Performance of the European Kidney Function Consortium (EKFC) creatinine-based equation in United States cohorts

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Estimating glomerular filtration rate (GFR) is important in daily practice to assess kidney function and adapting the best clinical care of patients with and without chronic kidney disease. The new creatinine-based European Kidney Function Consortium (EKFC) equation is used to estimate GFR. This equation was developed and validated mainly in European individuals and based on a rescaled creatinine, with the rescaling factor (Q-value) defined as the median normal value of serum creatinine in a given population. The validation was limited in Non-Black Americans and absent in Black Americans. Here, our cross-sectional analysis included 12,854 participants from nine studies encompassing large numbers of both non-Black and Black Americans with measured GFR by clearance of an exogenous marker (reference method), serum creatinine, age, sex, and self-reported race available. Two strategies were considered with population-specific Q-values in Black and non-Black men and women ($EKFC_{PS}$) or a race-free Q-value ($EKFC_{RF}$). In the whole population, only the $EKFC_{PS}$ equation showed no statistical median bias (0.14, 95% confidence interval [-0.07; 0.35] mL/min/1.73m^2), and the bias for the $EKFC_{RF}$ (0.74, [0.51; 0.94] mL/min/1.73m^2) was closer to zero than that for the Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) equation (1.22, [0.99; 1.47]) mL/min/1.73m^2]. The percentage of estimated GFR within 30% of measured GFR was similar for $CKD\text{-}EPI_{2021}$ (79.2% [78.5%; 79.9%]) and $EKFC_{RF}$ (80.1% [79.4%; 80.7%]), but improved for the $EKFC_{PS}$ equation (81.1% [80.5%; 81.8%]). Thus, our EKFC equations can be used to estimate GFR in the United States incorporating either self-reported race or unknown race at the patient's discretion per hospital registration records.

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Lay Summary

Estimating glomerular filtration rate with serum creatinine remains the most used method in clinical practice. Among different creatinine-based equations recently published, the European Kidney Function Consortium creatinine-based equation has been validated in Europe and Africa, but few data are available from the United States. In this cross-sectional analysis including 12,854 measured glomerular filtration rate and standardized serum creatinine values, we showed that the European Kidney Function Consortium equation was applicable in US populations, also without applying a race correction factor. The European Kidney Function Consortium equation can be a valid alternative to existing creatinine-based equations in the United States.

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Estimating glomerular filtration rate (GFR) remains of high importance in daily practice to assess kidney function and adapting at best clinical care of patients with and without chronic kidney disease.[1] Even if new biomarkers, such as cystatin C, are emerging, creatinine-based

equations remain the most used tools worldwide to estimate GFR.[2] Two major innovations have been launched in 2021 regarding such creatinine-based equations. First, a new version of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been developed that excludes race from the equation. By design, this race-free CKD-EPI$_{2021}$ equation underestimates GFR in Black persons and overestimates GFR in non-Black persons in US people.[3] This race-free equation is recommended for use in the United States by the American Society of Nephrology, the National Kidney Foundation, and the American Association for Clinical Chemistry.[4,5] Patients are effectively not given the option to have their race/ethnicity information used to obtain a more accurate GFR estimate. We developed an approach that empowers patients to decide if they want to self-report their race and, if so, to use that information to, on average, more accurately estimate GFR from their serum creatinine.

A new creatinine-based equation, called the European Kidney Function Consortium (EKFC) equation, has also been developed from a large data set of European participants.[6] This equation is based on rescaled creatinine, using a rescaling factor (Q value) that is the median value for serum creatinine in a normal population of any age, sex, or race. The EKFC equation performs equally well across the whole age and GFR spectrum and has been validated in White European, Black European, and Black African individuals.[7] Validation was limited in non-Black US individuals and absent in Black US individuals.[6,8,9] In the present analysis, we applied US-based Q values to compare this EKFC equation in different US cohorts with a large number of non-Black and Black US participants.

METHODS

Participants

We used data from the following cohorts available from the National Institute of Diabetes and Digestive and Kidney Diseases: Assessing Long Term Outcomes in Living Kidney Donors (ALTOLD),[10] Chronic Renal Insufficiency Cohort (CRIC),[11,12] Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP),[13] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC),[14,15] Preventing Early Renal Loss in Diabetes (PERL),[16] African American Study of Kidney Disease and Hypertension (AASK),[17] and Modified Diet in Renal Disease (MDRD) study.[18] GFR was measured by urinary clearance of iothalamate in CRIC, CRISP, DCCT/EDIC, AASK, and MDRD studies. GFR was measured by iohexol plasma clearance in ALTOLD and PERL studies. Serum creatinine measurements were recalibrated as described in previous publications to be considered as isotope dilution mass spectrometry traceable.[3,11,13,19,20] Serum creatinine was directly measured by an isotope dilution mass spectrometry–traceable enzymatic assay in PERL (Roche Diagnostics).[21] Data are unavailable for ALTOLD regarding the way (standardized or not) serum creatinine has been measured.

