Opinion Paper

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The new, race-free, Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation to estimate glomerular filtration rate: is it applicable in Europe? A position statement by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)

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Abstract: The EFLM recommends not to implement the race-free Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation in European laboratories and to keep the 2009 version of the CKD-EPI equation, without applying a race correction factor. This recommendation is completely in line with a recent Editorial published by the European Renal Association who has also proposed to change to a novel equation only when it has considerably better performance, trying to reach global consensus before implementing such a new glomerular filtration rate (GFR) estimation equation. In Europe, this equation could be for instance the new European Kidney Function Consortium (EKFC) equation, which is population-specific, developed from European cohorts and accurate from infants to the older old. Beyond serum creatinine, the estimating equations based on cystatin C will probably gain in popularity, especially because cystatin C seems independent of race. Finally, we must keep in mind that all GFR equations remain an estimation of GFR, especially rough at the individual level. Measuring GFR with a reference method, such as iohexol clearance, remains indicated in specific patients and/or specific situations, and here also, the role of the clinical laboratories is central and should still evolve positively in the future.

Keywords: chronic kidney disease epidemiology consortium (CKD-EPI); creatinine; equation; estimated glomerular filtration rate (eGFR); european kidney function consortium (EKFC).

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Compared to the "old" Cockcroft and Gault equation, the "new" creatinine-based equations to estimate glomerular filtration rate (GFR) allow a systematic estimation of the GFR (eGFR) with creatinine results by clinical laboratories. Yet, the decision to automatically report (or not) the eGFR on the results protocol and the choice of the equation used to estimate GFR engages the responsibility of the clinical laboratories [1]. However, the choice of the eGFR equation is not so easy. Indeed, several equations are available.

As the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) [2] equation, developed in the United States, is clearly the most popular and is also currently recommended by the International Nephrology guidelines (KDIGO) [3], other creatinine-based equations have also been proposed. Among them, we can mention the Revised Lund-Malmö equation [4], currently used in Sweden, and the promising European Kidney Function Consortium equation (EKFC), which has been recently developed from (mostly) European cohorts [5]. Compared to the CKD-EPI equation, this last equation has the advantage to be applicable from children (>2 years) to the oldest population without any transition problem between adolescence and adulthood. Hence, the EKFC equation can also be automatically used by laboratories in children, since it does not use height as a variable like the Schwartz equation [6]. The particularity of the EKFC equation relies on the use of the "Q value", defined as the median serum creatinine concentration in the population for which it is used. Recent data from Europe and Africa suggest that using a dedicated, population-specific Q value is easily feasible and improves the performance of the equation [7]. Indeed, it is obvious from the literature that the relationship between serum creatinine and GFR is different in different populations. The most illustrative example is observed in the USA. For the same level of GFR, the serum creatinine concentration will be different in Black and White Americans, with higher values observed in Black subjects [2, 8, 9]. We must acknowledge that we still do not really understand why such differences exist [8, 10, 11]. The observation of this difference prompted the authors of the MDRD and CKD-EPI equations to propose a correction coefficient to be applied to Black Americans [2, 9, 12]. This means that for the same level of serum creatinine, eGFR will be 16% higher in Black Americans than in White Americans. This correction has however been severely criticized, first from a strictly scientific point of view. Indeed, this correction factor is applied to all Black Americans, whereas the correction could be different in Black males and Black females. Indeed, the difference in serum creatinine between Black and White females in USA is minimal [10, 13–15]. More importantly for our purpose, the current race coefficient has been shown to be inapplicable in Black populations outside the USA, like in Europe, Africa and Brazil. In these areas, the CKD-EPI equation without the race coefficient demonstrated better performance than with the race coefficient [10, 13, 16–20]. These results strongly confirmed that the observed differences in serum creatinine have nothing to do with race (which is, in itself, a social construct, without any scientific or biologic justification) and even less with skin color [7]. In USA, the correction coefficient applied to CKD-EPI equation has even more been criticized for societal reasons. It is beyond the scope of the current editorial to list all valid arguments against the correction coefficient in the USA as a source of inequalities in health care [11, 21]. As a consequence to these arguments, both the National Kidney Foundation and the American Society of Nephrology have recommended to abandon the race coefficient and promote a new race-free version of the CKD-EPI equation which was been published in 2021 [22, 23]. This equation is very similar to the previous CKD-EPI equation published in 2009, but modified as to have the same bias in Black and non-Black populations. As a result, the absolute bias (between 3 and 4 mL/min/1.73 m^2) of the race-free CKD-EPI equation is now similar in Black and White populations in the United States. Even if such bias may be considered minimal and not clinically relevant at the patient level, the impact on the chronic kidney disease (CKD) prevalence at the population level is high since it shifts the former overestimation of 0.5 to 3.9 mL/min/1.73 m^2 in non-Black Americans and the former overestimation of 3.7 to an underestimation of GFR of 3.6 mL/min/1.73 m^2 in Black Americans. If the biases (in absolute value) are now comparable in both populations, the race-free equation is performing worse than the previous version of CKD-EPI in White subjects, and not really better in Black Americans [23]. The impact on the prevalence of CKD (defined as an eGFR< 60 mL/min/1.73 m^2) in the United States is important, with a higher prevalence of CKD in Black populations and a lower prevalence in White populations [24–26]. In Europe, using the new CKD-EPI equation has the same strong implications on CKD epidemiology. In Denmark for example, a country with a vast majority of non-Black population, using the new CKD-EPI equation will lead to a 25% lower prevalence of CKD [27]. According to these considerations, the utility of the new race-free equation in Europe is more than questionable [13]. First, there are obvious reasons to think that this equation is performing worse in White Europeans and the first results in Europe strongly confirm this fact [7, 28, 29]. Second, at the European level, but also in Africa and Brazil, there had never been a "race factor" (or no race correction) problem since it had been recommended *not* to use a racial coefficient with the previous CKD-EPI equation [10, 13, 16–20]. Hence, from a European perspective, we do wonder why we should use an equation that is performing worse in the majority of our patients and that is probably underestimating the real CKD prevalence in the European population due to a problem (race correction) that has been specific to the United States.

