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What should European nephrology do with the new CKD-EPI equation?

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BACKGROUND

Knowledge about a patient's glomerular filtration rate (GFR) is central to the practice of medicine. It is needed to diagnose and classify chronic kidney disease (CKD), and helpful to establish prognosis [1]. In addition, it is used to decide when to start specific medication, how to dose medication and when to refer patients for specialist nephrology care or when to start kidney function replacement treatment. GFR can best be measured (mGFR) by injection of exogenous tracers, such as iothalamate and iohexol, and serial blood sampling. This is a relatively cumbersome and expensive technique, and is therefore only used in specific cases. In clinical practice, equations are used to estimate GFR (Fig. 1 and Table 1). Theseequations use readily available information about patient characteristics, such as age and sex, and about creatinine as an endogenous filtration marker. The oldest equation is the one developed by Cockcroft and Gault in 1976 [2]. It should be noted that their equation does not estimate GFR, but creatinine clearance. Creatinine clearance is determined not only by glomerular filtration of creatinine, but also by tubular secretion of creatinine. Tubular creatinine clearance can amount to up to 50% of total creatinine clearance, especially in subjects with impaired kidney function and obesity [3]. Consequently, the Cockcroft–Gault equation should not be used to estimate kidney function because it can overestimate GFR considerably. In that respect it is surprising that the summary of product characteristics for many drugs evaluated by regulatory agencies, even novel drugs, still refer to the Cockcroft–Gault creatinine clearance for dose adjustment [4]. The Modification of Diet in Renal Disease (MDRD) equation was developed in 1999 to improve prediction of GFR, which was a major step forward also because it was widely accepted [5, 6]. In 2009 it was replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which was more accurate at higher GFR [7]. This latter equation has become the standard method for estimating GFR across the world.

PROBLEMS WITH THE 2009 CKD-EPI EQUATION

A problem with the 2009 CKD-EPI equation is that besides information on age, sex and creatinine, it also requires information on race. During recent years it has been argued that race is a social, political and legal rather than a biological construct, and that the incorrect use of race may have a negative effect on health equity [8]. The National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) announced therefore in 2021 that "race modifiers should not be included in equations used to estimate kidney function" and that "current race-based equations should be replaced by a substitute that is accurate, representative, unbiased, and provides a standardized approach to diagnosing kidney diseases" [9]. To achieve these goals the NKF and the ASN established a task force to reassess inclusion of race in the estimation of GFR in the USA.

WHY WOULD RACE MATTER WHEN ESTIMATING GFR?

Why the race coefficient was developed and scientific drawbacks of using it have recently been reviewed by Delanaye *et al.* [10]. During the development of the CKD-EPI equation it

