ORIGINAL ARTICLE

Cystatin C–Based Equation to Estimate GFR without the Inclusion of Race and Sex

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ABSTRACT

BACKGROUND

The accuracy of estimation of kidney function with the use of routine metabolic tests, such as measurement of the serum creatinine level, has been controversial. The European Kidney Function Consortium (EKFC) developed a creatinine-based equation (EKFC eGFRcr) to estimate the glomerular filtration rate (GFR) with a rescaled serum creatinine level (i.e., the serum creatinine level is divided by the median serum creatinine level among healthy persons to control for variation related to differences in age, sex, or race). Whether a cystatin C–based EKFC equation would increase the accuracy of estimated GFR is unknown.

METHODS

We used data from patients in Sweden to estimate the rescaling factor for the cystatin C level in adults. We then replaced rescaled serum creatinine in the EKFC eGFRcr equation with rescaled cystatin C, and we validated the resulting EKFC eGFRcys equation in cohorts of White patients and Black patients in Europe, the United States, and Africa, according to measured GFR, levels of serum creatinine and cystatin C, age, and sex.

RESULTS

On the basis of data from 227,643 patients in Sweden, the rescaling factor for cystatin C was estimated at 0.83 for men and women younger than 50 years of age and $0.83+0.005\times(\text{age}-50)$ for those 50 years of age or older. The EKFC eGFRcys equation was unbiased, had accuracy that was similar to that of the EKFC eGFRcr equation in both White patients and Black patients (11,231 patients from Europe, 1093 from the United States, and 508 from Africa), and was more accurate than the Chronic Kidney Disease Epidemiology Collaboration eGFRcys equation recommended by Kidney Disease: Improving Global Outcomes. The arithmetic mean of EKFC eGFRcr and EKFC eGFRcys further improved the accuracy of estimated GFR over estimates from either biomarker equation alone.

CONCLUSIONS

The EKFC eGFRcys equation had the same mathematical form as the EKFC eGFRcr equation, but it had a scaling factor for cystatin C that did not differ according to race or sex. In cohorts from Europe, the United States, and Africa, this equation improved the accuracy of GFR assessment over that of commonly used equations. (Funded by the Swedish Research Council.)

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An illustrated glossary is available at NEJM.org

The glomerular filtration rate (GFR) is used to diagnose chronic kidney disease (CKD) (defined as a GFR <60 ml per minute per 1.73 m^2 of body-surface area). If CKD is present, the GFR is used to determine whether the disease is severe enough (GFR <20 ml per minute per 1.73 m^2) to consider kidney transplantation (i.e., addition to a waiting list for deceased-donor transplantation or pursuit of living-donor transplantation) or dialysis (e.g., placement of an arteriovenous fistula to mature for eventual long-term hemodialysis). The GFR is also widely used to adjust the dose of numerous medications that are cleared primarily by the kidneys. Thus, an accurate estimated GFR is considered to be of paramount importance in the evaluation and management of kidney health in patients.[1]

With the current widespread and frequent use of estimated GFR, it is impractical to directly measure GFR with an expensive, labor-intensive, standard method involving an exogenous marker (e.g., ^{125}I-iothalamate or iohexol). Instead, estimated GFR is commonly determined with equations that are based on simultaneous measurement of serum creatinine and cystatin C levels. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for estimating GFR in adults — the creatinine-based CKD-EPI eGFRcr equation and the cystatin C–based CKD-EPI eGFRcys equation.[2,3] In 2021, the CKD-EPI research group developed a new CKD-EPI eGFRcr equation without the inclusion of race, but this equation still required a sex variable to account for differences between men and women.[4]

The European Kidney Function Consortium (EKFC) developed the EKFC eGFRcr equation, which is an alternative approach to estimation of GFR with serum creatinine.[5] This approach adjusts (or rescales) serum creatinine values such that the average healthy person — regardless of age, sex, or race — has a rescaled serum creatinine level of 1. This adjustment is accomplished by determining a rescaling "Q value" factor that is based on the median serum creatinine level in healthy populations across the age spectrum (including both children and adults), sex, and race.[5] After the serum creatinine level is divided by the derived rescaling factor, the patient's rescaled serum creatinine level represents the proportional increase in the serum creatinine level (if >1) relative to the average level in healthy persons of the same age, sex, and race. However, determination of accurate rescaling factors for serum creatinine across the diverse spectrum of human populations presents several challenges.[6]

Cystatin C, another biomarker for estimating the GFR, has less non-GFR variation related to age, sex, and race than serum creatinine.[7] We proposed the use of cystatin C in the same EKFC equation used for serum creatinine by simply replacing the rescaled serum creatinine with rescaled cystatin C. We posited that rescaled cystatin C may be simpler and would require fewer rescaling factors across the spectrum of age, sex, and race than serum creatinine. We also aimed to show that further accuracy could be achieved by using the arithmetic mean of a serum creatinine–based equation and a cystatin C–based equation to estimate GFR.[8-12]

In the present study, we hypothesized that in the existing EKFC eGFRcr equation, rescaled serum creatinine could be replaced with rescaled cystatin C. We also hypothesized that rescaling of cystatin C could be accomplished without the inclusion of race- or sex-specific rescaling factors.

