ORIGINAL ARTICLE

Nephrol Dial Transplant, 2024, **39**, 694–706
https://doi.org/10.1093/ndt/gfad219
Advance access publication date: 9 October 2023

Accuracy of GFR estimating equations based on creatinine, cystatin C or both in routine care

Edouard L. Fu[1,2,3], Andrew S. Levey[4], Josef Coresh[5], Morgan E. Grams[6], Anne-Laure Faucon[2,7], Carl-Gustaf Elinder[8], Friedo W. Dekker[3], Pierre Delanaye[9,10], Lesley A. Inker[4] and Juan-Jesus Carrero[2,11]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
[4]Division of Nephrology, Department of Internal Medicine, Tufts Medical Center, Boston, MA, USA
[5]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA
[6]Division of Precision Medicine, Department of Medicine, New York University Grossman School of Medicine, New York, NY, USA
[7]INSERM UMR 1018, Department of Clinical Epidemiology, Paris-Saclay University, Paris, France
[8]Division of Renal Medicine, Department of Clinical Intervention, and Technology, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden
[9]Department of Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium
[10]Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Nîmes, France
[11]Division of Nephrology, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
Correspondence to: Edouard L. Fu; E-mail: edfu@bwh.harvard.edu

ABSTRACT

Background. New equations to estimate glomerular filtration rate based on creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cys}$) or both ($eGFR_{cr\text{-}cys}$) have been developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the European Kidney Function Consortium (EKFC). There is a need to evaluate the performance of these equations in diverse European settings to inform implementation decisions, especially among people with key comorbid conditions.

Methods. We performed a cross-sectional study including 6174 adults referred for single-point plasma clearance of iohexol in Stockholm, Sweden, with 9579 concurrent measurements of creatinine and cystatin C. We assessed the performance of the CKD-EPI 2009/2012/2021, EKFC 2021/2023, revised Lund-Malmö (RLM) 2011 and Caucasian, Asian, Pediatric and Adult (CAPA) 2014 equations against measured GFR (mGFR).

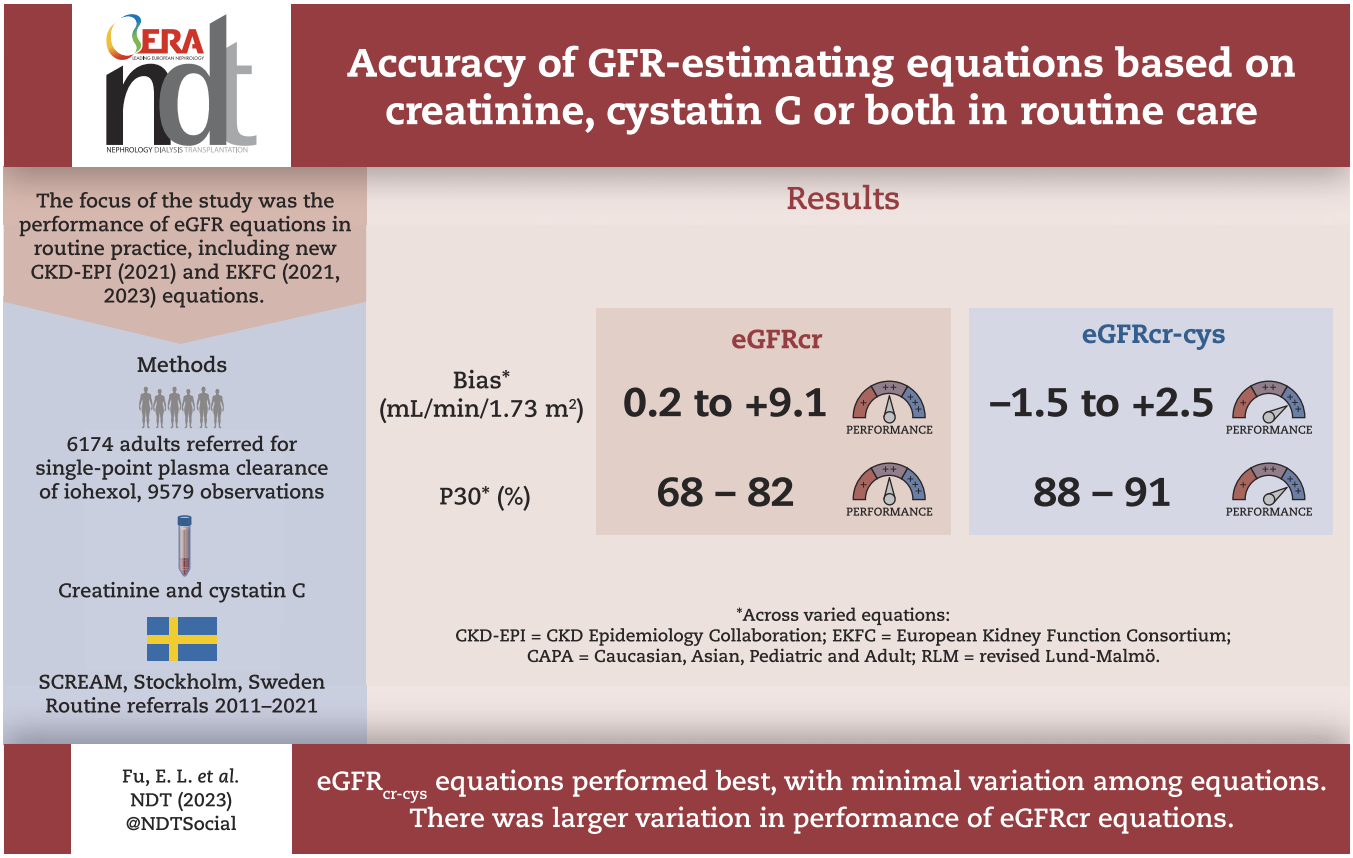
Results. Mean age was 56 years, median mGFR was 62 mL/min/1.73 m^2 and 40% were female. Comorbid conditions were common: cardiovascular disease (30%), liver disease (28%), diabetes (26%) and cancer (26%). All $eGFR_{cr\text{-}cys}$ equations had small bias and P_{30} (the percentage of estimated values within 30% of mGFR) close to 90%, and performed better than $eGFR_{cr}$ or $eGFR_{cys}$ equations. Among $eGFR_{cr}$ equations, CKD-EPI 2009 and CKD-EPI 2021 showed larger bias and lower P_{30} than EKFC 2021 and RLM. There were no meaningful differences in performance across $eGFR_{cys}$ equations. Findings were consistent across comorbid conditions, and $eGFR_{cr\text{-}cys}$ equations showed good performance in patients with liver disease, cancer and heart failure.

Conclusions. In conclusion, $eGFR_{cr\text{-}cys}$ equations performed best, with minimal variation among equations in this Swedish cohort. The lower performance of CKD-EPI $eGFR_{cr}$ equations compared with EKFC and RLM may reflect differences in population characteristics and mGFR methods. Implementing $eGFR_{cr}$ equations will require a trade-off between accuracy and uniformity across regions.

Keywords: CKD-EPI, creatinine, cystatin C, EKFC, glomerular filtration rate

Received: July 1, 2023; Editorial decision: September 4, 2023

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Novel equations have been developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the European Kidney Function Consortium (EKFC) to estimate glomerular filtration rate based on creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cys}$) or both ($eGFR_{cr\text{-}cys}$).
- Evaluation of their performances in diverse European settings is needed to inform implementation decisions.

This study adds:

- Among $eGFR_{cr}$ equations, CKD-EPI 2009 and CKD-EPI 2021 showed larger bias and lower P_{30} than EKFC 2021 and revised Lund-Malmö in this Swedish cohort of patients referred for single-point plasma iohexol clearance.
- There were no meaningful differences in performance across $eGFR_{cys}$ equations.
- All $eGFR_{cr\text{-}cys}$ equations had small bias and P_{30} close to 90%, and performed better than $eGFR_{cr}$ or $eGFR_{cys}$ equations.

Potential impact:

- Implementing $eGFR_{cr}$ equations in clinical practice may require a trade-off between accuracy and uniformity across regions.
- These findings also support recent recommendations by leading kidney organizations to "facilitate increased, routine and timely use of cystatin C."