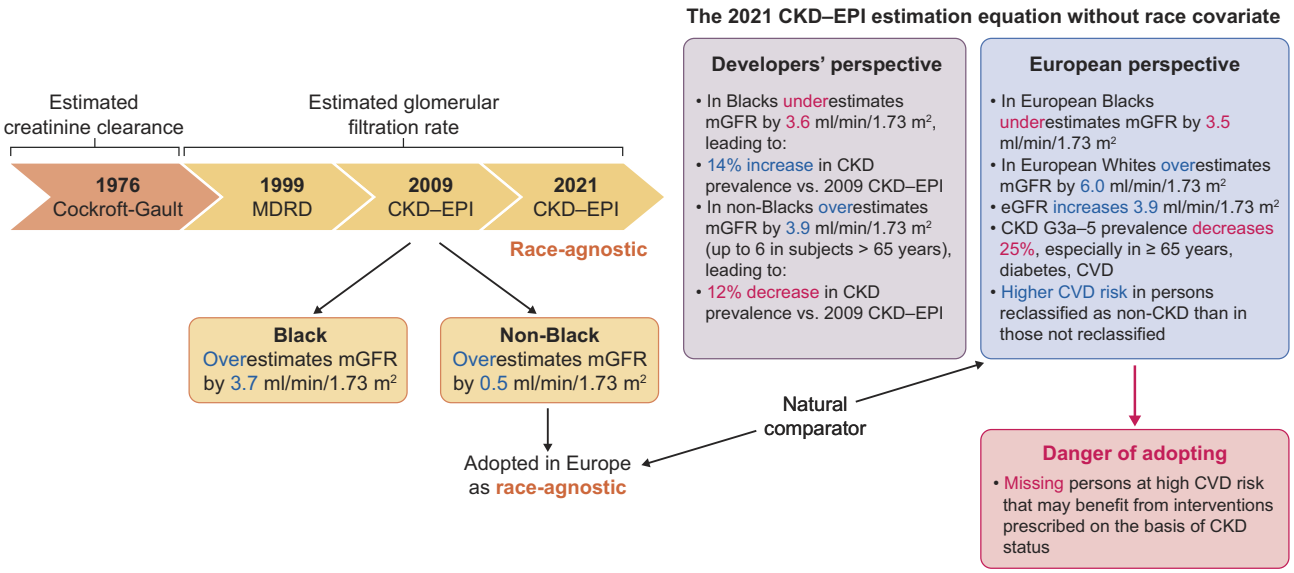

Figure 1: The development over time of the various GFR estimation equations, and their strengths and weaknesses.

Table 1: Oversight of the various equations to estimate kidney function.

(i) The Cockcroft–Gault equation to estimate 24-h creatinine clearance (in mL/min), developed in 1976 [2]:
(140 – age in years) × weight in kg/(0.81 × serum creatinine in μmol/L) (× 0.85 for women)

(ii) The 4-variable MDRD equation to estimate GFR (in mL/min/1.73 m^2), developed in 1999 [5, 6]:
175 × (serum creatinine in μmol/L)/88.4)$^{-1.154}$ × age in years$^{-0.203}$ (× 0.742 for women) (× 1.210 if individual is Black)

(iii) The 2009 CKD-EPI equation to estimate GFR (in mL/min/1.73 m^2), developed in 2009 with race coefficient [7]:
Female and SCr ≤0.7 mg/dL: 144 × (SCr/0.7)$^{-0.329}$ × 0.9929^{age} × 1.159 (if individual is Black)
Female and SCr >0.7 mg/dL: 144 × (SCr/0.7)$^{-1.209}$ × 0.9929^{age} × 1.159 (if individual is Black)
Male and SCr ≤0.9 mg/dL: 141 × (SCr/0.9)$^{-0.411}$ × 0.9929^{age} × 1.159 (if individual is Black)
Male and SCr >0.9 mg/dL: 141 × (SCr/0.9)$^{-1.209}$ × 0.9929^{age} × 1.159 (if individual is Black)

(iv) The 2021 CKD-EPI equation to estimate GFR (in mL/min/1.73 m^2), developed in 2021 without race coefficient [12]:
Female and SCr ≤0.7 mg/dL: 143 × (SCr/0.7)$^{-0.241}$ × 0.9938$^{age\ in\ years}$
Female and SCr >0.7 mg/dL: 143 × (SCr/0.7)$^{-1.200}$ × 0.9938$^{age\ in\ years}$
Male and SCr ≤0.9 mg/dL: 142 × (SCr/0.9)$^{-0.302}$ × 0.9938$^{age\ in\ years}$
Male and SCr >0.9 mg/dL: 142 × (SCr/0.9)$^{-1.200}$ × 0.9938 $^{age\ in\ years}$

(v) The EKFC equation to estimate GFR (in mL/min/1.73 m^2), developed in 2021 [18, 20]:
2–40 years and SCr/Q <1: 107.3 × (SCr/Q)$^{-0.322}$
2–40 years and SCr/Q ≥1: 107.3 × (SCr/Q)$^{-1.132}$
>40 years and SCr/Q <1: 107.3 × (SCr/Q)$^{-0.322}$ × 0.990$^{(age\ in\ years\ -\ 40)}$
>40 years and SCr/Q ≥1: 07.3 × (SCr/Q)$^{-1.132}$ × 0.990$^{(age\ in\ years\ -\ 40)}$

Q-values
For ages 18–25 years, males:
$\ln(Q) = 3.2 + 0.259 \times age - 0.543 \times \ln(age) - 0.00763 \times age^2 + 0.000079 \times age^3$

For ages 18–25 years, females:
$\ln(Q) = 3.08 + 0.177 \times age - 0.223 \times \ln(age) - 0.00596 \times age^2 + 0.0000686 \times age^3$
For ages ≥25 years, Caucasian European males: Q = 0.90 mg/dL
For ages ≥25 years, Caucasian European females: Q = 0.70 mg/dL