Methods

Study Design and Oversight

This study was a cross-sectional analysis of patient data from multiple centers in Europe, the United States, and Africa, where assessments of standardized serum creatinine and cystatin C levels, measured GFR, demographic characteristics (age, sex, and race), and anthropometric characteristics (height and weight), all of which were measured on the same day for each patient, were available. An overview of the source data sets is provided in Tables S1 and S2 and Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The EKFC equation was originally developed with serum creatinine alone as the biomarker. We applied this equation to two biomarkers (serum creatinine and cystatin C) after dividing each biomarker value by a unique rescaling Q

value factor (Section S2 and Fig. S1).[5] The general form of the EKFC eGFR equation is

$$\text{EKFC} - \text{eGFR} = 107.3/[\text{Biomarker/Q}]^{\alpha} \times [0.990^{(\text{Age}-40)} \text{ if age } >40 \text{ years}],$$

with $\alpha = 0.322$ when biomarker/Q is less than 1 and $\alpha = 1.132$ when biomarker/Q is 1 or more.

The study was funded by the Swedish Research Council. The data in the current study were obtained from different studies in which patients had provided written informed consent as well as from anonymized data from patients who had been referred to nephrology clinics and who had provided general informed consent that their anonymized data could be used for research purposes (Table S1). The authors vouch for the completeness and accuracy of the data.

DERIVATION OF RESCALING FACTORS

The rescaling Q factors for serum creatinine in the EKFC eGFRcr equation were the median serum creatinine values among several healthy populations. These values were previously described in White populations (Section S2.1)[5,11,12] and in Black populations in Africa and Europe (Section S2.2).[13]

To derive rescaling factors for serum cystatin C for the EKFC eGFRcys equation, we first assessed whether there were differences in cystatin C levels between Black patients and White patients. Specifically, in one cohort from a hospital in Paris, we matched Black patients (from a pool of 697 patients) and White patients (from a pool of 2262 patients) in a 1:1 ratio according to mean (±SD) age (±3 years), sex, body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) (±2.5), and measured GFR (±3 ml per minute per 1.73 m^2) (Section S3 and Table S3). After we established that mean cystatin C levels were similar between these Black patients and White patients (Fig. S2 and Table S4), we used a sample of healthy White patients to define the rescaling factors for cystatin C. We used measurements of cystatin C obtained between 2007 and 2020 from departments (other than the nephrology department) at Uppsala University Hospital in Sweden. For the cystatin C rescaling factor, we used quantile regression and a linear spline with a knot at 50 years to determine the median values according to age in adults 18 years of age or older or according to sex (Section S4 and Figs. S3 and S4).

VALIDATION COHORTS

We assessed the performance of estimating equations (EKFC eGFRcys; the mean of EKFC eGFRcr and EKFC eGFRcys [EKFC eGFRcr-cys]; CKD-EPI eGFRcys; and the composite CKD-EPI eGFRcr-cys) by comparing the estimated GFR determined by those equations with measured GFR in the EKFC multicenter cohort of 7727 patients[5] and in data sets from Paris (858 Black patients and 2646 White patients), the United States (1093 White patients in Rochester, Minnesota), and sub-Saharan Africa (285 Black patients in Ivory Coast and 223 Black patients in the Democratic Republic of Congo).[13,14] Since the coefficients of the EKFC equation were derived with the use of the serum creatinine and measured GFR data from the European cohorts in the EKFC data set (7727 patients), except for the cohorts in Kent, United Kingdom, and Lund, Sweden, these two cohorts were also used for external validation (Section S5 and Table S5). All data were restricted to the first available measurement of cystatin C and measured GFR.

All the patients were 18 years of age or older. Data were anonymized, and all procedures involving patients and data were consistent with the ethical principles for medical research involving human patients established by the World Medical Association Declaration of Helsinki.

QUANTIFICATION OF SERUM CREATININE, SERUM CYSTATIN C, AND MEASURED GFR

All the creatinine assays were calibrated to the standard method (isotope dilution mass spectrometry), and all the cystatin C assays were standardized to the international reference material (ERM-DA471/IFCC). Measured GFR was obtained with the use of either plasma clearance (based on the decay of the plasma concentrations over time) or urinary clearance (based on the urine excretion rate divided by the plasma concentration) of exogenous filtration markers (iohexol, inulin, technetium-99–labeled diethylenetriamine pentaacetic acid, ^{125}I-iothalamate, or chromium-51–labeled EDTA). These methods are commonly used to measure GFR.[15] All the measured GFR results were indexed to 1.73 m^2

Glossary

Median bias: The middle value (median) that is reported when the individual differences (estimated GFR minus measured GFR) are rank-ordered. A value closer to 0 is less biased and more accurate.