INTRODUCTION

Estimated glomerular filtration rate (eGFR) is central to the diagnosis, staging, prognosis and management of patients with kidney disease [1, 2]. The 2012 international guidelines by Kidney Disease: Improving Global Outcomes (KDIGO) recommended use of the 2009 creatinine-based equation ($eGFR_{cr}$) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), or alternatives that were more accurate [3], as the first-line test. Furthermore, the CKD-EPI 2012 equations based on cystatin C and creatinine–cystatin C ($eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$, respectively) were recommended for use when $eGFR_{cr}$ is less accurate. Recently, several new eGFR equations have been developed by CKD-EPI [4] (2021) and European Kidney Function Consortium (EKFC) [5, 6] (2021, 2023). The US National Kidney Foundation and American Society of Nephrology have recommended implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation which does not include terms for race either in its development or in its computation [7–13]. However, European organizations have not endorsed implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation on the basis of poorer

performance compared with the 2009 equation in predominately white European populations [14–17].

There is a need to evaluate the performance of the CKD-EPI and EKFC equations in diverse European settings to inform implementation decisions. Furthermore, while these equations were developed in relatively healthy individuals with stable/predictable muscle mass and few comorbid conditions [18], eGFR is used in a much wider set of clinical settings including persons with comorbid conditions such as heart failure, cancer, extreme body mass index (BMI) or liver disease. The performance of the novel eGFR equations has not been well investigated in these populations.

The objective of this study was to compare novel CKD-EPI and EKFC eGFR equations ($eGFR_{cr}$, $eGFR_{cys}$ and $GFR_{cr\text{-}cys}$) against measured GFR (mGFR). To achieve this goal, we analyzed more than 9500 simultaneous measurements of serum creatinine and cystatin C in a real-world, independent cohort of referrals for iohexol clearance in Stockholm, Sweden.

MATERIALS AND METHODS

Data source and study population

We used data from the Stockholm Creatinine Measurements (SCREAM) project [19]. SCREAM contains healthcare utilization data from residents of Stockholm, Sweden between 2006 and 2021. A single healthcare provider in the Stockholm region provides universal and tax-funded healthcare to 20%–25% of the population of Sweden. Through unique personal identification numbers [20], we linked regional and national administrative databases with complete information on demographics, healthcare utilization, dispensed drugs [21], diagnoses [22], vital status [23], kidney replacement therapy [24] and completed laboratory tests. The Regional Ethical Review Board in Stockholm approved the study (2017/793-31); informed consent was not deemed necessary since all data were de-identified at the Swedish Board of Health and Welfare.

All patients older than 18 years who received iohexol clearance testing between 1 January 2011 and 31 December 2021 were included for this study (Supplementary data, Fig. S1). Additional eligibility criteria were presence of a plasma creatinine and cystatin C test in the 30 days before or after the iohexol clearance measurement; no history of maintenance dialysis; and no implausible mGFR values (<0 or >150 mL/min/1.73 m^2). Whenever multiple concurrent iohexol–creatinine–cystatin C tests were available for the same patient during follow-up, we included all measurements to increase statistical efficiency; in sensitivity analyses we restricted to the first measurement per patient.

Measurement of GFR

Iohexol clearance was analyzed at a central laboratory, the Department of Clinical Chemistry, at Karolinska University Hospital in Stockholm, with clearance procedures performed by indication at specialist departments in the region of Stockholm following standardized protocols (additional details in Supplementary data) [25]. GFR was measured using single-point plasma clearance of iohexol [26]. Single-point iohexol clearance is highly correlated with multisample iohexol; the mean [standard deviation (SD)] difference is 0.52 (4.3) and 95% limits of agreement are −8.1 to 9.1 compared with multisample iohexol [27–29]. Ultra-high performance liquid chromatography separation and UV detection was used to determine serum iohexol concentrations. The performance of the creatinine, cystatin C and iohexol assays was monitored through internal controls as well as an external quality assessment program standardization across the country by the monitoring company Equalis (Uppsala, Sweden).

Filtration markers, GFR estimating equations and covariates

Creatinine was measured with either an enzymatic or Jaffe method (kinetic alkaline picrate reaction) and standardized to isotope dilution mass spectrometry (IDMS) traceable methods. Cystatin C measurements were also standardized [30, 31]. Analyzers or reagents at the hospital laboratories have varied over the years for both analytes. In total, we validated 11 eGFR equations: 4 $eGFR_{cr}$ [CKD-EPI 2009 [32] (with race), CKD-EPI 2021 [4] (without race), EKFC 2021 [5], revised Lund-Malmö (RLM) 2011 [33]], 3 $eGFR_{cys}$ [CKD-EPI 2012 [34] (without race), EKFC 2023 [6], Caucasian, Asian, Pediatric and Adult (CAPA) 2014 [35]] and 4 $eGFR_{cr\text{-}cys}$ [CKD-EPI 2012 [34] (with race), CKD-EPI 2021 [4] (without race), mean of EKFC 2021 [5] and EKFC 2023 [6], mean of RLM 2011 [33] and CAPA 2014 [35]]. The formulas for each equation are provided in the Supplementary data. Since it is not permitted to collect information on race in Sweden in order to prevent discrimination, the CKD-EPI 2009 $eGFR_{cr}$ and 2012 $eGFR_{cr\text{-}cys}$ equations were calculated without the Black race coefficient. Data on country of birth are collected and published by the government annually. From these, we estimated that around 2.5% of the included cohort were born in African countries [36]. These participants were not excluded from our analyses.

For each individual, we extracted the following covariates: age, sex, BMI, cardiovascular disease (composite of myocardial infarction, other ischemic heart disease, heart failure, stroke, other cerebrovascular disease, arrhythmia and peripheral vascular disease), hypertension, cancer, liver disease, whether the individual had a kidney transplant or was a kidney donor (definitions are provided in Supplementary data, Table S1).

Analysis

The performance of all equations compared with mGFR was evaluated using the following metrics: bias, interquartile range (IQR), P_{30} and correct classification of GFR categories. Bias was expressed as the median difference in eGFR minus mGFR, with negative biases indicating underestimation of mGFR. A bias <±5 mL/min/1.73 m^2 was considered small, ±5–10 mL/min/1.73 m^2 as moderate and >±10 mL/min/1.73 m^2 as large. IQR was defined as the magnitude of the IQR of the differences between mGFR and eGFR, and is a measure of precision, with higher values reflecting greater imprecision. P_{30}, described as the percentage of estimated values within 30% of mGFR, is a measure of accuracy and is affected by both bias and imprecision. A P_{30} value of 75%–90% is considered to be acceptable for GFR evaluation in many circumstances [37], and a P_{30} value of ≥90% is preferred; these values correspond to approximately 60%–70% agreement and >70% agreement of eGFR with measured GFR in GFR categories. Correct classification of GFR categories was defined as agreement of eGFR and mGFR categories using the KDIGO GFR categories (<15, 15–29, 30–44, 45–59, 60–89 and ≥90 mL/min/1.73 m^2). We used the bootstrap method to calculate 95% confidence intervals (CIs) for each metric, using 10 000 bootstrap samples. The bootstrap accounts for the fact that the same individual could contribute multiple measurements to the analysis. All analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing) [38].

Subgroup and sensitivity analyses

Performance within subgroups of interest was assessed with bias, P_{30} and correct classification. *A priori*–defined strata included age (<40, ≥45–64 or ≥65 years), sex, BMI (<25 or ≥25 kg/m^2), eGFR (<60 or ≥60 mL/min/1.73 m^2), and the presence of cardiovascular disease, heart failure, diabetes mellitus, liver disease and cancer. We also assessed bias for each eGFR equation according to continuous age, BMI and eGFR levels. In these analyses, we truncated the population at the 2.5th and 97.5th percentiles. We did not investigate performance categorized by mGFR, since a correlation is expected between mGFR and eGFR minus mGFR, even for an unbiased eGFR estimation, as shown by Hsu *et al*. [39].