Thus, at this point, we recommend not to implement the race-free CKD-EPI equation in European laboratories

and to keep the 2009 version of the CKD-EPI equation, without applying a race correction factor. This recommendation is completely in line with a recent Editorial published by the European Renal Association who has also proposed to change to a novel equation only when it has considerably better performance, trying to reach global consensus before implementing such a new GFR estimation equation [30]. In Europe, this equation could be for instance the new EKFC equation, which is population-specific, developed from European cohorts and accurate from infants to the older old. Beyond serum creatinine, the estimating equations based on cystatin C will probably gain in popularity, especially because cystatin C seems independent of race [31, 32]. Finally, we must keep in mind that all GFR equations remain an *estimation* of GFR, especially rough at the individual level [33–36]. Measuring GFR with a reference method, such as iohexol clearance, remains indicated in specific patients and/or specific situations [37, 38], and here also, the role of the clinical laboratories is central and should still evolve positively in the future [39, 40].

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References

1. Levey AS, Stevens LA, Hostetter T. Automatic reporting of estimated glomerular filtration rate–just what the doctor ordered. Clin Chem 2006;52:2188–93.
2. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
3. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3: 1–150.
4. Björk J, Grubb A, Larsson A, Hansson L-O, Flodin M, Sterner G, et al. Accuracy of GFR estimating equations combining standardized cystatin C and creatinine assays: a cross-sectional study in Sweden. Clin Chem Lab Med 2015;53:403–14.
5. Pottel H, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate. A cross-sectional analysis of pooled data. Ann Intern Med 2021; 174:183–91.
6. Pottel H, Björk J, Bökenkamp A, Berg U, Asling-Monemi K, Selistre L, et al. Estimating glomerular filtration rate at the transition from pediatric to adult care. Kidney Int 2019;95: 1234–43.
7. Delanaye P, Vidal-Petiot E, Björk J, Ebert N, Eriksen BO, Dubourg L, 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 2022. https://doi.org/10.1093/ndt/gfac241.
8. Hsu C, Yang W, Parikh RV, Anderson AH, Chen TK, Cohen DL, et al. Race, genetic ancestry, and estimating kidney function in CKD. N Engl J Med 2021;385:1750–60.
9. Levey AS, Tighiouart H, Titan SM, Inker LA. Estimation of glomerular filtration rate with vs without including patient race. JAMA Intern Med 2020;180:793–5.
10. Delanaye P, Mariat C, Cavalier E, Glassock RJ, Gemenne F, Pottel H. The « race » correction in estimating glomerular filtration rate: an European point of view. Curr Opin Nephrol Hypertens 2021;30:525–30.
11. Eneanya ND, Boulware LE, Tsai J, Bruce MA, Ford CL, Harris C, et al. Health inequities and the inappropriate use of race in nephrology. Nat Rev Nephrol 2022;18:84–94.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. modification of diet in renal disease study group. Ann Intern Med 1999;130: 461–70.
13. Delanaye P, Pottel H, Glassock RJ. Americentrism in estimation of glomerular filtration rate equations. Kidney Int 2022;101:856–8.
14. Shi J, Lindo EG, Baird GS, Young B, Ryan M, Jefferson JA, et al. Calculating estimated glomerular filtration rate without the race correction factor: observations at a large academic medical system. Clin Chim Acta 2021;520:16–22.
15. Delanaye P, Mariat C, Maillard N, Krzesinski J-M, Cavalier E. Are the creatinine-based equations accurate to estimate glomerular filtration rate in african american populations? Clin J Am Soc Nephrol 2011;6:906–12.
16. Bukabau JB, Yayo E, Gnionsahé A, Monnet D, Pottel H, Cavalier E, et al. Performance of creatinine- or cystatin C–based equations to estimate glomerular filtration rate in sub-Saharan African populations. Kidney Int 2019;95:1181–9.
17. Flamant M, Vidal-Petiot E, Metzger M, Haymann J-P, Letavernier E, Delatour V, et al. Performance of GFR estimating equations in African Europeans: basis for a lower race-ethnicity factor than in African Americans. Am J Kidney Dis 2013;62:182–4.
18. van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. Clin Chem 2008;54:1197–202.
19. Rocha AD, Garcia S, Santos AB, Eduardo JCC, Mesquita CT, Lugon JR, et al. No race-ethnicity adjustment in CKD-EPI equations is required for estimating glomerular filtration rate in the Brazilian population. Internet J Nephrol 2020;2020:2141038.