For Black Africans, females: Q = Q + 0.02
For Black Africans, males: Q = Q + 0.06
For Black European, females: Q = Q + 0.04
For Black European, males: Q = Q + 0.12

SCr, serum creatinine.

was observed that the relationship between mGFR and serum creatinine was different in Black and White participants. It was argued that these divergent results may be explained by the difference in muscle mass between Black and White people. An African-American race coefficient was therefore introduced. The results for non-Blacks were to be multiplied by the factor 1.159 to obtain an estimated GFR (eGFR) value for African-Americans. A problem, however, might be the selection of Black people in the study that led to the 2009 CKD-EPI equation. As Delanaye *et al.* argue, the great majority of Black participants came from one study, the African American Study of Kidney Disease and Hypertension (AASK) [10]. Specific

methodological aspects of this study could therefore have had a serious impact on the accuracy of the CKD-EPI equation for Black people. For instance, the body composition with respect to muscle mass of Black participants in the AASK study may not be representative for the overall Black population in the USA and elsewhere. Other theoretical reasons why serum creatinine may differ between Black and White people at a same level of GFR could be differences in tubular secretion of creatinine or a difference in the intake of meat as exogenous source of creatinine. It should be noted that these factors have all been poorly studied.

DEVELOPMENT OF THE 2021 CKD-EPI EQUATION WITHOUT THE RACE TERM

In the wake of racial reckoning since the spring of 2020 in the USA, efforts have led to the examination of traditional medical algorithms that incorporate race modifiers [11]. Prominent among these efforts has been reconsideration of race-based adjustment in GFR estimation equations, and most important has been the initiative by the CKD-EPI research group. In 2021 these investigators developed new equations that do not use race, and compared their accuracy with that of their previous, 2009 CKD-EPI equation [12]. In their validation set which included 4050 subjects, of which 579 were Black individuals, the old 2009 CKD-EPI equation which uses sex, age, race and creatinine overestimated mGFR by 3.7 mL/min/1.73 m^2 in Blacks and by 0.5 mL/min/1.73 m^2 in non-Blacks. The new 2021 CKD-EPI equation that has no race coefficient performs slightly worse on a population level because it underestimated mGFR by 3.6 mL/min/1.73 m^2 in Blacks and overestimated mGFR by 3.9 mL/min/1.73 m^2 in non-Blacks. Thus, in Blacks the absolute bias in estimating mGFR is similar with the old and new equations, albeit the 3.7 mL/min/1.73 m^2 overestimation has become a 3.6 mL/min/1.73 m^2 underestimation. Although absolute bias may mathematically have remained similar in Blacks, this change from over- into underestimation will be important from a healthcare perspective, because it is expected to lead to, for instance, earlier referral for start of dialysis or kidney transplantation [13, 14].

The 2020 census showed that the US population consists of 12.4% Black and 87.6% non-Black subjects [15]. In the larger population of non-Blacks, the new 2021 CKD-EPI equation is less accurate, with an overestimation of now 3.9 instead of 0.5 mL/min/1.73 m^2, whereas imprecision remained nearly similar (more than 10% of eGFR values are more than 30% different from mGFR) [12]. It was calculated that when adopting the 2021 CKD-EPI equation, the prevalence of CKD among Black persons will go up from 14.3% to 16.3%. In contrast, in non-Blacks it will go down from 11.7% to 10.3% [12]. The largest difference in accuracy in non-Blacks with the new versus the old CKD-EPI equation was found in subjects >65 years old, with an overestimation of mGFR by around 6 instead of around 1 mL/min/1.73 m^2 [12]. For an individual, this bias is relatively small compared with the imprecision. The CKD-EPI investigators felt therefore that the change in accuracy was not meaningful. At a population level, however, these changes in bias can lead to important differences in CKD prevalence and risk prediction, with different results for Black and non-Black race groups.

As a side note, the CKD-EPI also developed new equations based on cystatin C only, and on creatinine plus cystatin C. It was shown that the equation for cystatin C only did not perform better than the one for creatinine only [16], and that these combined equations performed slightly better than equations incorporating only creatinine or only cystatin C [12, 16].

Shortly after publication of these results, the NKF-ASN task force issued several recommendations, among which was to implement immediately for US adults the new 2021 CKD-EPI equation, which does not contain a race coefficient [17]. The slightly poorer performance of the new eGFR equation in non-Black people was apparently felt to be a reasonable price to pay to avoid the questionable race coefficient.