Two other cohorts were available from Mayo Clinic (ADR). The first cohort combined data from the Genetic Epidemiology Network of Arteriopathy (GENOA) and Epidemiology of Coronary Artery Calcification (ECAC) studies.[22] The second cohort is based on data from individuals referred to Mayo Clinic, Rochester, Minnesota, to have measured GFR.[23] Only participants having measured GFR and serum creatinine on the same days were considered. In these 2 cohorts, serum creatinine was assayed using an isotope dilution mass spectrometry–traceable enzymatic assay (Roche Diagnostics) and GFR was measured by urinary clearance of iothalamate.[22,23] For the whole database, only 1 GFR result per participant and only adults (≥18 years) were considered. Race was self-reported by participants in most of these studies as previously reported.[3]

Data were anonymized from the source cohorts for the analysis performed at Lund University, Sweden. All procedures involving participants and data were in agreement with the ethical principles for medical research involving human participants established in the World Medical Association Declaration of Helsinki. Written consent had been obtained from the participants of AASK, MDRD, ALTOLD, CRIC, CRISP, DCCT/EDIC, GENOA/ECAC and PERL studies. A waiver of consent was obtained from the Mayo Clinic Institutional Review Board to study patients from the Mayo Clinic Renal Studies Unit database because of the retrospective nature of these clinical data.

Covariates

Sex- and age-specific median creatinine values (Q values) in healthy adults from different populations were previously established (Supplementary Table S1).[6] To establish Q values in White Europeans, we considered a large amount of data from different laboratories in Sweden and Belgium.[24] For US Q values, we used the same type of results published by Shi *et al.*,[25] also based on laboratory data. These authors collected individual creatinine from patients evaluated at the University of Washington Medicine health care system from January 2018 to August 2019 (creatinine measured using the Jaffe method; isotope dilution mass spectrometry–traceable assay, Beckman Coulter AU system). Q values were 1.00 mg/dl (n = 10,865) and 0.73 mg/dl (n = 9849) in Black men and women, respectively. Among non-Black (non-Asian) populations, Q values were 0.93 mg/dl (n = 97,255) and 0.73 mg/dl (n = 98,720) in men and women, respectively. Another source of Q values can also be obtained from the National Health and Nutrition Examination Survey, and the results were similar (Q = 1.03 and 0.72 mg/dl for Black men and Black women, 0.94 and 0.70 mg/dl for non-Black men and non-Black women, and 0.99 and 0.71 mg/dl for the race-free Q values; Supplementary Table S1).

We have previously shown that the median creatinine concentration in a healthy adult population, that is, the Q value, could be different in Black and White European populations (whereas the difference between Black Africans and White Europeans is actually low; Supplementary Table S1).[2] There is also evidence for these differences in serum creatinine between White and Black US populations that is independent of GFR.[12] However, there is no evidence for a difference in GFR between White and Black healthy adults.[26] Therefore, we considered 2 strategies: (i) when we accept that there are differences in creatinine generation according to the population, we may consider population-specific Q values (EKFC$_{PS}$, PS = population specific), or (ii) when we omit the difference in creatinine generation, we might use a Q value that is totally race free (EKFC$_{RF}$, RF = race free). In the latter case, we were accepting potential statistical bias in performance when we used a Q value that is the mean of Q values obtained in Black and non-Black populations, that is, 0.97 mg/dl in men and 0.73 mg/dl in women. In the present analysis, both strategies were tested, knowing that differences will be relevant only in male cohorts (as the Q value in Black and non-Black women is the same).[25] The EKFC equations using both

Table 1 | Description of the cohorts

Cohort	Sample size	Age, yr	Measured GFR, ml/min per 1.73 m^2	% of women	% of Black participants	% of individuals with urinary clearance
All	*12,854*	*56.0 [42.9; 65.0]*	*57 [37; 83]*	*44.3*	*21.7*	*93.2*
AASK	1844	54.5 [46.0; 62.0]	57 [40; 74]	35.9	100	100
ALTOLD	381	43.3 [33.5; 52.6]	97 [89; 107]	65.1	1.8	0
CRIC	1194	59.0 [48.2; 65.9]	48 [35; 63]	44.4	44.7	100
CRISP	217	34.0 [27.0; 40.0]	93 [78; 112]	59.0	11.1	100
DCCT/EDIC	809	31.0 [27.0; 36.0]	119 [107; 132]	47.8	1.4	100
GENOA/ECAC	1093	66.1 [59.1; 71.2]	80 [66; 93]	56.6	0	100
Mayo Clinic	5069	59.0 [48.0; 69.0]	50 [32; 72]	44.6	2.0	100
MDRD study	1756	51.0 [40.0; 61.0]	36 [24; 53]	39.5	12.4	100
PERL	491	52.0 [44.0; 59.0]	70 [56; 82]	33.6	10.8	0

AASK, African American Study of Kidney Disease and Hypertension; ALTOLD, Assessing Long Term Outcomes in Living Kidney Donors; CRIC, Chronic Renal Insufficiency Cohort; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; ECAC, Epidemiology of Coronary Artery Calcification; GENOA, Genetic Epidemiology Network of Arteriopathy; GFR, glomerular filtration rate; MDRD, Modified Diet in Renal Disease; PERL, Preventing Early Renal Loss in Diabetes.
Results are expressed as percentage or median [quartile 1; quartile 3].

strategies were compared with the CKD-EPI$_{2021}$ equation (see description of equations in Supplementary Table S2).