Interquartile range (IQR): A measurement of the variation in the differences between estimated GFR and measured GFR (estimated GFR minus measured GFR). The individual differences are rank-ordered, and the range of values between the 25th percentile and the 75th percentile is calculated. A smaller value reflects better accuracy of estimated GFR.

Root-mean-square error: Another measurement of the variation in the differences between estimated and measured GFR. The root-mean-square error is the square root of the average of the squared differences between estimated and measured GFR. The root-mean-square error is expressed on the same scale as GFR (in ml per minute per 1.73 m^2 of body-surface area), and a smaller value reflects better accuracy of estimated GFR.

P_{10}: The percentage of patients with an estimated GFR that is within 10% of the measured GFR. A higher value reflects better accuracy of estimated GFR.

P_{30}: The percentage of patients with an estimated GFR that is within 30% of the measured GFR. A higher value reflects better accuracy of estimated GFR. A P_{30} greater than 75% has been considered "sufficient for good clinical decision making" by the Kidney Disease Outcomes Quality Initiative, although the goal is to reach a P_{30} greater than 90%.[21]

of body-surface area with the equation described by Du Bois and Du Bois.[16]

STATISTICAL ANALYSIS

The accuracy of the EKFC eGFRcys, EKFC eGFRcr, and EKFC eGFRcr-cys equations in estimating the measured GFR was compared primarily with that of the three CKD-EPI equations recommended by KDIGO: the CKD-EPI eGFRcr equation (both the 2009 and the 2021 race-free versions),[2,4] the CKD-EPI eGFRcys equation, and the CKD-EPI eGFRcr-cys equation.[3] The EKFC eGFRcys and EKFC eGFRcr-cys equations were also compared with other full-age-range cystatin C–based or combined serum creatinine– and cystatin C–based equations, including the full-age-spectrum equation[11,17]; the Caucasian, Asian, Pediatric, and Adult (CAPA) equation[18]; and the mean of the Lund–Malmö revised equation[19] and the cystatin C–based CAPA equation.[20] These equations are provided in Section S6 and Table S6. We performed overall comparisons and comparisons within age subgroups (18 to <40 years, 40 to <65 years, and ≥65 years) (Section S7 and Tables S7.1 through S7.5).

Several commonly used statistics (see Glossary) along with the 95% confidence interval were used to assess the accuracy of the difference in values between estimated GFR and measured GFR. The median bias between the estimated GFR and measured GFR across the age spectrum was graphically presented with the use of median quantile regression. Likewise, the P_{30} (the percentage of patients with an estimated GFR that is within 30% of the measured GFR) according to age was shown graphically with the use of cubic splines. All analyses and calculations were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

RACIAL DIFFERENCES IN SERUM CREATININE AND CYSTATIN C LEVELS

In total, 577 Black patients were matched with 577 White patients from the same hospital in Paris (200 women [35%] and 377 men [65%] in each group) according to age, sex, BMI, and measured GFR. Although the serum creatinine level was higher at the same measured GFR in the Black patients than in the White patients, the serum cystatin C level was similar at the same measured GFR.

RESCALING FACTORS (Q VALUES) FOR SERUM CYSTATIN C

Given the lack of a racial difference in the serum cystatin C level at the same measured GFR, we used a large sample of 227,643 White patients (95,469 women and 132,174 men) at Uppsala University Hospital, Sweden, to calculate rescaling factors (Q values) for cystatin C. Specifically, we plotted the median cystatin C level for each 1-year interval according to age and sex. In patients who were 18 to 50 years of age, the median cystatin C levels were relatively constant with age, but these levels were higher in men than in women. After approximately 50 years of age, the median cystatin C levels increased with age and could be reasonably approximated with a linear spline regression with a knot at 50 years. That is, we fit a two-piece linear spline with an age cutoff at 50 years. This choice was made on the basis of visual inspection and for convenient interpretation, but it may not have been the cutoff that yielded the optimal fitting adjustment curve. Thus, a sex-specific rescaling factor for cystatin C was defined as 0.86 mg per liter in men and 0.79 mg per liter in women until 50 years of age, after which $0.005 \times (\text{age} - 50)$ was also added for patients who were 50 years of age

or older. Since the differences between men and women with respect to the median level of cystatin C were small, a rescaling factor for cystatin C without the inclusion of sex was also defined with the use of the overall median (0.83 mg per liter) until 50 years of age, and 0.005 × (age − 50) was added for patients who were 50 years of age or older.