We performed four sensitivity analyses. First, differences in performance between equations may be explained by the fact that different GFR measurement methods were used in the cohorts in which equations were developed [40]. The CKD-EPI equations were developed in cohorts that used urinary iothalamate clearance (the most common method used in the USA), whereas EKFC and RLM cohorts predominantly used plasma iohexol clearance (the most common method used in Europe). Iothalamate clearance is the sum of glomerular filtration as well as tubular secretion of iothalamate, and thus is expected to be higher than iohexol clearance [28]. To investigate how sensitive the results are to differences in GFR measurement methods, we increased the mGFR values in the SCREAM study population uniformly between 1% and 15%, and re-evaluated the performance of the CKD-EPI equations under each scenario. We used a range of values since the precise relative difference between urinary iothalamate and plasma iohexol clearance is uncertain [26, 41, 42]. This analysis assumes that the relative difference between both GFR measurement methods is constant, and does not depend on characteristics such as age, comorbid conditions or GFR level. Note that true calibration would require simultaneous measurement of both urinary iothalamate clearance and plasma iohexol clearance for each individual. Second, the EKFC developed cystatin C–based equations with and without sex. The equation without sex-specific rescaling factors ($EKFC_A$) was used in our main analysis, but we also evaluated the EKFC cystatin C equation that used sex-specific rescaling factors ($EKFC_{AS}$). Third, we restricted our analysis to measurements of iohexol, creatinine and cystatin C taken on the same day, instead of using a 30-day window ($n = 7818$ measurements). Fourth, we used the first measurement for each patient rather than all measurements ($n = 6174$ measurements). Lastly, we combined both sensitivity analyses by restricting to same-day measurements of iohexol, creatinine and cystatin C and only including each patient once, by selecting the first available measurement ($n = 5015$ measurements/unique persons).

RESULTS

Baseline characteristics

We included 6174 individuals who contributed 9579 mGFR measurements (Supplementary data, Fig. S2). Mean (SD) age was 56 (17) years, with 37% of the sample aged 65 years or older, and 40% were female (Table 1). Comorbid conditions such as cardiovascular disease (30%), liver disease (28%), diabetes (26%) and cancer (26%) occurred frequently. The median mGFR was 62 mL/min/1.73 m^2 (IQR 41–83 mL/min/1.73 m^2). Distributions for each eGFR equation are shown in Supplementary data, Fig. S3. In general, the highest eGFR was observed for $eGFR_{cr}$ and the lowest for $eGFR_{cys}$, with $eGFR_{cr\text{-}cys}$ in between (Table 1, Supplementary data, Fig. S3). For instance, median $eGFR_{cr}$, $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ were 67, 59 and 64 mL/min/1.73 m^2, respectively, when using the EKFC equations, and 74, 57 and 65 mL/min/1.73 m^2 when using the most recent CKD-EPI equations.

Performance of equations based on creatinine, cystatin C or both

Scatterplots for eGFR against mGFR are shown in Supplementary data, Figs S4–S6 and Bland–Altman plots in Supplementary data, Figs S7–S9. $eGFR_{cr\text{-}cys}$ equations performed better than $eGFR_{cr}$ or $eGFR_{cys}$ equations, regardless of the specific equation used (Table 2). All $eGFR_{cr\text{-}cys}$ equations had small bias: 0.8 for CKD-EPI 2012, 2.5 for CKD-EPI 2021, 1.0 for EKFC and −1.5 mL/min/1.73 m^2 for the mean of RLM/CAPA. IQR was 12–13 mL/min/1.73 m^2, P_{30} was close to 90% and correct classification was around 66%.

Among $eGFR_{cr}$ equations, CKD-EPI 2009 and CKD-EPI 2021 showed larger overestimates of mGFR than EKFC and RLM, with biases of 5.6, 9.1, 2.7 and 0.2 mL/min/1.73 m^2, respectively. Furthermore, the EKFC and RLM equations had lower IQR and higher P_{30} than the CKD-EPI equations. For instance, P_{30} was 82.2% for RLM 2011, 79.5% for EKFC, 74.1% for CKD-EPI 2009 and 68.1% for CKD-EPI 2021. The correct classification ranged from 51.8% for CKD-EPI 2021 to 58.9% for EKFC.

There were no meaningful differences in performance across $eGFR_{cys}$ equations, with biases of −2.6 for CKD-EPI, −1.1 for EKFC and −3.7 mL/min/1.73 m^2 for CAPA, and P_{30} of 82.5%, 84.5% and 83.2%, respectively.

Performance of equations in subgroups

Among subgroups, $eGFR_{cr\text{-}cys}$ had better performance than equations using each marker alone (Fig. 1, Supplementary data, Table S2). This was particularly evident among patients with heart failure, liver disease and cancer, where P_{30} for $eGFR_{cr}$ ranged between 52% and 84.7%, and for $eGFR_{cr\text{-}cys}$ between 75.9% and 91.8%.

Among older patients, $eGFR_{cr}$ equations tended to overestimate and $eGFR_{cys}$ equations tended to underestimate mGFR, whereas equations using both filtration markers had smaller bias (Fig. 2). The CKD-EPI $eGFR_{cr}$ equations showed large overestimation at younger age (<30 years), whereas such overestimation was not seen for the EKFC and RLM equations.

At low BMI, $eGFR_{cr}$ equations tended to overestimate GFR regardless of the equation used, whereas bias was smaller for $eGFR_{cys}$ equations (Fig. 3). Again, there was wider variation between $eGFR_{cr}$, and less variation between $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ equations.

All $eGFR_{cr\text{-}cys}$ equations had small bias at eGFR levels <60 mL/min/1.73 m^2 (Fig. 4), but larger bias at higher eGFR levels. Furthermore, variation in performance of $eGFR_{cr}$ equations was smaller among those with $eGFR_{cr}$ <60 mL/min/1.73 m^2: bias was 2.0 for CKD-EPI 2009, 4.1 for CKD-EPI 2021, 1.4 for EKFC and 0.2 mL/min/1.73 m^2 for RLM. P_{30} were 72.0%, 66.0%, 74.4% and 76.2%, respectively. Regardless of filtration marker or equation used, bias was larger at higher eGFR than at lower eGFR (Fig. 4, Supplementary data, Figs S4–S6).

Sensitivity analyses

The performance of the CKD-EPI equations was re-evaluated under different scenarios to account for the fact that GFR measured with urinary iothalamate differs from iohexol clearance. For each percentage that urinary iothalamate would be higher than iohexol, bias of CKD-EPI equations would decrease by

Table 1: Baseline characteristics of 6174 persons (with 9579 observations) referred for iohexol clearance testing in Stockholm during 2011–21, overall and stratified by mGFR categories.