Statistical analyses

All analyses and calculations were performed using SAS 9.4 (SAS Institute Inc.). Data were presented as mean ± SD when the distribution was normal and as median with interquartile range (quartile 1; quartile 3) when not. Normality was assessed using the Kolmogorov-Smirnov test.

The performance of GFR equations was compared with usual metrics: median bias (i.e., estimated GFR – measured GFR) with 95% confidence interval, imprecision (interquartile range), as well as P30 and P20 accuracies (percentage of estimated GFR values within ±30% or 20% of measured GFR) with 95% confidence intervals. The target for statistical bias was zero, but an absolute statistical bias of at most 5 ml/min per 1.73 m^2 might be considered reasonable. Imprecision should be as low as possible.[27] The target for P30 was to reach >90%, yet P30 > 75% has been considered as "sufficient for good clinical decision making" by the Kidney Disease Outcomes Quality Initiative.[28] A result was considered as better than another one when 95% confidence intervals were not overlapping. Median statistical bias versus age and GFR was graphically presented using median quantile regression with fourth-degree polynomials. Likewise, P30 accuracy was graphically presented versus age and GFR using cubic splines with 3 free knots and using third-degree polynomials. Analyses were performed in the whole population and in the 4 main groups: Black men, Black women, non-Black men and non-Black women.

Stratified analysis in different GFR subgroups was performed according to measured GFR ranges (<15, [15–30[, [30–45[, [45–60[, ≥60 ml/min per 1.73 m^2).[1,29] We also performed analyses stratified by age ([18–40[, [40–65[, and ≥ 65 years). These subanalyses were performed in Black and non-Black populations by sex. Finally, a subanalysis was performed per cohort.

Because the characteristics of Black people were different in the various cohorts, notably in terms of GFR levels, we separately matched Black with non-Black using the following matching criteria: age (±3 years), sex (equal), measured GFR (±3 ml/min per 1.73 m^2), and body mass index (±2.5 kg/m^2). We wanted to investigate whether the performance of the EKFC equations was different in these matching cohorts. For the matched analyses, we considered individuals with body mass index available (n = 4198 non-Black and n = 831 Black). We followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement for reporting of observational cross-sectional studies.

RESULTS

Characteristics of participants

Table 1 summarizes the characteristics of the cohorts and Table 2 the characteristics of the 4 main populations (Black men, Black women, non-Black men, and non-Black women). Table 3 presents the performance of the CKD-EPI$_{2021}$ and EKFC equations in the whole population and in the 4 main groups.

Validation in the whole population

In the whole population, only the EKFC$_{PS}$ equation was unbiased, and also the statistical bias for the EKFC$_{RF}$ equation was closer to zero than that for the CKD-EPI$_{2021}$ equation. P20 and P30 were similar (i.e., 95% confidence intervals are overlapping) for CKD-EPI$_{2021}$ and EKFC$_{RF}$, whereas P30 and P20 for EKFC$_{PS}$ were slightly better than those for CKD-EPI$_{2021}$.

Validation in the 4 main populations

In the 4 main groups, the statistical bias for both EKFC$_{PS}$ and EKFC$_{RF}$ was closer to zero than that for CKD-EPI$_{2021}$ in non-Black women and Black men. The statistical bias was also better for EKFC$_{PS}$ than for CKD-EPI$_{2021}$ in non-Black men. Accuracies of the 3 equations were similar in the 4 groups (except P30 for EKFC$_{PS}$, which was better than that for CKD-EPI$_{2021}$ in non-Black men).

The statistical bias and P30 for the 3 equations according to age are shown in Figure 1a and b, respectively, for the whole population and in Supplementary Figures S1 to S4 for the 4 main groups (because women have the same Q values, EKFC$_{RF}$ and EKFC$_{PS}$ are identical in women and merged as EKFC). Results according to age are also presented in Supplementary Table S3 ([18–40], [40–65], and ≥65 years). From Table 3 and Supplementary Tables S3 and S4, it can be seen that performance of the 3 equations was similar in Black and non-Black women (only statistical bias and P30 for non-Black