VALIDATION OF THE CYSTATIN C–BASED EKFC EQUATION AND THE COMBINED EKFC EQUATION

Tables 1 and 2 show the performance of equations to estimate GFR in five different populations. In general, the EKFC estimating equations (EKFC eGFRcys, EKFC eGFRcr, and EKFC eGFRcr-cys) performed better than the parallel CKD-EPI equations, with similar or less bias and a lower interquartile range and a higher P_{10} (the percentage of patients with an estimated GFR that was within 10% of the measured GFR) and P_{30} relative to measured GFR. This improvement in the performance of EKFC equations over CKD-EPI equations was evident in the independent cohorts in Kent, United Kingdom, and Lund, Sweden, for the EKFC eGFRcys and EKFC eGFRcr equations but not for the EKFC eGFRcr-cys equation. The statistical performance of the EKFC eGFRcys equation with respect to estimation of measured GFR was similar to that of the EKFC eGFRcr equation. There were no meaningful differences between the EKFC eGFRcys and EKFC eGFRcr-cys equations in estimation of the GFR when rescaling factors that did not include sex were used rather than sex-specific rescaling factors for cystatin C (Tables S8.1 and S8.2).

The full-age-spectrum, Lund–Malmö revised, and CAPA equations were compared in the five populations in subgroups defined according to age, measured GFR (<60 or ≥60 ml per minute per 1.73 m^2), sex (Tables S9.1 through S9.4), and BMI category (Tables S10.1 through S10.4). The performance of the EKFC equations in individual cohorts is summarized in Section S11 and Table S11.

The bias and P_{30} for each EKFC and CKD-EPI equation according to patient age are shown in Figure 1. Data are from the pooled data set of the EKFC cohort, the Paris cohorts (both White patients and Black patients), the White cohort in the United States, and the Black cohort in Africa. The bias and P_{30} in other equations according to age, race, and sex are shown in Figures S5 and S10. Bias across levels of measured GFR is shown in Figure S11. Scatterplots of the EKFC eGFRcys and EKFC eGFRcr-cys equations according to measured GFR show more alignment with the line of identity (±30%) than was evident with the CKD-EPI eGFRcys and CKD-EPI eGFRcr-cys equations according to measured GFR (Figs. S12 through S14).

DISCUSSION

Our cystatin C–based equation (EKFC eGFRcys) did not have better accuracy in estimating measured GFR than a serum creatinine–based equation (EKFC eGFRcr). These results were consistent with those of previous studies.[3,22,23] Improvement in estimation of the GFR was observed only in the combined EKFC eGFRcr-cys equation. These EKFC equations require appropriately rescaled serum creatinine and cystatin C levels that are generated by dividing by the median values (rescaling factors) in a healthy population. Unlike the EKFC eGFRcr equation, the EKFC eGFRcys equation can use age-based rescaling factors without the inclusion of race or sex. We also found that the mean of the EKFC eGFRcr and EKFC eGFRcys equations improved accuracy in estimation of the GFR.

The use of tests to measure cystatin C is still not widespread, possibly because of their cost.[24] However, our data underscore an additional advantage of their adoption, because unlike serum creatinine, a cystatin C–based equation does not require sex or race variables for the determination of estimated GFR.

In our study, the EKFC eGFRcys and EKFC eGFRcr-cys equations also had better accuracy in estimating the GFR than the recommended CKD-EPI equations and other full-age-range cystatin C equations, including the full-age-spectrum[11] and CAPA[18] equations. To show that cystatin C levels did not have to be adjusted for race in order to estimate GFR, we first confirmed that there was no substantial difference in cystatin C levels between Black patients and White patients of the same age, sex, BMI, and measured GFR. We then used a rescaling factor for cystatin C that was based on a White cohort in Europe, but the resulting EKFC eGFRcys equation performed as well in the Black cohorts in

Table 1. Performance of Single Biomarker (Serum Creatinine or Cystatin C)–Based Equations to Estimate the Glomerular Filtration Rate.*