		mGFR category (mL/min/1.73 m^2)						
	Overall	≥105	90–104	60–89	45–59	30–44	15–29	<15
Iohexol measurements, *n* (%)	9579	608	1126	3386	1729	1358	1022	350
Mean age (SD), years	56 (17)	39 (15)	44 (16)	53 (16)	61 (14)	65 (13)	65 (15)	63 (15)
Age ≥65 years, *n* (%)	3581 (37)	36 (6)	122 (11)	975 (29)	813 (47)	814 (60)	630 (62)	191 (55)
Female sex, *n* (%)	3826 (40)	230 (38)	382 (34)	1323 (39)	726 (42)	568 (42)	441 (43)	156 (45)
Mean BMI (SD), kg/m^2	26 (8)	26 (18)	25 (4)	26 (10)	26 (5)	26 (5)	27 (6)	27 (6)
BMI category, *n* (%)[b]								
Missing	2074 (22)	220 (36)	436 (39)	779 (23)	241 (14)	180 (13)	156 (15)	62 (18)
<20	690 (7)	37 (6)	66 (6)	216 (6)	139 (8)	104 (8)	99 (10)	29 (8)
20 to <25	2951 (31)	182 (30)	299 (27)	1089 (32)	597 (35)	415 (31)	279 (27)	90 (26)
25 to <30	2531 (26)	123 (20)	223 (20)	898 (27)	494 (29)	420 (31)	275 (27)	98 (28)
≥30	1333 (14)	46 (8)	102 (9)	404 (12)	258 (15)	239 (18)	213 (21)	71 (20)
GFR evaluations, median (IQR)								
Creatinine, μmol/L[a]	94 (76, 125)	66 (55, 77)	74 (63, 85)	82 (70, 96)	102 (89, 118)	128 (109, 150)	193 (149, 255)	373 (277, 494)
Cystatin C, mg/L	1.26 (0.98–1.76)	0.79 (0.72–0.90)	0.89 (0.80–0.98)	1.08 (0.95–1.22)	1.44 (1.29–1.62)	1.83 (1.61–2.11)	2.73 (2.32–3.27)	3.88 (3.44–4.54)
Measured GFR, mL/min/1.73 m^2	62 (41, 83)	112 (108, 120)	96 (93, 100)	74 (67, 82)	52 (48, 56)	38 (34, 41)	23 (19, 26)	11 (9, 13)
Creatinine-based equations, mL/min/1.73 m^2								
CKD-EPI 2009	70 (47, 92)	109 (100, 121)	99 (89, 110)	82 (71, 94)	60 (51, 70)	45 (38, 53)	27 (20, 36)	12 (9, 17)
CKD-EPI 2021	74 (51, 96)	112 (104, 123)	103 (94, 113)	87 (75, 99)	64 (55, 75)	48 (40, 57)	29 (22, 39)	13 (10, 18)
EKFC	67 (46, 86)	104 (93, 111)	93 (84, 103)	78 (68, 88)	57 (50, 67)	43 (36, 51)	27 (21, 36)	13 (10, 17)
RLM	65 (45, 81)	96 (87, 106)	87 (79, 95)	74 (65, 83)	56 (49, 64)	42 (34, 51)	24 (19, 33)	13 (10, 17)
Cystatin C–based equations, mL/min/1.73 m^2								
CKD-EPI 2012	57 (35, 83)	109 (95, 120)	96 (84, 107)	71 (60, 85)	47 (40, 55)	34 (28, 40)	20 (16, 25)	12 (10, 15)
EKFC	59 (39, 82)	103 (90, 110)	91 (82, 103)	72 (61, 83)	50 (44, 57)	38 (32, 44)	24 (20, 29)	16 (13, 19)
CAPA	57 (37, 78)	102 (89, 117)	89 (79, 100)	69 (58, 81)	48 (41, 55)	35 (29, 41)	20 (16, 26)	12 (9, 15)
Combined equations, mL/min/1.73 m^2								
CKD-EPI 2012	63 (41, 87)	111 (99, 120)	98 (89, 107)	76 (66, 88)	53 (46, 60)	38 (33, 44)	22 (18, 28)	12 (10, 14)
CKD-EPI 2021	65 (43, 89)	113 (103, 122)	101 (92, 110)	79 (69, 90)	55 (48, 62)	40 (34, 46)	23 (18, 29)	12 (10, 15)
EKFC	64 (44, 83)	102 (93, 109)	91 (85, 100)	75 (67, 84)	54 (48, 61)	41 (36, 46)	26 (21, 32)	15 (12, 18)
Mean of RLM and CAPA	61 (42, 80)	100 (89, 109)	88 (81, 96)	71 (64, 80)	52 (47, 58)	39 (33, 45)	22 (18, 29)	12 (10, 15)
Medical history, *n* (%)								
Cardiovascular disease[b]	2828 (30)	45 (7)	108 (10)	761 (22)	624 (36)	592 (44)	529 (52)	169 (48)
Heart failure	988 (10)	5 (1)	23 (2)	187 (6)	202 (12)	215 (16)	263 (26)	93 (27)
Diabetes mellitus	2503 (26)	82 (13)	140 (12)	676 (20)	523 (30)	511 (38)	428 (42)	143 (41)
Cancer	2468 (26)	168 (28)	286 (25)	906 (27)	528 (31)	386 (28)	164 (16)	30 (9)
Liver disease	2705 (28)	118 (19)	213 (19)	956 (28)	668 (39)	449 (33)	267 (26)	34 (10)
Kidney transplantation	291 (3)	1 (0)	3 (0)	66 (2)	71 (4)	62 (5)	59 (6)	29 (8)
Kidney donor	303 (3)	19 (3)	41 (4)	170 (5)	72 (4)	0 (0)	1 (0)	0 (0)

[a]To convert plasma creatinine from μmol/L to mg/dL, multiply by 0.0113.
[b]Cardiovascular disease was defined as a composite of myocardial infarction, other ischemic heart disease, heart failure, stroke, other cerebrovascular disease, arrhythmia and peripheral vascular disease.

0.5–0.6 mL/min/1.73 m^2 from the baseline bias (Supplementary data, Table S3). For example, if urinary iothalamate would lead to a 5% higher mGFR value, then bias for $eGFR_{cr}$ equations would be 2.8 for CKD-EPI 2009 and 6.2 mL/min/1.73 m^2 for CKD-EPI 2021; −5.3 mL/min/1.73 m^2 for CKD-EPI 2012 $eGFR_{cys}$ equation; and −1.7 for CKD-EPI 2012 and 0.0 mL/min/1.73 m^2 for CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equations. Under more extreme scenarios (e.g. 15%), CKD-EPI $eGFR_{cr}$ equations would have smaller bias than CKD-EPI $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ equations. P_{30} for $eGFR_{cr}$ and $eGFR_{cys}$ equations followed a similar pattern to that of the bias (Supplementary data, Table S4). However, P_{30} of CKD-EPI $eGFR_{cr\text{-}cys}$ equations remained higher than CKD-EPI $eGFR_{cr}$ or $eGFR_{cys}$ equations, even in the extreme scenarios. No meaningful differences were found between the EKFC $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ equations when sex-specific rescaling factors were used (Supplementary data, Table S5). Findings were consistent when restricting to same-day measurements (Supplementary data, Table S6), when restricting to one measurement per patient (Supplementary data, Table S7) or when combining both analyses (Supplementary data, Table S8).

DISCUSSION

In this comparative study of eGFR equations, we used a large cohort of iohexol plasma clearance referrals with concurrent testing for creatinine and cystatin C using methods traceable to reference standards. We found that $eGFR_{cr\text{-}cys}$ equations had superior performance to $eGFR_{cr}$ or $eGFR_{cys}$ regardless of specific equation used, with small bias and high P_{30}. We also observed that all $eGFR_{cys}$ equations had more homogeneous performance than $eGFR_{cr}$.

Table 2: Bias, IQR, P_{30} and correct classification of different GFR estimating equations compared with single-point plasma iohexol clearance.

	Bias, mL/min/1.73 m^2 (95% CI)[a]	IQR, mL/min/1.73 m^2 (Q1, Q3)[b]	P_{30}, % (95% CI)[c]	Correct classification, % (95% CI)[d]
Creatinine-based equations				
CKD-EPI 2009	5.6 (5.3 to 6.0)	17.6 (−2.3 to 15.3)	74.1 (73.2 to 75.0)	56.4 (55.4 to 57.4)
CKD-EPI 2021	9.1 (8.8 to 9.5)	18.6 (0.6 to 19.2)	68.1 (67.2 to 69.1)	51.8 (50.9 to 52.8)
EKFC 2021	2.7 (2.5 to 3.0)	15.6 (−4.6 to 11.0)	79.5 (78.7 to 80.3)	58.9 (57.9 to 59.9)
RLM 2011	0.2 (−0.2 to 0.4)	15.6 (−7.7 to 7.9)	82.2 (81.4 to 82.9)	58.6 (57.6 to 59.5)
Cystatin C–based equations				
CKD-EPI 2012	−2.6 (−2.9 to −2.3)	15.0 (−10.4 to 4.6)	82.5 (81.7 to 83.3)	58.3 (57.4 to 59.3)
EKFC 2023	−1.1 (−1.4 to −0.9)	14.6 (−11.5 to 3.1)	84.5 (83.8 to 85.2)	60.8 (59.8 to 61.7)
CAPA 2014	−3.7 (−4.0 to −3.4)	14.8 (−9.0 to 5.8)	83.2 (82.5 to 84.0)	58.1 (57.2 to 59.1)
Creatinine–cystatin C–based equations				
CKD-EPI 2012	0.8 (0.6 to 1.0)	12.6 (−5.0 to 7.6)	89.1 (88.4 to 89.7)	66.7 (65.7 to 67.6)
CKD-EPI 2021	2.5 (2.3 to 2.8)	13.1 (−3.3 to 9.8)	87.6 (86.9 to 88.2)	66.3 (65.3 to 67.2)
Mean of EKFC eGFRcr and EKFC eGFRcys	1.0 (0.8 to 1.3)	12.0 (−7.9 to 4.1)	88.5 (87.9 to 89.2)	66.8 (65.8 to 67.7)
Mean of RLM and CAPA	−1.5 (−1.7 to −1.3)	12.0 (−5.2 to 6.8)	90.8 (90.2 to 91.4)	65.8 (64.8 to 66.7)

[a]Bias was expressed as the median difference in eGFR minus mGFR (95% CI). A negative bias indicates underestimation of the mGFR, and a positive bias indicates overestimation of the mGFR.
[b]IQR is defined as the IQR and a measure of precision (the dispersion of individual errors around the bias).
[c]P_{30} was defined as the percentage of individuals with eGFRs within 30% of mGFR (95% CI).
[d]Correct classification of GFR categories was defined as agreement of eGFR and mGFR categories using the KDIGO GFR categories (<15, 15–29, 30–44, 45–59, 60–89 and ≥90 mL/min/1.73 m^2).