Table 2 | Clinical and biological characteristics of the main groups

Characteristic	Whole cohort (N = 12,854)	Non-Black men (n = 5459)	Non-Black women (n = 4605)	Black men (n = 1703)	Black women (n = 1087)
Age, yr	56.0 [42.9; 65.0]	57.0 [42.0; 66.0]	55.0 [41.0; 65.0]	54.0 [45.0; 62.0]	55.0 [45.0; 63.0]
Measured GFR, ml/min per 1.73 m^2	57 [37; 83]	57 [36; 84]	61 [37; 89]	57 [40; 74]	49 [34; 67]
% of urinary clearance	93.2	92.3	91.6	97.9	97.8
Serum creatinine, mg/dl	1.30 [0.93; 1.80]	1.40 [1.00; 1.90]	1.00 [0.76; 1.50]	1.60 [1.26; 2.07]	1.35 [1.06; 1.89]
Estimated GFR – CKD-EPI$_{2021}$, ml/min per 1.73 m^2	59 [39; 86]	61 [40; 90]	66 [42; 95]	52 [37; 66]	46 [31; 62]
Estimated GFR – EKFC$_{RF}$, ml/min per 1.73 m^2	58 [39; 82]	61 [41; 86]	63 [41; 88]	53 [38; 67]	45 [32; 60]
Estimated GFR – EKFC$_{PS}$, ml/min per 1.73 m^2	58 [39; 82]	58 [39; 84]	63 [41; 88]	55 [40; 70]	45 [32; 60]

CKD-EPI$_{2021}$, race-free Chronic Kidney Disease Epidemiology Collaboration; EKFC$_{PS}$, European Kidney Function Consortium with population-specific Q values; EKFC$_{RF}$, European Kidney Function Consortium with race-free Q values; GFR, glomerular filtration rate.
Results are expressed as percentage or median [quartile 1; quartile 3].

women was better for both EKFC equations than for CKD-EPI$_{2021}$). In non-Black men, statistical bias was better for EKFC$_{PS}$ in the age groups (where the statistical bias for EKFC$_{RF}$ was similar, larger, or lower than that for CKD-EPI$_{2021}$ in patients aged between 18 and 40, between 40 and 65, and ≥65 years, respectively). In Black men, performance was similar but a better statistical bias for both EKFC equations than that for CKD-EPI$_{2021}$ was observed between 40 and 65 years. From Figure 1 and Supplementary Figures S1 to S4, it can be viewed that both statistical bias and P30 for the 2 EKFC equations were more consistent over the complete age range whereas the CKD-EPI$_{2021}$ equation overestimates GFR in young people (between 18 and 30 years). This observation was especially relevant in non-Black populations.

Table 3 | Performance of the CKD-EPI$_{2021}$ and EKFC equations to estimate glomerular filtration rate

Populations	CKD-EPI$_{2021}$	EKFC$_{RF}$	EKFC$_{PS}$
Whole population (N = 12,854)			
Median bias (95% CI)	1.22 (0.99; 1.47)	0.74 (0.51; 0.94)	0.14 (−0.07; 0.35)
IQR (Q1; Q3)	16.0 [−6.6; 9.4]	15.7 [−7.6; 8.0]	15.4 [−8.1; 7.3]
P30 (95% CI)	79.2 (78.5; 79.9)	80.1 (79.4; 80.7)	81.1 (80.5; 81.8)
P20 (95% CI)	61.6 (60.7; 62.4)	62.4 (61.6; 63.3)	63.7 (62.9; 64.5)
Non-Black population (n = 10,064)			
Median bias (95% CI)	2.78 (2.55; 3.04)	1.93 (1.67; 2.18)	0.85 (0.62; 1.09)
IQR (Q1; Q3)	16.1 [−4.8; 11.3]	15.6 [−6.4; 9.3]	15.6 [−7.6; 8.0]
P30 (95% CI)	78.3 (77.5; 79.1)	79.0 (78.2; 79.8)	80.4 (79.6; 81.2)
P20 (95% CI)	61.4 (60.5; 62.4)	61.9 (61.0; 62.9)	63.3 (62.4; 64.3)
Black population (n = 2790)			
Median bias (95% CI)	−4.01 (−4.44; −3.56)	−3.12 (−3.70; −2.62)	−2.22 (−2.72; −1.83)
IQR (Q1; Q3)	13.9 [−11.6; 2.3]	14.3 [−11.1; 3.2]	14.1 [−10.0; 4.2]
P30 (95% CI)	82.5 (81.1; 83.9)	83.8 (82.4; 85.2)	83.7 (82.4; 85.1)
P20 (95% CI)	62.1 (60.3; 63.9)	64.3 (62.5; 66.0)	64.9 (63.1; 66.7)
Non-Black women (n = 4605)			
Median bias (95% CI)	2.54 (2.20; 2.92)	0.45 (0.08; 0.86)	0.45 (0.08; 0.86)
IQR (Q1; Q3)	16.3 [−5.2; 11.1]	15.7 [−7.9; 7.8]	15.7 [−7.9; 7.8]
P30 (95% CI)	78.9 (77.7; 80.1)	80.9 (79.8; 82.0)	80.9 (79.8; 82.0)
P20 (95% CI)	62.0 (60.6; 63.4)	63.7 (62.3; 65.1)	63.7 (62.3; 65.1)
Non-Black men (n = 5459)			
Median bias (95% CI)	3.01 (2.66; 3.43)	3.09 (2.76; 3.41)	1.14 (0.85; 1.43)
IQR (Q1; Q3)	15.9 [−4.5; 11.3]	15.7 [−5.0; 10.7]	15.6 [−7.3; 8.3]
P30 (95% CI)	77.7 (76.6; 78.8)	77.4 (76.3; 78.5)	80.0 (79.0; 81.1)
P20 (95% CI)	60.9 (59.7; 62.2)	60.4 (59.1; 61.7)	63.1 (61.8; 64.4)
Black women (n = 1087)			
Median bias (95% CI)	−2.98 (−3.75; −2.30)	−3.39 (−4.12; −2.67)	−3.39 (−4.12; −2.67)
IQR (Q1; Q3)	13.6 [−10.7; 2.9]	14.0 [−11.6; 2.4]	14.0 [−11.6; 2.4]
P30 (95% CI)	79.8 (77.4; 82.2)	80.3 (78.0; 82.7)	80.3 (78.0; 82.7)
P20 (95% CI)	60.5 (57.6; 63.4)	60.8 (57.9; 63.7)	60.8 (57.9; 63.7)
Black men (n = 1703)			
Median bias (95% CI)	−4.64 (−5.15; −4.10)	−2.91 (−3.69; −2.30)	−1.35 (−1.97; −0.75)
IQR (Q1; Q3)	14.4 [−12.3; 2.1]	14.4 [−10.7; 3.7]	14.2 [−8.8; 5.4]
P30 (95% CI)	84.3 (82.5; 86.0)	86.0 (84.4; 87.7)	85.9 (84.3; 87.6)
P20 (95% CI)	63.1 (60.8; 65.4)	66.5 (64.2; 68.7)	67.5 (65.2; 69.7)