WHAT DOES THE JOURNAL ADD TO THIS DISCUSSION?

In this issue of *Nephrology Dialysis Transplantation* (*NDT*) two original articles are published that test the 2021 CKD-EPI equation in European settings. The first investigated how well it performs to estimate GFR in various Black and White populations [18]. The second studied the impact of using 2021 CKD-EPI equation on CKD prevalence and prognostic accuracy [19]. Both studies are of interest for several reasons, among which because they report on large numbers of subjects, which renders these results robust. The results are also described in much detail, with an abundance of supplementary material made available to the readers, which allows an independent judgement. Also important is that they report on European or predominantly European populations, which may help guide European nephrology in deciding what to do with the new CKD-EPI equation. These two studies are described in the two paragraphs below.

How well does the 2021 CKD-EPI equation estimate GFR?

Delanaye *et al.* studied on behalf of the European Kidney Function Consortium (EKFC) the accuracy of the 2009 and 2021 CKD-EPI equations, as well as the accuracy of a GFR estimation equation that this consortium previously developed, the EKFC equation [18, 20]. This equation uses sex-, age- and race-specific median creatinine values obtained from healthy subjects to mathematically estimate GFR from a given serum creatinine value [20]. This study was performed in a relatively large population of 13 856 subjects (of which 1572 were Black) in whom GFR was measured with exogenous tracers. The authors found that in European Whites the accuracy of the 2021 CKD-EPI equation was lower than in non-Blacks in the publication by CKD-EPI. In fact, of the three equations tested, the accuracy of the 2021 CKD-EPI equation was the lowest, with an overestimation of mGFR by 6.0 mL/min/1.73 m^2, followed by an overestimation by 3.0 mL/min/1.73 m^2 by the 2009 CKD-EPI equation [18]. The best performance was noted for the EKFC equation, with

a slight underestimation of 0.3 mL/min/1.73 m^2 [18]. The authors offer several explanations for why the 2021 CKD-EPI equation performs less well in their study. First, an equation always performs better in the cohort in which it has been developed. This explanation can of course be used to plead against the CKD-EPI equation which was developed and tested by CKD-EPI, as well as for the EKFC equation which was developed and tested by the EKFC. Second, in the CKD-EPI development population the majority of studies used renal clearance of iothalamate as the gold standard to measure GFR, whereas the EKFC used various plasma clearance techniques. What the effect is of these differences in GFR measurements techniques in the development of CKD-EPI versus EKFC equations is as yet unknown, because the so-called gold standard techniques are unfortunately not well standardized nor validated against each other [21]. Third, the CKD-EPI equation considered non-Blacks as a whole, including Native American, Mexican, Asians and Hispanic people, whereas the non-Black populations in the EKFC equation was potentially more homogenous and more representative at least for the European population.

How well does 2021 CKD-EPI eGFR predict CKD complications?

The other original study published in this issue of *NDT* has been performed by Fu *et al.* [19]. These authors investigated how adopting the 2021 CKD-EPI equation would impact prevalence of CKD and risk prediction. Based on creatinine data of 1.6 million Stockholm adults with serum creatinine measurements available from routine healthcare between 2007 and 2019 (the SCREAM cohort, Stockholm CREAtinine Measurements), they showed that on average eGFR would go up by a median of 3.9 (interquartile range 2.9–4.8) mL/min/1.73 m^2. Especially older individuals and males had a larger eGFR increase. Consequently, the population prevalence of CKD G3a–5 would decrease by around 25%, from 5.1% to 3.8%. Remarkably, the absolute decease in CKD prevalence was highest in participants ≥65 years old, and in those with diabetes or cardiovascular disease. This is surprising, because we know from clinical practice that these subgroups have a particularly high chance of progressive CKD. The clinical translation would be that fewer individuals are perceived as having a high cardiovascular risk based on their eGFR results. In addition, individuals reclassified to a higher eGFR based on the 2021 CKD-EPI equation exhibited a higher risk of all-cause/cardiovascular death and major adverse cardiovascular events than those not reclassified with a similar eGFR. Notwithstanding these results, the association of eGFR with kidney, cardiovascular and mortality outcomes did not differ significantly when using the 2021 CKD-EPI equation instead of the 2009 CKD-EPI equation. A limitation of this study is that no information on race was available. This may be a scientific limitation, but in clinical practice in nearly all countries across Europe the race coefficient is not used for the 2009 CKD-EPI equation because legally it is not permitted to collect data on ethnicity.