Indeed, $eGFR_{cr}$ equations had the largest variation in performance, with the CKD-EPI equations performing worse than EKFC or RLM, especially in the younger age group. Our findings were consistent in various sensitivity analyses and subgroups, including patients with comorbid conditions known to affect serum creatinine or cystatin C levels.

Clinical implications and comparison with previous studies

Our findings of superior performance of $eGFR_{cr\text{-}cys}$ equations to any of the $eGFR_{cr}$ or $eGFR_{cys}$ equations align with previous observations from research cohorts [4, 6] and support recent recommendations by leading kidney organizations to "facilitate increased, routine and timely use of cystatin C" [13]. Importantly, we extend the findings of previous studies by demonstrating the superior accuracy of $eGFR_{cr\text{-}cys}$ in a real-world setting with individuals having one or more comorbid conditions. Differences in performance between equations were small, and implementation of any of the equations in the setting of SCREAM would be suitable.

Among $eGFR_{cr}$ equations, we found that each of the equations performed worse in SCREAM than in their respective validation cohorts. For instance, we found a bias of 9.1 mL/min/1.73 m^2 and P_{30} of 68.1% for the CKD-EPI 2021 equation, whereas the CKD-EPI validation cohort reported a bias of 3.9 mL/min/1.73 m^2 and P_{30} of 86.5% among non-Black participants [4]. For the EKFC 2021 equation, we observed a bias of 2.7 mL/min/1.73 m^2 and P_{30} of 79.5%, whereas bias and P_{30} were better in the EKFC validation cohort (0.6 mL/min/1.73 m^2 and 85.8%, respectively) [6]. The poorer performance in SCREAM may be explained by the higher prevalence of comorbid conditions affecting non-GFR determinants of creatinine in our routine care cohort compared with the development and validation datasets which included research populations that are likely to have been healthier. This difference in characteristics may be a reflection of the indications for measuring GFR in clinical practice.

We also found larger variation in the performance of $eGFR_{cr}$ equations within SCREAM, with EKFC and RLM showing better performance than the CKD-EPI equations. Thus, implementation of the EKFC and RLM would be preferred for the setting of SCREAM. The difference in performance between equations may be due to population differences between the development datasets and our study. EKFC and RLM were developed in white populations similar to SCREAM [5, 33], whereas the CKD-EPI equations were developed in a more diverse population, including 31% Black individuals. Black individuals in North America and Europe have higher serum creatinine levels than white individuals for the same age, sex and mGFR [43]. The CKD-EPI 2009 equation included a race variable to account for this observation, whereas the race variable was removed in 2021 equation. This likely explains the better performance of the CKD-EPI 2009 than the CKD-EPI 2021 in our predominantly white population, as has been shown elsewhere [4]. Furthermore, studies have shown that the race coefficient in the CKD-EPI 2009 equation was not accurate for African populations and overestimated GFR [44, 45], and that current equations exhibit variable performance in African and Asian populations [44, 46–48]. These findings suggest that the performance of $eGFR_{cr}$ equations may vary between geographic regions depending on population characteristics. This lends support to the proposal that large regions (countries or health systems) consider using $eGFR_{cr}$ equations that are optimal for their settings. However, variation in use of $eGFR_{cr}$ equations across regions may lead to regional variations in clinical practice and difficulty in harmonizing research studies and public health policies. Thus, it appears that there would be an unavoidable trade-off between accuracy vs uniformity in selection of $eGFR_{cr}$ equations for use across regions. In contrast, previous research has shown minimal influence of race and source population on serum cystatin C levels [43]. Our findings that all $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ equations had more consistent performance across populations than $eGFR_{cr}$ equations suggests that $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ equations could be more routinely

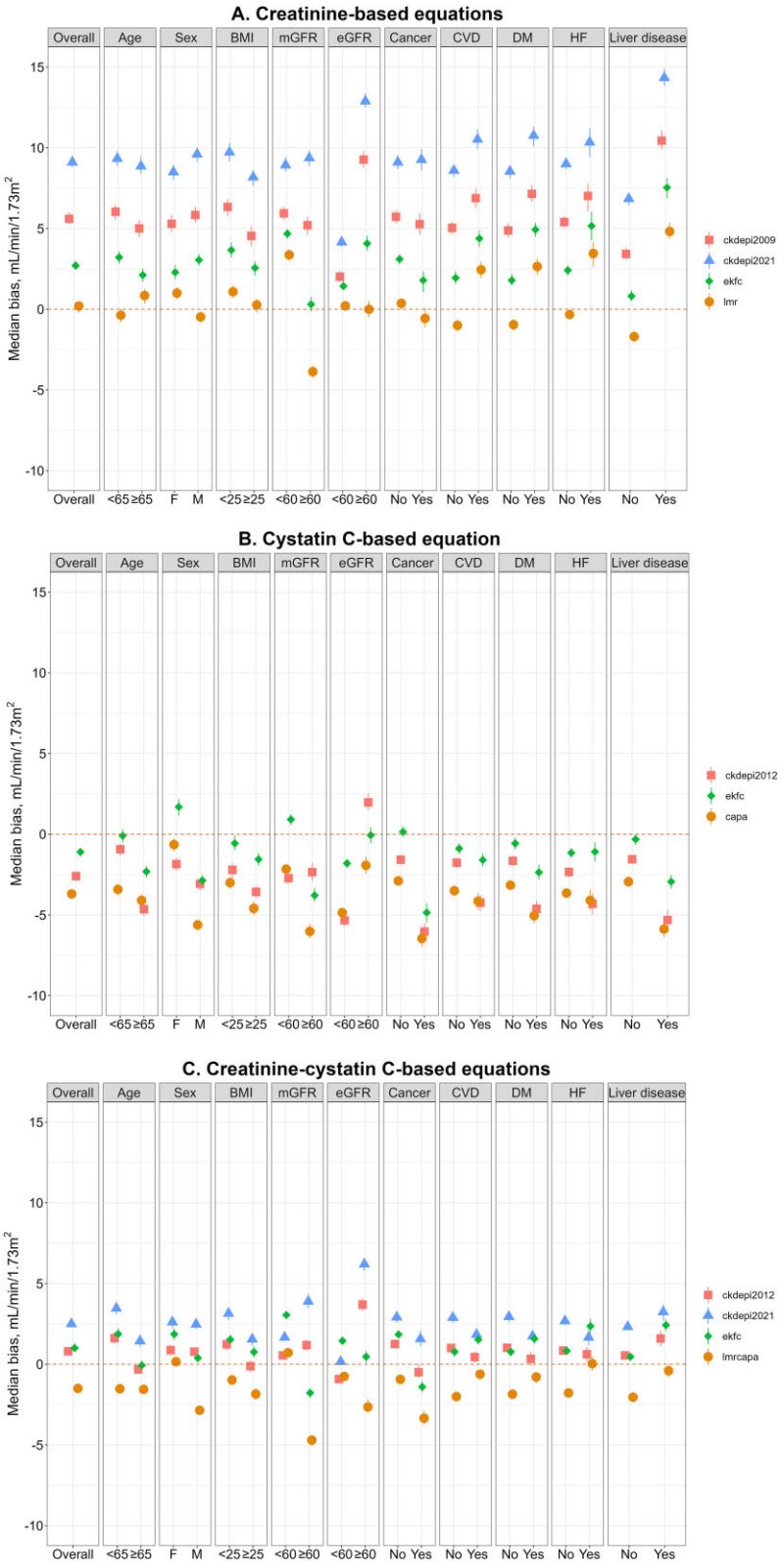


Figure 1: Bias for GFR estimating equations across subgroups of age, sex, BMI, eGFR, cancer, cardiovascular disease, diabetes, heart failure and liver disease. CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure.