CKD-EPI$_{2021}$, race-free Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; EKFC$_{PS}$, European Kidney Function Consortium with population-specific Q values; EKFC$_{RF}$, European Kidney Function Consortium with race-free Q values; IQR, interquartile range; P20, accuracy within 20%; P30, accuracy within 30%; Q1, quartile 1; Q3, quartile 3.
Bias and IQR are expressed in milliliters per minute per 1.73 meter square. P30 and P20 are expressed in percentage.

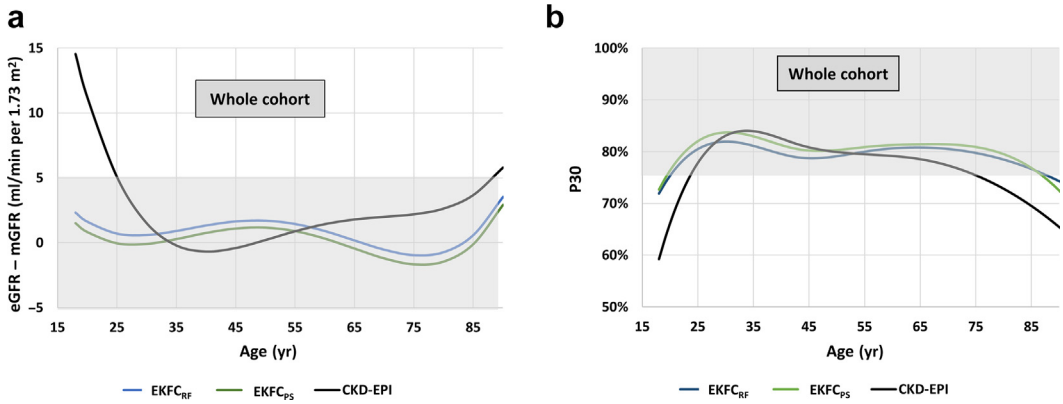

Figure 1 | (a) Statistical bias and (b) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI$_{2021}$), European Kidney Function Consortium with race-free *Q* values (EKFC$_{RF}$), and European Kidney Function with population-specific *Q* values (EKFC$_{PS}$) equations in the whole population (*N* = 12,854) according to age. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

The statistical bias and P30 for both equations according to the patients' measured GFR are shown in Figure 2a and b, respectively, for the whole population and in Supplementary Figures S5 to S8 for the 4 main groups. Results according to measured GFR are also presented in Supplementary Table S4 (<60 and ≥60 ml/min per 1.73 m^2). Regarding GFR, performance was similar in non-Black and Black women (only in non-Black women with GFR ≥ 60 ml/min per 1.73 m^2, the statistical bias was better for CKD-EPI$_{2021}$ whereas P30 was better for the 2 EKFC equations). In non-Black men with GFR < 60 ml/min per 1.73 m^2, the statistical bias and P20 were better for CKD-EPI$_{2021}$ than for EKFC$_{RF}$ but the statistical bias was lower than for EKFC$_{PS}$. If GFR is ≥60 ml/min per 1.73 m^2, the statistical bias for both EKFC equations is further from zero than that for CKD-EPI$_{2021}$. In Black men, performance was similar, expect for a better statistical bias for EKFC$_{PS}$ when GFR is ≥60 ml/min per 1.73 m^2.