20. Zanocco JA, Nishida SK, Passos MT, Pereira AR, Silva MS, Pereira AB, et al. Race adjustment for estimating glomerular filtration rate is not always necessary. Nephron Extra 2012;2: 293–302.
21. Eneanya ND, Yang W, Reese PP. Reconsidering the consequences of using race to estimate kidney function. JAMA 2019;322:113–4.
22. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task force on reassessing the inclusion of race in diagnosing kidney disease. J Am Soc Nephrol 2021;32:2994–3015.
23. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med 2021;385:1737–49.
24. Walther CP, Winkelmayer WC, Navaneethan SD. Black race coefficient in GFR estimation and diabetes medications in CKD: national estimates. J Am Soc Nephrol 2021;32:1319–21.
25. Walther CP, Winkelmayer WC, Navaneethan SD. Updated US prevalence estimates for chronic kidney disease stage and complications using the new race-free equation to estimate glomerular filtration rate. JAMA Netw Open 2022;5: e220460.
26. Diao JA, Powe NR, Manrai AK. Race-free equations for eGFR: comparing effects on CKD classification. J Am Soc Nephrol 2021; 32:1868–70.
27. Vestergaard SV, Heide-Jørgensen U, Birn H, Christiansen CF. Effect of the refitted race-free eGFR formula on the CKD prevalence and mortality in the Danish population. Clin J Am Soc Nephrol 2022;17:426–8.
28. Delanaye P, Masson I, Maillard N, Pottel H, Mariat C. The new 2021 CKD-EPI equation without race in an European cohort of renal transplanted patients. Transplantation 2022. https://doi.org/10.1097/TP.0000000000004234.
29. Fu EL, Coresh J, Grams ME, Clase CM, Elinder C-G, Paik Paik, et al. Removing race from the CKD-EPI equation and its impact on prognosis in a predominantly White European population. Nephrol Dial Transplant 2022. https://doi.org/10.1093/ndt/gfac197.
30. Gansevoort RT, Anders H-J, Cozzolino M, Filser D, Fouque D, Ortiz A, et al. What should European nephrology do with the new CKD-EPI equation? Nephrol Dial Transplant 2022. https://doi.org/10.1093/ndt/gfac254.
31. Grubb A, Nyman U, Björk J, Lindström V, Rippe B, Sterner B, et al. Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and the Counahan-Barratt prediction equations for children. Clin Chem 2005;51:1420–31.
32. Ottosson Frost C, Gille-Johnson P, Blomstrand E, St-Aubin V, Leion F, Grubb A. Cystatin C-based equations for estimating glomerular filtration rate do not require race or sex coefficients. Scand J Clin Lab Invest 2022;82:162–6.
33. Shafi T, Zhu X, Lirette ST, Rule AD, Mosley T, Butler KR, et al. Quantifying individual-level inaccuracy in glomerular filtration rate estimation. A cross-sectional study. Ann Intern Med 2022; 175:1073–82.
34. Luis-Lima S, Escamilla-Cabrera B, Negrín-Mena N, Estupinan S, Delgado-Mallen P, Cobo-Caso MA, et al. CKD staging with cystatin C or creatinine-based formulas: flipping the coin. Nephrol Dial Transplant 2019;34:287–94.
35. Porrini E, Ruggenenti P, Luis-Lima S, Carrara F, Jiménez A, de Vries APJ, et al. Estimated GFR: time for a critical appraisal. Nat Rev Nephrol 2019;15:177–90.
36. Miller WG. Perspective on new equations for estimating glomerular filtration rate. Clin Chem 2021;67:820–2.
37. Agarwal R, Delanaye P. Glomerular filtration rate: when to measure and in which patients? Nephrol Dial Transplant 2019;34: 2001–7.
38. Ebert N, Bevc S, Bökenkamp A, Gaillard F, Hornum M, Jager KJ, et al. Assessment of kidney function: clinical indications for measured GFR. Clin Kidney J 2021;14:1861–70.
39. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol. Clin Kidney J 2016;9:682–99.
40. Nyssen L, Delanaye P, Le Goff C, Peeters S, Cavalier E. A simple LC-MS method for the determination of iohexol and iothalamate in serum, using ioversol as an internal standard. Clin Chim Acta 2016;463:96–102.