we achieve with creatinine or cystatin. The main path forward is likely discovery of novel filtration markers, which alone or in combination with creatinine and cystatin C, can lead to true improvements in

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estimation of GFR. In addition, we need large-scale studies to measure GFR in populations currently not well represented in our data sets. Globally, we need more measurements in people with acute or chronic illnesses to know here too how to best evaluate the GFR.

Finally, we should not forget the "e" in eGFR, regardless of filtration marker. When there are clinical decisions that require a higher level of accuracy, ideally GFR should be measured using clearance of exogenous filtration markers. New methods are being developed; I am hopeful GFR can be measured more frequently to support critical decisions in patients across the spectrum of health and disease.

Nonstandard Abbreviations: NKF, National Kidney Foundation; ASN, American Society of Nephrology; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; $eGFR_{cr}$, eGFR by creatinine.

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