Validation per cohort

The performance of the 3 equations per cohort is displayed in Supplementary Table S5. The performance of the 3 equations was similar in the CRIC, CRISP, and PERL cohorts. The statistical bias for both EKFC equations was better than that for CKD-EPI$_{2021}$ in the ALTOLD, GENOA/ECAC, and Mayo Clinic cohorts. The statistical bias for the EKFC$_{PS}$ equation was better than that for CKD-EPI$_{2021}$ in the AASK cohort. The statistical bias for the CKD-EPI$_{2021}$ equation was better than that for EKFC$_{RF}$ in the MDRD study cohort and better than those for the 2 EKFC equations in the DCCT/EDIC cohort. Regarding P30, the results are similar in most cohorts, except for a better P30 for CKD-EPI$_{2021}$ than for EKFC$_{RF}$, for both EKFC equations than for CKD-EPI$_{2021}$, and for EKFC$_{PS}$ than for CKD-EPI$_{2021}$ in MDRD, GENOA/ECAC, and Mayo Clinic cohorts, respectively.

Matched analysis

We matched individuals from the Black population (n = 831) with individuals from the non-Black population (n = 1198). We could identify matching partners for 667 Black participants (80.2%). Individuals without matches were omitted in further analyses. The results of matching according to sex are presented in Supplementary Table S6. As expected, mean age,

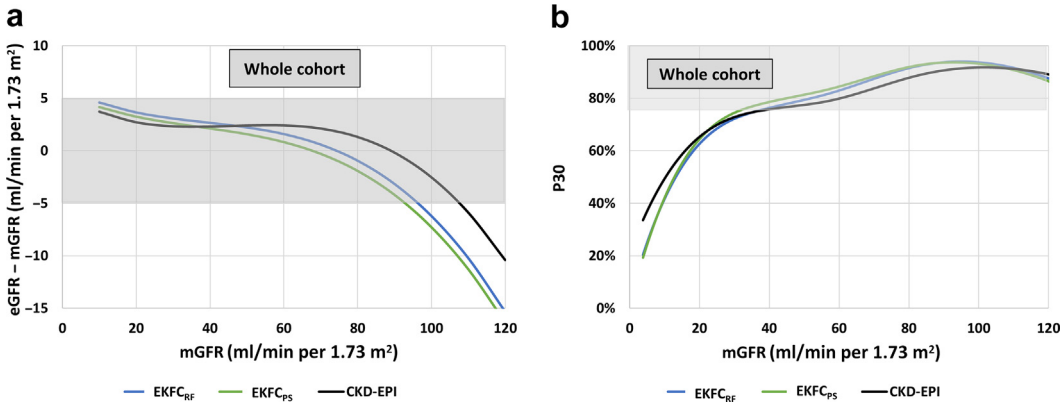

Figure 2 | (a) Statistical bias and (b) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI$_{2021}$), European Kidney Function Consortium with race-free *Q* values (EKFC$_{RF}$), and European Kidney Function with population-specific *Q* values (EKFC$_{PS}$) equations in the whole population (*N* = 12,854) according to measured glomerular filtration rate (mGFR). eGFR, estimated glomerular filtration rate.

sex, measured GFR, and body mass index were similar but the median serum creatinine concentrations were different. From Supplementary Table S7, it can be seen that both the $EKFC_{PS}$ and $EKFC_{RF}$ equations have the same absolute bias and the same P30 values in Black and non-Black populations.

DISCUSSION

In the present analysis of large US cohorts, we showed that the new creatinine-based EKFC equation is valid with a similar performance to the CKD-EPI_{2021} equation. The EKFC equation has the ambition to be applicable in different populations as long as a *Q* value, defined as the median "normal" serum creatinine, in the given population is available.[9,30,31] Then, the *Q* value is used to rescale serum creatinine and can be integrated into the EKFC equation, which has been developed to be accurate in the whole age range.[6] The EKFC equation can also be used with other biomarkers, such as cystatin C (with *Q* value specifically obtained for cystatin C).[2] Up to now, the equation has been validated in Europe and Africa.[6,9] Preliminary results in Asia are promising,[32–35] but data were limited in the United States.[2,6,8] In the present analysis, we demonstrated that the EKFC equation is as accurate as, and in some subanalyses more accurate than, the creatinine-based CKD-EPI_{2021} equation. Recently, the race variable, frequently used in creatinine-based equations before 2021, has been considered as discriminatory,[4] leading the CKD-EPI consortium to propose the race-free CKD-EPI_{2021} equation.[3] The EKFC equation does not include the variable race because all differences between populations potentially influencing serum creatinine concentration are integrated into *Q* values. For US *Q* values, we considered the values published in the literature obtained from a large laboratory database,[25] as we did for European *Q* values.[24,30] Interestingly, differences in *Q* values between Black and non-Black populations are relevant only for men but not for women. The similar *Q* value in Black and non-Black women is a strong argument to assert that the *Q* value is more dependent on populations than on race. We do not advocate race-based reporting of the GFR estimation result with the EKFC equations. Rather, we would defer to the patient to decide how they self-identify with respect to race: non-Black, Black, or unknown/not reported. For patients who identify themselves as Black or non-Black populations, $EKFC_{PS}$ can be used with specific *Q* values.[2,25] For patients who choose not to identify themselves as a particular race or as unknown, or for mixed populations, the *Q* value is the mean of the *Q* values obtained in Black and non-Black populations, making it race free. Self-reporting of race in hospital registration records can be used to determine the *Q* value to use without race-based reporting of estimated GFR results. Although there is a slightly more accurate GFR estimation with population-based *Q* values, the loss of performance (only in men, as *Q* values are not different by race in women) is quite modest.