Variable	Serum Creatinine–Based Equations			Cystatin C–Based Equations	
	CKD-EPI eGFRcr(ASR)	CKD-EPI eGFRcr(AS)	EKFC eGFRcr	CKD-EPI eGFRcys	EKFC eGFRcys without Sex
EKFC cohort, 7727 White patients					
Median bias (95% CI) — ml/min/1.73 m²†	3.96 (3.67 to 4.32)	7.40 (7.02 to 7.76)	0.58 (0.32 to 0.86)	0.28 (−0.02 to 0.64)	0.00 (−0.37 to 0.27)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	15.5 (−3.0 to 12.5)	16.3 (0.0 to 16.3)	14.5 (−6.5 to 8.0)	19.1 (−7.9 to 11.2)	14.4 (−7.9 to 6.5)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	14.8 (14.4 to 15.2)	16.3 (15.9 to 16.6)	13.1 (12.8 to 13.4)	15.8 (15.5 to 16.1)	13.5 (12.9 to 14.1)
P_{10} — % (95% CI) ¶	40.3 (39.2 to 41.4)	34.7 (33.6 to 35.8)	43.3 (42.2 to 44.4)	32.0 (31.0 to 33.0)	41.7 (40.6 to 42.8)
P_{30} — % (95% CI) ‖	81.6 (80.8 to 82.5)	75.7 (74.8 to 76.7)	85.8 (85.0 to 86.5)	80.8 (79.9 to 81.7)	86.2 (85.4 to 87.0)
Paris cohort, 2646 White patients					
Median bias (95% CI) — ml/min/1.73 m²†	0.30 (−0.21 to 0.78)	3.22 (2.69 to 3.86)	−1.24 (−1.75 to −0.74)	−2.85 (−3.35 to −2.21)	−0.79 (−1.26 to −0.31)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	15.2 (−6.8 to 8.4)	15.9 (−4.1 to 11.7)	14.6 (−8.3 to 6.3)	16.4 (−10.3 to 6.1)	15.3 (−8.5 to 6.7)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	14.2 (13.6 to 14.8)	14.8 (14.2 to 15.4)	13.6 (13.0 to 14.1)	14.5 (13.9 to 15.1)	13.5 (12.9 to 14.1)
P_{10} — % (95% CI) ¶	39.5 (37.7 to 41.4)	38.2 (36.4 to 40.1)	40.9 (39.0 to 42.7)	34.2 (32.4 to 36.0)	38.2 (36.4 to 40.1)
P_{30} — % (95% CI) ‖	84.5 (83.1 to 85.8)	82.5 (81.1 to 84.0)	86.5 (85.2 to 87.7)	82.7 (81.3 to 84.2)	87.6 (86.3 to 88.9)
U.S. cohort, 1093 White patients					
Median bias (95% CI) — ml/min/1.73 m²†	2.83 (1.65 to 3.64)	7.11 (6.15 to 7.97)	−2.69 (−3.68 to −1.79)	12.1 (11.1 to 13.3)	4.26 (3.33 to 5.08)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	18.8 (−6.6 to 12.2)	18.7 (−2.2 to 16.5)	18.5 (−11.9 to 6.6)	21.5 (1.5 to 23.0)	18.3 (−5.3 to 13.0)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	16.2 (15.0 to 17.4)	17.5 (16.4 to 18.6)	16.2 (14.9 to 17.4)	21.3 (20.3 to 22.2)	16.8 (15.7 to 17.9)
P_{10} — % (95% CI) ¶	41.9 (39.0 to 44.8)	39.4 (36.5 to 42.3)	41.4 (38.5 to 44.4)	29.4 (26.7 to 32.1)	41.5 (38.6 to 44.5)
P_{30} — % (95% CI) ‖	86.0 (83.9 to 88.1)	81.0 (78.6 to 83.3)	89.3 (87.5 to 91.1)	72.9 (70.3 to 75.6)	83.9 (81.7 to 86.1)

Paris cohort, 858 Black patients					
Median bias (95% CI) — ml/min/1.73 m^2†	0.24 (–0.64 to 0.81)	–5.09 (–5.68 to –4.14)	–2.58 (–3.49 to –1.71)	–0.62 (–1.71 to 0.28)	1.40 (0.38 to 2.23)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	19.3 (–12.7 to 4.1)	16.8 (–12.7 to 4.1)	14.9 (–9.9 to 5.1)	17.9 (–8.1 to 9.8)	14.3 (–5.6 to 8.8)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	16.0 (14.7 to 17.2)	14.9 (13.5 to 16.1)	13.9 (12.4 to 15.2)	15.4 (14.0 to 16.6)	13.5 (12.1 to 14.7)
P_{10} — % (95% CI)¶	35.4 (32.2 to 38.6)	33.0 (29.8 to 36.1)	37.5 (34.3 to 40.8)	36.2 (33.0 to 39.5)	41.0 (37.7 to 44.3)
P_{30} — % (95% CI)‖	79.8 (77.1 to 82.5)	82.3 (79.7 to 84.8)	85.5 (83.2 to 87.9)	81.5 (78.9 to 84.1)	87.4 (85.2 to 89.6)
African cohort, 508 Black patients					
Median bias (95% CI) — ml/min/1.73 m^2†	12.2 (10.7 to 15.0)	2.48 (0.72 to 4.15)	–1.45 (–2.82 to 0.62)	2.82 (1.43 to 4.48)	1.74 (0.28 to 3.25)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	30.0 (–3.2 to 26.8)	23.3 (–9.0 to 14.3)	20.4 (–10.6 to 9.9)	23.7 (–7.7 to 16.0)	19.5 (–7.4 to 12.1)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	24.5 (22.7 to 26.1)	18.1 (16.6 to 19.4)	16.4 (15.0 to 17.8)	18.5 (17.1 to 19.8)	16.0 (14.7 to 17.2)
P_{10} — % (95% CI)¶	19.5 (16.0 to 22.9)	34.4 (30.3 to 38.6)	38.0 (33.8 to 42.2)	33.1 (29.0 to 37.2)	40.6 (36.3 to 44.8)
P_{30} — % (95% CI)‖	63.6 (59.4 to 67.8)	74.4 (70.6 to 78.2)	78.9 (75.4 to 82.5)	77.4 (73.7 to 81.0)	83.5 (80.2 to 86.7)