ARGUMENTS FAVORING AND OPPOSING CHANGING THE CKD-EPI EQUATION

Given the presently available data, the question is now what European nephrology should do with the new 2021 CKD-EPI equation—should it be adopted or ignored?

There are compelling arguments to adopt it. We suggest that nephrology use the same language, definitions and equations across the globe. In 2019 KDIGO organized a Consensus Conference to make sure that we use uniform nomenclature to describe kidney function and disease. This helps effective communication by stakeholders in the kidney health community, and is instrumental to raise public awareness of the importance of CKD [22]. We would also favor that nephrology across the globe uses the same equations to estimate GFR. It would be awkward if a different equation were to be used in the USA from that used in Europe. This would impact the prevalence of CKD differentially. When intervention trials are designed, the inclusion and exclusion criteria with respect to kidney function may become different in the USA versus Europe. These are all issues that should be avoided.

There are also convincing arguments against changing the CKD-EPI equation that is currently used in Europe. The first is that nearly all European countries do not use the race coefficient for the 2009 CKD-EPI equation. There is therefore no sense of urgency to change to the official race-free 2021 CKD-EPI equation. Another important reason is that the new equation does not perform better, but worse. Because GFR is overestimated in the larger part of the population, the overall CKD prevalence figures would decrease overnight. Also, the composition of the CKD population would change, since especially patients whom we previously thought of as high-risk patients are affected, i.e. males, elderly individuals, and subjects with a history of diabetes or cardiovascular disease. Would this imply that epidemiological studies that showed that especially these subjects are at risk of developing CKD and its complications might have to be redone? In addition, how should the abrupt changes in eGFR induced by adopting a new equation be explained to patients, general practitioners and other medical specialists? On an individual level, the substantial reclassification to higher eGFR categories may also have unwanted implications for medication initiation, discontinuation and dosing, and financial coverage, and may lead to later nephrologist referral, planning for dialysis and evaluation for kidney transplantation.

HOW TO MOVE FORWARD?

Weighing the above arguments, we favor the opinion that, at the moment, European nephrology does not adopt the 2021 CKD-EPI equation to estimate GFR. When we want to change the existing equation, it should be a step forward. That does not seem to be the case now. Of course, we would like to align with our American colleagues, but at the same time it should be acknowledged that the dilemma of whether or not to adopt the 2021 CKD-EPI equation is caused by American nephrology, because ASN and NKF decided to change without consulting their counterparts in other parts

of the world. In retrospect, that should have been done in consensus. European nephrology can therefore not be held accountable for inconsistencies when it now does not align.

If European nephrology wants to make a real step forward in developing more accurate GFR estimation equations, there are three possible solutions. First, when creatinine is maintained as the sole kidney function marker to be used in CKD-EPI-like GFR estimation equations, anthropometrics could be included as additional covariates to adjust for interindividual differences in muscle mass, as the most important determinant of serum creatinine concentration besides kidney function. The older equations did not use weight and height as proxies for muscle mass because at that time such information was not routinely available for many patients in clinical chemistry labs. Nowadays, with the widespread use of electronic patient files, this information is stored and easy to use. But even weight and height may not be sufficient as proxies for muscle mass in an individual, as Hsu *et al*. pointed out recently [23]. What might work is when, alongside a standard GFR estimation equation, additional equations are developed for subjects with disproportionally low, and for subjects with disproportionally high muscle mass for their age and sex.

Second, the type of equation could be changed. The equation that was developed by the EKFC works, and is an example of a fundamentally different approach. It uses so-called Q values, which are sex- and age-specific median creatinine values in healthy subjects, to estimate GFR for an individual. These Q values can be obtained for different populations (instead of different races) according to age and gender, for instance from large local hospital databases. The validation results by the EKFC are promising. Performance in terms of bias and accuracy seems better [18, 20], but external validation is needed, preferably by independent research groups using large datasets including populations from outside Europe. An advantage could also be that this equation can be used for all age groups, and not only for adults, as holds for the CKD-EPI equation (Table 1). A disadvantage could be that the eGFR results are dependent on the normal Q values that are used for various populations, because the selection of these normal values may have an arbitrary component. In addition, the EKFC equation has a standard Q value for Caucasian European males and females, and adjusts these Q values for other populations including Black individuals (Table 1). This is reminiscent of using the race conversion factor in the 2009 CKD-EPI equation, the issue which started the discussion about the need to replace this equation. The Q values for the EKFC equation may therefore better be based on biological characteristics and not have an implicit reference population.