More importantly, the EKFC equations have globally the same performance as the CKD-EPI_{2021} equation, with statistical bias being even better for the EKFC equations in non-Black women, non-Black men, and Black men. The performance of the EKFC equations is also more consistent throughout the whole age range, especially in non-Black populations (with a lower statistical bias in young populations). The better performance of the EKFC equation in young Black populations is less obvious, but it must be reminded that the better performance of the EKFC equation in young populations is especially important in individuals with GFR $>$ 60 ml/min per 1.73 m^2. Very few healthy young Black individuals were available in the present cohorts. Also, the analysis per cohort demonstrates that the EKFC equation is performing at least as good as (and sometimes better than) the present CKD-EPI_{2021} equation. The last point is remarkable. Indeed, an equation is always performing better in the cohorts that have been used for its development, and it must be reminded that AASK, MDRD, DCCT/EDIC, and CRIC were used in the development data set and PERL and ALTOLD in the validation data set of the CKD-EPI_{2021} equation.[3] The fact that the EKFC equations are performing as good as (and better than for some cohorts) CKD-EPI_{2021} in these cohorts (except in the MDRD study cohort) was not expected. Moreover, CKD-EPI_{2021} has been developed with iothalamate urinary clearances as a reference method to measure GFR, although the EKFC equation has been mostly developed with GFR measured by iohexol plasma clearances.[3,6] This discrepancy in measuring GFR methods could theoretically disadvantage the performance of the EKFC equation (but eventually it did not). The fact that the EKFC equations are still performing similarly to CKD-EPI_{2021} demonstrates its consistent accuracy.

The strength of our study is the large sample size, which was reached by the inclusion of large cohorts, including both Black and non-Black populations. Our analysis also had limitations. First, the data set did not include children and adolescents. In the seminal article, a major strength of the EKFC equation was the continuity at the transition between adolescent and young adulthood.[6,36] Although there is no reason that this would be different in US populations, this continuity still needs to be demonstrated in US cohorts with children, adolescents, and young adults. Second, our data set is not representative of the general US population. The main limitation is the very few numbers of Black individuals with GFR $>$ 60 ml/min per 1.73 m^2. The fact that the vast majority of Black people included in the present analysis are patients with chronic kidney disease is a limitation shared in the development of the CKD-EPI equations.[37,38] Because the characteristics of Black participants were different, a matched analysis was performed between Black and non-Black populations, which suggested that the performance of the 2 EKFC equations was similar in the 2 populations. Third, US *Q* values were established with laboratory data from the University of Washington Medicine health care system.[25] It can be argued that these data could not be representative of the United States. However, *Q* values can also be obtained from the National Health and Nutrition Examination Survey (Supplementary Table S1).[31,38,39] The performance of the

EKFC equations with the National Health and Nutrition Examination Survey *Q* values is displayed in Supplementary Table S8 and is similar to that obtained with Washington laboratory data. Fourth, cystatin C concentration was not available for analyses in our largest cohort (Mayo Clinic). Still, our main aim was to propose and compare a race-free creatinine-based EKFC equation as it is already known that cystatin C concentration is not influenced by race. Lastly, we must emphasize the absence of an Asian US cohort in our analyses with measured GFR. We can however note that a population-specific *Q* value for Asian US individuals is available from laboratory data from the University of Washington Medicine health care system (0.93 and 0.67 mg/dl for men and women, respectively).[25]

In conclusion, the creatinine-based EKFC equations can be used in the United States with population-specific *Q* values. The population, and therefore *Q* values, can be defined differently (like we did in the present analysis with $EKFC_{RF}$ and $EKFC_{PS}$). We showed a similar performance of the EKFC and $CKD\text{-}EPI_{2021}$ equations in US cohorts. The performance of $EKFC_{PS}$ is even slightly better than that of the $CKD\text{-}EPI_{2021}$ equation. This result combined with prior observations, showing that the EKFC equation is performing better in Europe, Asia, and Africa than the $CKD\text{-}EPI_{2021}$ equation,[6,9,32–34] demonstrates that the EKFC equation with population-specific *Q* values is applicable worldwide. All equations, however, remain a GFR estimation. If they are useful at the population level, their accuracy might be insufficient for clinical decision at the individual level, and a GFR measurement might still be necessary in some situations.[40,41]

DISCLOSURE

The results presented in this paper have not been published previously in whole or part. PD and EC serve as consultants for Nephrolyx. ES receives honoraria from the National Kidney Foundation and serves as a consultant for AstraZeneca. All the other authors declared no competing interests.