* The accuracy of different serum creatinine– and cystatin C–based equations to estimate the glomerular filtration rate (GFR) in five cohorts is shown. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFRcr(ASR) equation and the CKD-EPI eGFRcr(AS) equation, which estimate GFR with the use of serum creatinine (with ASR denoting age, sex, and race and AS denoting age and sex), and the CKD-EPI eGFRcys equation, which estimates GFR with the use of cystatin C, serve as benchmarks. The CKD-EPI equations are recommended by Kidney Disease: Improving Global Outcomes. Race was reported by the patients or investigators or was assumed according to geographic area (see Table S2 in the Supplementary Appendix). CI denotes confidence interval, EKFC European Kidney Function Consortium, and IQR interquartile range.

† In the calculation of median bias, the individual differences (estimated GFR minus measured GFR) are rank-ordered, and the middle value (the median) is reported. A value closer to 0 is less biased and more accurate.

‡ The IQR measures variation in the differences between estimated GFR and measured GFR (estimated GFR minus measured GFR). The individual differences are rank-ordered, and the range of values between the 25th percentile and the 75th percentile is calculated. A smaller value reflects better accuracy of estimated GFR.

§ The root-mean-square error measures variation in the differences between estimated and measured GFR. It is the square root of the average of the squared differences between estimated and measured GFR. Root-mean-square error is expressed on the same scale as GFR (in ml per minute per 1.73 m^2 of body-surface area), and a smaller value reflects better accuracy of estimated GFR.

¶ P_{10} is the percentage of patients with an estimated GFR that is within 10% of measured GFR. A higher value reflects better accuracy of estimated GFR.

‖ P_{30} is the percentage of patients with an estimated GFR that is within 30% of measured GFR. A higher value reflects better accuracy of estimated GFR. A P_{30} greater than 75% has been considered "sufficient for good clinical decision making" by the Kidney Disease Outcomes Quality Initiative, although the goal is to reach a P_{30} greater than 90%.[21]

Table 2. Performance of Combined Serum Creatinine– and Cystatin C–Based Equations to Estimate GFR.*

Variable	CKD-EPI eGFRcr-cys(ASR)	CKD-EPI eGFRcr-cys(AS)	EKFC eGFRcr-cys without Sex
EKFC cohort, 7727 White patients			
Median bias (95% CI) — ml/min/1.73 m²†	2.50 (2.17 to 2.76)	5.04 (4.69 to 5.36)	0.37 (0.14 to 0.66)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	14.8 (–3.6 to 11.2)	16.7 (–1.8 to 14.9)	12.0 (–5.9 to 6.1)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	13.1 (12.8 to 13.4)	14.7 (14.4 to 15.0)	11.3 (11.0 to 11.6)
P_{10} — % (95% CI)¶	41.5 (40.4 to 42.6)	37.2 (36.2 to 38.3)	48.9 (47.8 to 50.0)
P_{30} — % (95% CI)‖	88.3 (87.6 to 89.0)	84.2 (83.4 to 85.0)	90.4 (89.8 to 91.1)
Paris cohort, 2646 White patients			
Median bias (95% CI) — ml/min/1.73 m²†	–1.35 (–1.82 to –0.97)	0.64 (0.16 to 1.15)	–0.65 (–1.06 to –0.23)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	13.4 (–7.5 to 5.8)	14.1 (–5.8 to 8.3)	12.4 (–6.8 to 5.6)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	12.1 (11.6 to 12.7)	12.6 (12.0 to 13.1)	11.8 (11.2 to 12.4)
P_{10} — % (95% CI)¶	43.9 (42.0 to 45.8)	42.3 (40.4 to 44.1)	45.8 (43.9 to 47.7)
P_{30} — % (95% CI)‖	89.7 (88.5 to 90.8)	89.2 (88.0 to 90.4)	92.1 (91.1 to 93.1)
U.S. cohort, 1093 White patients			
Median bias (95% CI) — ml/min/1.73 m²†	9.23 (8.45 to 10.10)	13.9 (13.1 to 14.9)	0.97 (0.01 to 2.12)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	18.4 (0.5 to 18.8)	18.1 (5.1 to 23.3)	17.4 (–8.2 to 9.2)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	18.1 (17.1 to 19.1)	21.0 (20.1 to 22.0)	15.5 (14.3 to 16.7)
P_{10} — % (95% CI)¶	37.1 (34.3 to 40.0)	28.1 (25.4 to 30.8)	45.7 (42.7 to 48.6)
P_{30} — % (95% CI)‖	79.5 (77.1 to 81.9)	72.1 (69.4 to 74.8)	88.7 (86.9 to 90.6)
Paris cohort, 858 Black patients			
Median bias (95% CI) — ml/min/1.73 m²†	–0.37 (–1.06 to 0.57)	–2.08 (–2.71 to –1.32)	–0.65 (–1.23 to 0.11)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	15.2 (–6.4 to 8.8)	14.0 (–7.9 to 6.1)	12.4 (–6.2 to 6.2)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	13.3 (11.9 to 14.6)	12.6 (11.2 to 13.9)	11.6 (10.0 to 13.0)
P_{10} — % (95% CI)¶	38.7 (35.4 to 42.0)	38.9 (35.7 to 42.2)	48.3 (44.9 to 51.6)
P_{30} — % (95% CI)‖	87.9 (85.7 to 90.1)	89.0 (87.0 to 91.1)	92.0 (90.1 to 93.8)
African cohort, 508 Black patients			
Median bias (95% CI) — ml/min/1.73 m²†	8.55 (6.87 to 10.30)	4.08 (2.37 to 5.78)	0.42 (–1.03 to 1.51)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	24.7 (–4.5 to 20.1)	22.0 (–7.4 to 14.7)	17.1 (–7.2 to 10.0)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	19.7 (18.2 to 21.1)	17.2 (15.8 to 18.5)	14.7 (13.3 to 16.0)
P_{10} — % (95% CI)¶	28.7 (24.8 to 32.7)	34.3 (30.1 to 38.4)	43.5 (39.2 to 47.8)
P_{30} — % (95% CI)‖	75.0 (71.2 to 78.8)	77.6 (73.9 to 81.2)	84.3 (81.1 to 87.4)