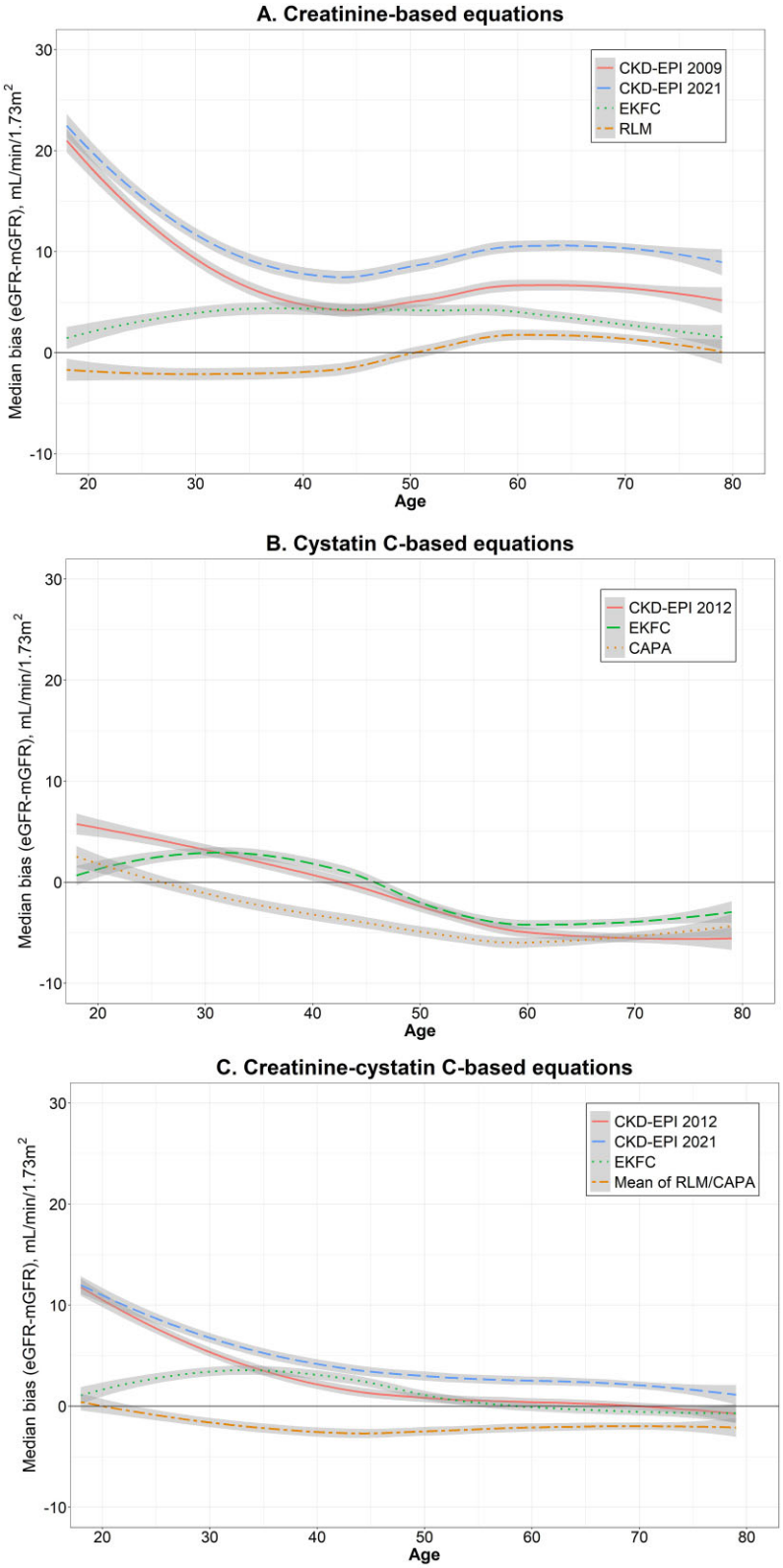


Figure 2: Bias for GFR estimating equations across continuous age. The x-axis is truncated at the 2.5th and 97.5th percentiles.

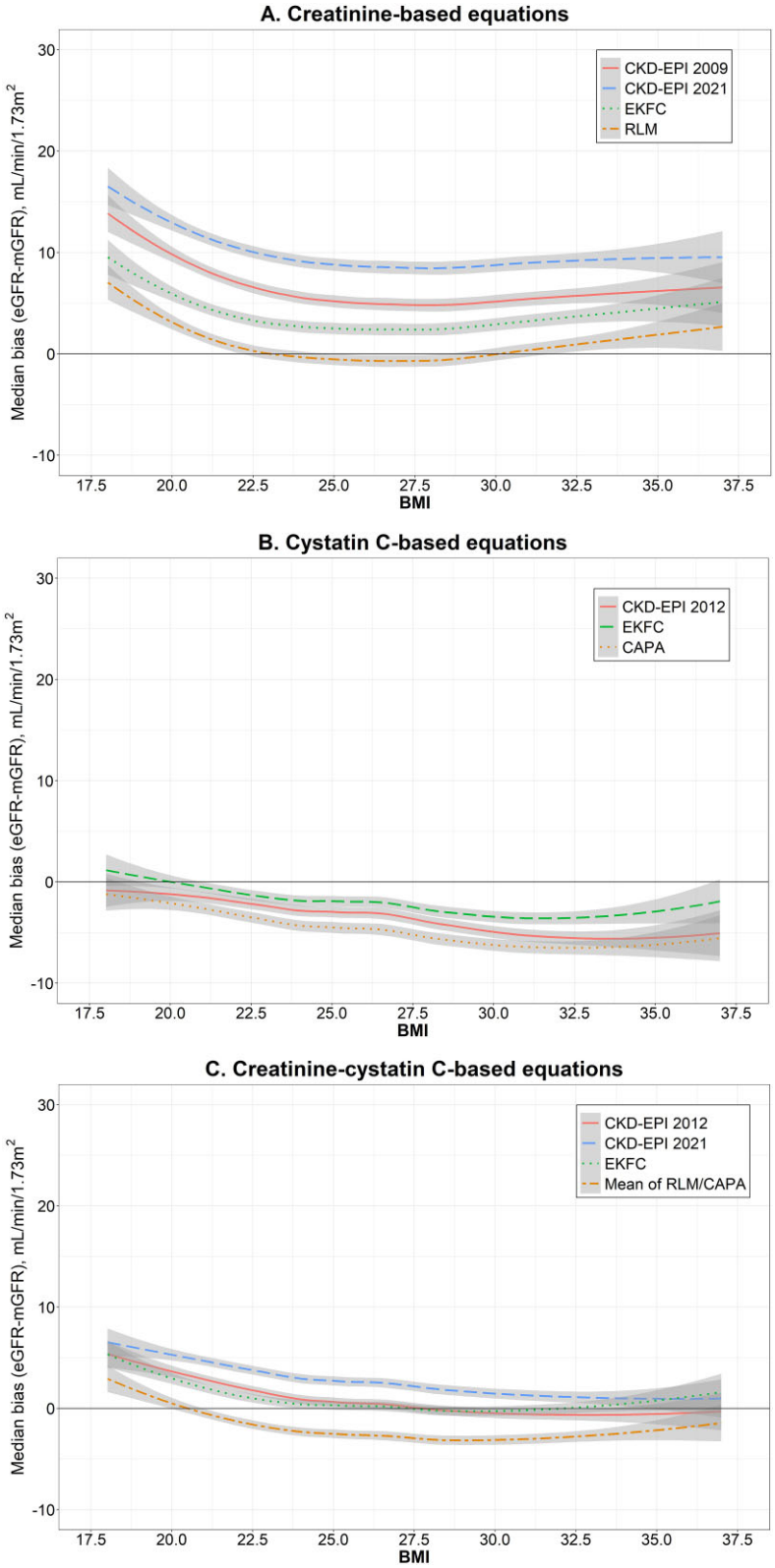


Figure 3: Bias for GFR estimating equations across continuous BMI. The x-axis is truncated at the 2.5th and 97.5th percentiles.