DATA STATEMENT

The short protocol is available to interested readers by contacting Pierre Delanaye at pdelanaye@chuliege.be.

The SAS code is available to interested readers by contacting Hans Pottel at hans.pottel@kuleuven.be.

The data from the Assessing Long Term Outcomes in Living Kidney Donors, Chronic Renal Insufficiency Cohort, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications, Preventing Early Renal Loss in Diabetes, African American Study of Kidney Disease and Hypertension, and Modified Diet in Renal Disease studies reported here are available on request in the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository. The data from the Mayo Clinic and Genetic Epidemiology Network of Arteriopathy/Epidemiology of Coronary Artery Calcification studies are not publicly available because of the confidential nature of patient information obtained for clinical care. Legal and ethical restrictions prevent public sharing of the data set. Data can be made available for collaborations on request to interested researchers but would generally require a new ethical permission and the permission of each of the data owners.

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The Assessing Long Term Outcomes in Living Kidney Donors, Chronic Renal Insufficiency Cohort, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications, Preventing Early Renal Loss in Diabetes, African American Study of Kidney Disease and Hypertension, and Modified Diet in Renal Disease studies were performed by respective investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The data from these studies reported here were supplied by the NIDDK Central Repository. This manuscript was not prepared in collaboration with the investigators of the different studies and does not necessarily reflect the opinions or views of these studies, the NIDDK Central Repository, or the NIDDK.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. *Q* values determined in different populations.

Supplementary Table S2. Overview of estimating glomerular filtration rate (GFR) equations.

Supplementary Table S3. Performance of the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) and European Kidney Function Consortium (EKFC) equations to estimate glomerular filtration rate according to age.

Supplementary Table S4. Performance of the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) and European Kidney Function Consortium (EKFC) equations to estimate glomerular filtration rate (GFR) according to measured GFR.

Supplementary Table S5. Performance of the equations in different cohorts.

Supplementary Table S6. Patient characteristics of the matched cohorts (Black and non-Black individuals).

Supplementary Table S7. Results of the European Kidney Function Consortium with population-specific *Q* values ($EFKC_{PS}$) and European Kidney Function Consortium with race-free *Q* values ($EKFC_{RF}$) equations in the matched cohorts.

Supplementary Table S8. Performance of the European Kidney Function Consortium (EKFC) equations to estimate glomerular filtration rate with *Q* values obtained from the Washington Medicine health care system (WMS) or National Health and Nutrition Examination Survey (NHANES).

Supplementary Figure S1. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) and European Kidney Function Consortium (EKFC) equations in non-Black women ($n = 4605$) according to age.

Supplementary Figure S2. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$), European Kidney Function Consortium with race-free *Q* values ($EKFC_{RF}$), and European Kidney Function with

population-specific Q values ($EKFC_{PS}$) equations in non-Black men ($n = 5459$) according to age.

Supplementary Figure S3. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) and European Kidney Function Consortium (EKFC) equations in Black women ($n = 1087$) according to age.

Supplementary Figure S4. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$), European Kidney Function Consortium with race-free Q values ($EKFC_{RF}$), and European Kidney Function with population-specific Q values ($EKFC_{PS}$) equations in Black men ($n = 1703$) according to age.

Supplementary Figure S5. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) and European Kidney Function Consortium (EKFC) equations in non-Black women ($n = 4605$) according to measured glomerular filtration rate (GFR).

Supplementary Figure S6. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$), European Kidney Function Consortium with race-free Q values ($EKFC_{RF}$), and European Kidney Function with population-specific Q values ($EKFC_{PS}$) equations in non-Black men ($n = 5459$) according to measured glomerular filtration rate (GFR).

Supplementary Figure S7. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$) and European Kidney Function Consortium (EKFC) equations in Black women ($n = 1087$) according to measured glomerular filtration rate (GFR).

Supplementary Figure S8. (**A**) Bias and (**B**) accuracy within 30% (P30) for the race-free Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{2021}$), European Kidney Function Consortium with race-free Q values ($EKFC_{RF}$), and European Kidney Function with population-specific Q values ($EKFC_{PS}$) equations in Black men ($n = 1703$) according to measured glomerular filtration rate (GFR).

Supplementary References.

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