* The accuracy of different combined serum creatinine– and cystatin C–based equations to estimate the GFR in five cohorts is shown. The CKD-EPI eGFRcr-cys(ASR) and the CKD-EPI eGFRcr-cys(AS) equations serve as benchmarks; these equations are recommended by Kidney Disease: Improving Global Outcomes. EKFC eGFRcr-cys is the arithmetic mean of EKFC eGFRcr and EKFC eGFRcys.

† In the calculation of median bias, the individual differences (estimated GFR minus measured GFR) are rank-ordered, and the middle value (the median) is reported. A value closer to 0 is less biased and more accurate.

‡ The IQR measures variation in the differences between estimated GFR and measured GFR (estimated GFR minus measured GFR). The individual differences are rank-ordered, and the range of values between the 25th percentile and the 75th percentile is calculated. A smaller value reflects better accuracy of estimated GFR.

§ The root-mean-square error measures variation in the differences between estimated and measured GFR. It is the square root of the average of the squared differences between estimated and measured GFR. Root-mean-square error is expressed on the same scale as GFR (in ml per minute per 1.73 m² of body-surface area), and a smaller value reflects better accuracy of estimated GFR.

¶ P_{10} is the percentage of patients with an estimated GFR that is within 10% of the measured GFR. A higher value reflects better accuracy of estimated GFR.

‖ P_{30} is the percentage of patients with an estimated GFR that is within 30% of measured GFR. A higher value reflects better accuracy of estimated GFR. A P_{30} greater than 75% has been considered "sufficient for good clinical decision making" by the Kidney Disease Outcomes Quality Initiative, although the goal is to reach a P_{30} greater than 90%.[21]

Europe, the Democratic Republic of Congo, and Ivory Coast as in the White cohorts in Europe and the United States. A single rescaling factor for cystatin C that did not account for sex differences performed as well in estimating GFR as two separate sex-specific rescaling factors.

In all five cohorts, the 2021 CKD-EPI eGFRcr(AS) equation (with AS denoting age and sex) had bias closer to zero and worse P_{10} and P_{30} accuracy than the serum creatinine–based EKFC eGFR equation (EKFC eGFRcr). In the White cohorts, but not the Black cohorts, the original 2009 CKD-EPI eGFRcr(ASR) equation (with ASR denoting age, sex, and race) had greater accuracy than the 2021 CKD-EPI eGFRcr(AS) equation. When we matched Black patients with White patients according to stringent criteria for age, sex, BMI, and measured GFR, we found that there were clear differences between Black patients and White patients, and between men and women, with respect to the serum creatinine level. Therefore, for the most accurate (unbiased) estimation of GFR on the basis of serum creatinine, population- and demographic-specific adjustments in the serum creatinine level are warranted. The EKFC eGFRcr equation first rescales serum creatinine to eliminate well-described race and sex differences in serum creatinine levels.[23] This rescaling preserves the performance of the serum creatinine–based equation without directly adding race and sex to the GFR estimating equation. However, such population-specific adjustments are not required for cystatin C, and the EKFC eGFRcys equation can be used without the inclusion of race and sex. The cystatin C–based full-age-spectrum[11] and CAPA[18] equations also can be used without the inclusion of race and sex, but our study showed that the EKFC eGFRcys equation had better performance properties.