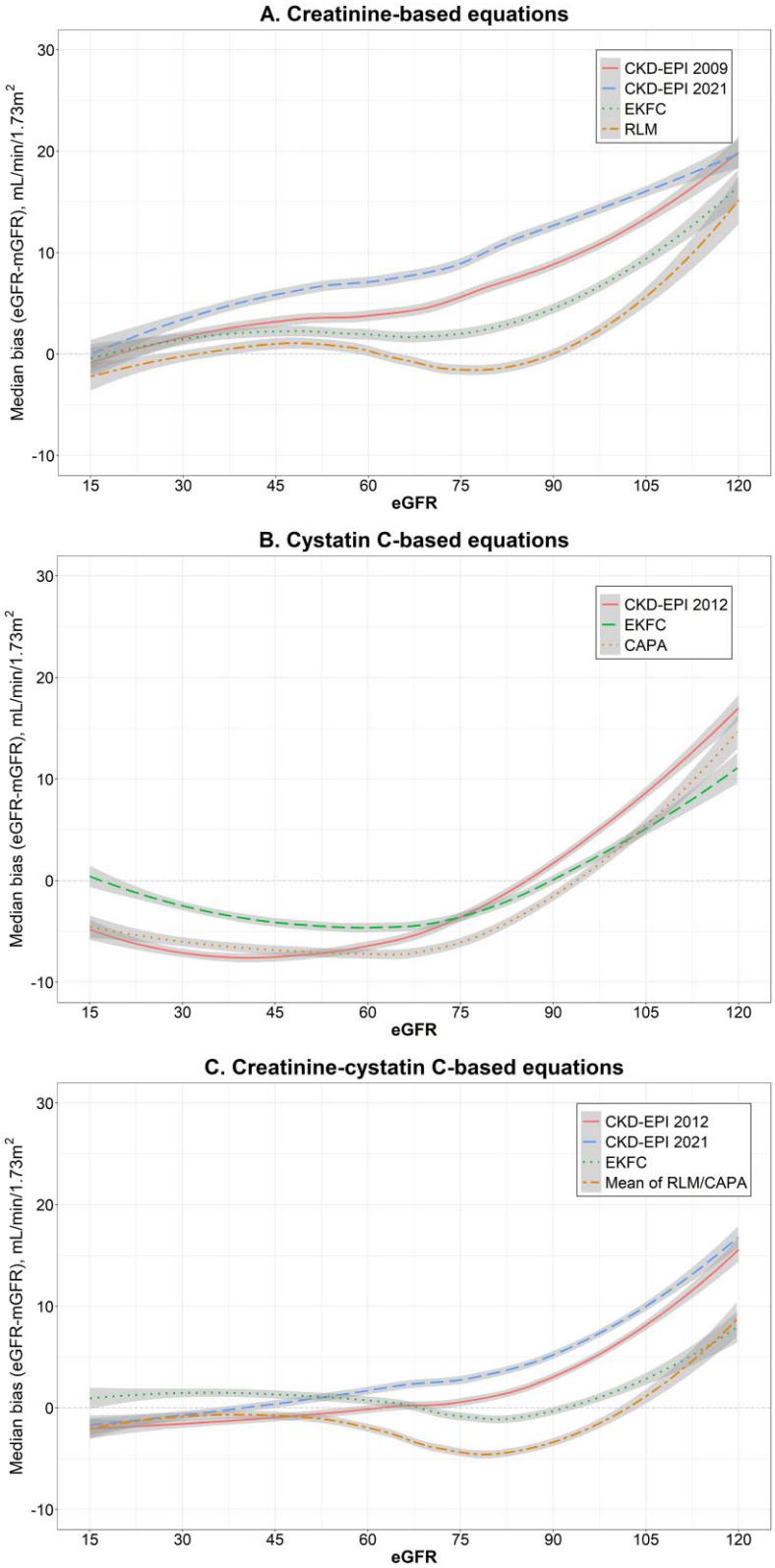


Figure 4: Bias for GFR estimating equations across continuous eGFR. The x-axis is truncated at the 2.5th and 97.5th percentiles.

implemented without necessitating a trade-off between accuracy and uniformity.

Our study highlights that variation in measurement methods used when developing the equations may be an important contributor to the variation in performance between $eGFR_{cr}$ equations. The measurement methods for GFR in SCREAM were more similar to those used for development of the EKFC and RLM equations (plasma iohexol clearance for mGFR) than for CKD-EPI equations (urinary iothalamate clearance for mGFR). Furthermore, differences also exist between single-point vs multipoint iohexol clearance [27–29]. Accounting for possible systematic difference between methods in a sensitivity analysis attenuated differences between EKFC and RLM vs CKD-EPI equations, with little effect on differences among $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ equations. However, this analysis was based on strong assumptions. Furthermore, we note that the true difference between GFR measurement methods used in these studies is unknown, and there is currently no consensus on whether such a correction should be applied. In addition, there are also differences in serum creatinine measurements between CKD-EPI (more corrected Jaffe method) and EKFC (more enzymatic assays). While there has been substantial effort to harmonize serum assays for creatinine [49, 50] and cystatin C [30, 31], residual variation remains. Variation in methods for mGFR has received less attention, and while we attempted to address potential differences between mGFR methods used for development of these equations in a sensitivity analysis, calibration of mGFR methods to urinary clearance of inulin, the reference standard, is uncertain for these and most other methods, and a direction for future research [26].

An important novelty is that our cohort included many people with comorbid conditions, such as cardiovascular disease, cancer, liver disease and diabetes. Some of these populations have been minimally included in the research cohorts in which the novel equations were developed or validated; and therefore the performance of the eGFR equations in these patients has been uncertain [18]. We showed that $eGFR_{cr\text{-}cys}$ equations had small bias and $P_{30} > 85\%$, and performed better than $eGFR_{cr}$ or $eGFR_{cys}$ equations among people at older age or who had liver disease or cancer. Our finding that $eGFR_{cr\text{-}cys}$ was more accurate than either $eGFR_{cr}$ or $eGFR_{cys}$ suggests substantial variation in non-GFR determinants of both creatinine and cystatin C in these groups. In certain patients with these comorbid conditions, $eGFR_{cr\text{-}cys}$ may thus be an acceptable alternative to measuring GFR. Furthermore, bias for GFR estimating equations was larger at the higher eGFR range than the lower eGFR range, regardless of the specific filtration marker or equation used. However, one may argue that precision is more important at low eGFR, as decision-making is often based on GFR thresholds. This overestimation was more apparent for the CKD-EPI 2021 than the 2009 equation.

The greater bias of $eGFR_{cr}$ in the younger age group for the CKD-EPI vs EKFC and RLM equations is consistent with previously reported results in the EKFC population and in Sweden, but not with results from the CKD-EPI validation study population [5, 51–54]. These findings are not explained, but may be partly due to differences in how the variable "age" is considered in the different equations [55, 56]. Furthermore, it may be another example of differences in study populations in which the equations were developed. For example, many of the young people in the CKD-EPI development population were people with type 1 diabetes participating in research studies or kidney donor candidates with higher GFR, while many of the young people in EKFC or RLM development populations may have been referred because of lower GFR associated with comorbid conditions, which may have been more likely to affect the non-GFR determinants of creatinine than cystatin C. Additional studies are needed in young adults.