Third, we could change the analyte from creatinine, or add an analyte to creatinine as marker for kidney function. In this respect cystatin C has received most attention. In contrast to creatinine, cystatin C is produced by all nucleated cells, and not only by myocytes. Its serum concentration is therefore not dependent on muscle mass. The CKD-EPI research group showed that new eGFR equations that incorporate creatinine and cystatin C, but omit race, are more accurate and led to smaller differences between Black participants and non-Black participants than new equations without race with creatinine alone [16]. Moreover, the use of cystatin C alone or in combination with creatinine strengthens the association between eGFR and the risks of death and kidney failure across diverse population [24]. Unfortunately, cystatin C is not widely available for clinical use because not every clinical chemistry lab offers its measurement, and because related costs are in general considerably higher than for serum creatinine [25]. Moreover, also cystatin C is not independent of specific subjects' characteristics. For instance, it is increased in obesity [26], hyperthyroidism [27] and inflammatory states [28], and steroids also increase cystatin C values [29]. Furthermore, standardization of cystatin C measurement has not yet been fully optimized [30]. Efforts should therefore be made to make cystatin C available at lower costs, and to improve its standardization. At the moment measurement of cystatin C for GFR estimation is especially advised for subjects with clear abnormal muscle mass for their age and sex, and for subjects with an eGFR creatinine between 45 and 60 mL/min/1.73 m^2 without albuminuria, to confirm that these subjects indeed have CKD. Besides cystatin C other filtration markers have been suggested, such as beta-2 microglobulin and beta-trace protein [31], but as yet these analytes have been too poorly studied to be considered.

Whichever way forward is chosen to improve GFR estimation, we think that we should only change to a novel equation when it has considerably better performance. We should not be distracted by minor advancements because changing our standard equations will inherently cause discussion and confusion, and holds the danger that we lose credibility with other specialties that base some of their treatment decisions on eGFR values. When a change is considered, we should try to reach global consensus before implementing such a new GFR estimation equation. When international nephrology uses the same or at least a similar equation around the world, this will have many advantages for healthcare on an individual patient and on a population level, as well as for science.

CONCLUSION

To avoid the incorrect use of race as a biological construct and the resulting negative effect on health equity, the novel 2021 CKD-EPI equation was designed not to include a race coefficient. At present European nephrology in general uses the 2009 CKD-EPI equation to estimate kidney function for all subjects, without the Black race coefficient that this equation originally offered. From an ethical point of view changing from the 2009 to the 2021 CKD-EPI equation is therefore not felt to be an improvement. Since the 2021 CKD-EPI equation also seems to estimate GFR less accurately than the 2009 CKD-EPI equation, by overestimating GFR in the larger part of the European population, there is no strong evidence to adopt the new equation. European nephrology would do better to await novel developments to improve GFR estimation, such as adding anthropometrics to estimation equations, fundamentally changing these GFR equations or using/adding analytes other than creatinine as alternative filtration markers. When a significant improvement in accuracy and bias is achieved and validated independently, efforts should be made to reach global

consensus before novel equations are implemented to replace the current ones.

CONFLICT OF INTEREST STATEMENT

R.T.G. and A.O. are members of the Council of the European Renal Association (ERA), H.-J.A. is Editor-in-Chief elect of *Nephrology Dialysis Transplantation* (*NDT*), M.C. is Chair of the European Renal Best Practice, D.Fliser is Renal Science Chair of the ERA, D.Fouque is Editor-in-Chief of *NDT*, M.J.S. is Editor-in-Chief of the *Clinical Kidney Journal* and C.W. is President of the ERA.

(See related article by Fu *et al*. Removing race from the CKD-EPI equation and its impact on prognosis in a predominantly White European population. *Nephrol Dial Transplant* 2023; 38: 119–128; See related article by Delanaye *et al.* Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa. *Nephrol Dial Transplant* 2023; 38: 106–118)

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