The strengths of the current validation study include the large study population, including patients from Europe, the United States, and Africa; calibration of the serum creatinine assays to the standard method (isotope dilution mass spectrometry); cystatin C assays standardized to the certified reference material; and methods for measuring GFR that are used clinically and considered by Soveri et al.[15] to have acceptable accuracy. Although the methods used for determining measured GFR varied among the cohorts, this has been a long-standing problem in the development of GFR estimating equations. A standardized method for measuring GFR is lacking to ensure consistent data across numerous centers that often contribute to the development of GFR estimating equations. Additional limitations of this study include the lack of validation cohorts composed of White patients and Black patients from the United States and Asia and the lack of

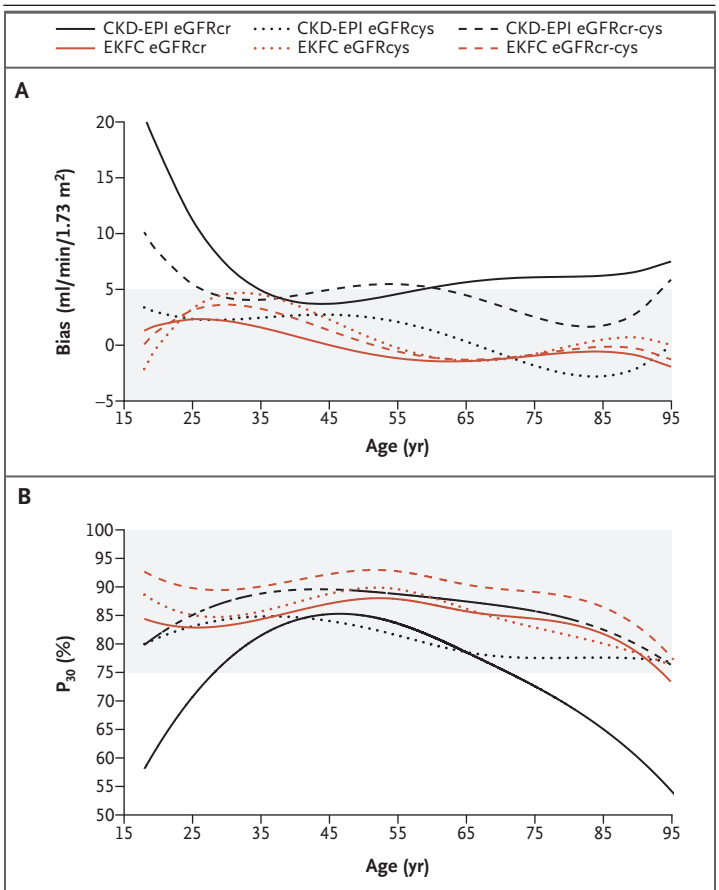

Figure 1. Performance of Different Equations to Estimate the Glomerular Filtration Rate with Respect to Bias and P_{30}, According to Age.

The data shown are from a pooled data set of 12,832 White patients from Europe and the United States and Black patients from Europe and Africa. The equations are referred to in accordance with the relevant filtration marker or markers — eGFRcr (estimated glomerular filtration rate [GFR] creatinine), eGFRcys (eGFR cystatin C), and eGFRcr-cys (eGFR creatinine–cystatin C). Panel A shows bias (estimated GFR minus measured GFR) according to age. The gray area indicates the region where bias is zero ±5. For bias according to age, the difference in medians was compared by means of quantile regression with the use of fourth-degree polynomials. Panel B shows P_{30} (the percentage of patients with an estimated GFR that is <30% of measured GFR) accuracy according to age. The gray area indicates the region where P_{30} is 75% or greater. P_{30} according to age was plotted by means of cubic splines with three free knots, with the use of third-degree polynomials. CKD-EPI denotes Chronic Kidney Disease Epidemiology Collaboration, and EKFC European Kidney Function Consortium.

cohorts of children. Further studies involving such populations may show that a race- or sex-specific rescaling factor for cystatin C is needed in some populations.

We found that a single mathematical equation (the EKFC equation) with serum creatinine could also be used with cystatin C to accurately estimate GFR. The performance of the EKFC eGFRcys equation tested in this study was equivalent to that of the EKFC eGFRcr equation, and the EKFC eGFRcys equation had somewhat better accuracy than the 2021 CKD-EPI equations (refitted without the race coefficient) that have been the subject of recent reports.[25-29]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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