Strengths and limitations

Strengths of our analysis include its large size and its routine care setting, with ample representation of comorbid conditions. As such, our study may better capture the performance of GFR estimating equations in clinical practice compared with research cohorts that included relatively healthy individuals. Furthermore, our cohort was not involved in the development or validation of any of the equations that were assessed. Lastly, Sweden has tax-funded healthcare which may minimize selection bias from disparate access to care due to lack of insurance. Our study also has limitations. First, our findings may be less generalizable to other regions as our dataset solely included patients from Stockholm, Sweden, especially regions with a greater racial and ethnic mix. Therefore, we encourage independent validation studies of the novel eGFR equations in cohorts from different geographic regions. Second, we used International Classification of Diseases, 10th revision (ICD-10) codes to define comorbid conditions such as liver disease, heart failure and cancer. Although ICD-10 codes in general have high positive predictive value, they do not capture the severity of disease. Furthermore, the patients included in our study may have had a history of comorbid conditions rather than active comorbid conditions. Third, we used single-sample plasma iohexol clearance as reference method. A previous study showed small bias compared with multisample iohexol clearance, but limits of agreement were wide [27, 29]. Nevertheless single-sample plasma iohexol is frequently used in Swedish clinical practice. Fourth, we did not know the precise indications for GFR testing. Fifth, serum creatinine in our study was measured using both modified Jaffe and enzymatic assays. Despite standardization, differences between the two may remain. Sixth, our study included measurements from routine clinical practice, and the indications for measuring GFR may have affected the performance of eGFR equations. Lastly, although the SCREAM cohort was not involved in the development or validation of the EKFC equations, EKFC included among others a cohort of 641 adult patients from Stockholm which may partly overlap with our population.

Conclusion

In conclusion, in this large routine care and independent cohort, we found that $eGFR_{cr\text{-}cys}$ equations performed better than $eGFR_{cr}$ or $eGFR_{cys}$ equations overall and in key subgroups, with little variation in performance across equations. Furthermore, there was larger variation in the performance of $eGFR_{cr}$ than $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ across equations and subgroups, likely reflecting population differences. Implementing $eGFR_{cr}$ equations in clinical practice may require a trade-off between accuracy and uniformity across regions.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

FUNDING

Research reported in this publication was supported by the Swedish Research Council and the Dutch Kidney Foundation (22OK2026). E.L.F. is supported by a Rubicon Grant from the Netherlands Organization for Scientific Research (NWO) and an internal funding grant from Karolinska Institute.

AUTHORS' CONTRIBUTIONS

E.L.F. and J.-J.C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: E.L.F., A.S.L., L.A.I. and J.-J.C. Acquisition of data: J.-J.C. Analysis and interpretation of data: all authors. Drafting of the manuscript: E.L.F. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: E.L.F. Administrative, technical or material support: all authors. Supervision: A.S.L., L.A.I. and J.-J.C.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data may be shared on reasonable request for academic research collaborations that fulfill GDPR, as well as national and institutional ethics regulations and standards by contacting J.-J.C. (juan.jesus.carrero@ki.se).

CONFLICT OF INTEREST STATEMENT

A.S.L., L.A.I., J.C. and M.E.G. were involved in the development of the CKD-EPI equations. P.D. was involved in the development of the EKFC equations, and is a consultant for Nephrolyx, which aims to develop easy-to-use iohexol measurements. None of the other authors declares relevant financial or scientific interests that would represent a conflict of interest.

REFERENCES

1. Levey AS, Grams ME, Inker LA. Uses of GFR and albuminuria level in acute and chronic kidney disease. *N Engl J Med* 2022;**386**:2120–8. https://doi.org/10.1056/NEJMra2201153
2. Levey AS, Coresh J, Tighiouart H *et al.* Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol* 2020;**16**:51–64. https://doi.org/10.1038/s41581-019-0191-y
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
4. Inker LA, Eneanya ND, Coresh J *et al.* New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. https://doi.org/10.1056/NEJMoa2102953
5. Pottel H, Bjork J, Courbebaisse M *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. https://doi.org/10.7326/M20-4366
6. Pottel H, Björk J, Rule AD *et al.* Cystatin C–based equation to estimate GFR without the inclusion of race and sex. *N Engl J Med* 2023;**388**:333–43. https://doi.org/10.1056/NEJMoa2203769
7. Delgado C, Baweja M, Burrows NR *et al.* Reassessing the inclusion of race in diagnosing kidney diseases: an interim report from the NKF-ASN Task Force. *J Am Soc Nephrol* 2021;**32**:1305–17. https://doi.org/10.1681/ASN.2021010039
8. Lucas A, Wyatt CM, Inker LA. Removing race from GFR estimates: balancing potential benefits and unintended consequences. *Kidney Int* 2021;**100**:11–3. https://doi.org/10.1016/j.kint.2021.02.017
9. Powe NR. Black kidney function matters: use or misuse of race? *JAMA* 2020;**324**:737–8. https://doi.org/10.1001/jama.2020.13378
10. Grubbs V. Precision in GFR reporting: let's stop playing the race card. *Clin J Am Soc Nephrol* 2020;**15**:1201–2. https://doi.org/10.2215/CJN.00690120
11. Gopalakrishnan C, Patorno E. Time to end the misuse of race in medicine: cases from nephrology. *BMJ* 2021;**375**:n2435. https://doi.org/10.1136/bmj.n2435
12. Gama RM, Kalyesubula R, Fabian J *et al.* NICE takes ethnicity out of estimating kidney function. *BMJ* 2021;**374**:n2159. https://doi.org/10.1136/bmj.n2159
13. Delgado C, Baweja M, Crews DC *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* 2022;**79**:268–88.e1.
14. Gansevoort RT, Anders H-J, Cozzolino M *et al.* What should European nephrology do with the new CKD-EPI equation? *Nephrol Dial Transplant* 2022;**38**:1–6. https://doi.org/10.1093/ndt/gfac254
15. Delanaye P, Vidal-Petiot E, Bjork J *et al.* Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa. *Nephrol Dial Transplant* 2023;**38**:106–18. https://doi.org/10.1093/ndt/gfac241
16. Delanaye P, Schaeffner E, Cozzolino M *et al.* 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). *Clin Chem Lab Med* 2023;**61**:44–7. https://doi.org/10.1515/cclm-2022-0928
17. Delanaye P, Pottel H, Glassock RJ. Americentrism in estimation of glomerular filtration rate equations. *Kidney Int* 2022;**101**:856–8. https://doi.org/10.1016/j.kint.2022.02.022
18. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis* 2013;**62**:595–603. https://doi.org/10.1053/j.ajkd.2013.03.027
19. Carrero JJ, Elinder CG. The Stockholm CREAtinine Measurements (SCREAM) project: fostering improvements in chronic kidney disease care. *J Intern Med* 2022;**291**:254–68. https://doi.org/10.1111/joim.13418
20. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU *et al.* The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**:659–67. https://doi.org/10.1007/s10654-009-9350-y
21. Wettermark B, Hammar N, Fored CM *et al.* The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;**16**:726–35. https://doi.org/10.1002/pds.1294
22. Ludvigsson JF, Andersson E, Ekbom A *et al.* External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450. https://doi.org/10.1186/1471-2458-11-450
23. Brooke HL, Talback M, Hornblad J *et al.* The Swedish cause of death register. *Eur J Epidemiol* 2017;**32**:765–73. https://doi.org/10.1007/s10654-017-0316-1
24. Fu EL, Evans M, Carrero JJ *et al.* Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. *BMJ* 2021;**375**:e066306. https://doi.org/10.1136/bmj-2021-066306
25. Iohexol Clearance Protocol Stockholm. https://www.karolinska.se/49eb42/globalassets/global/2-funktioner/funktion-kul/klinisk-kemi/dokument-kopplade-till-pta/belastningar-anvisningar-och-protokoll/iohexolclerarance-pt-undersokning-for-externt-bruk.pdf (6 September 2022, date last accessed).

26. Soveri I, Berg UB, Bjork J *et al.* Measuring GFR: a systematic review. *Am J Kidney Dis* 2014;**64**:411–24. https://doi.org/10.1053/j.ajkd.2014.04.010
27. Bird NJ, Peters C, Michell AR *et al.* Comparison of GFR measurements assessed from single versus multiple samples. *Am J Kidney Dis* 2009;**54**:278–88. https://doi.org/10.1053/j.ajkd.2009.03.026
28. Delanaye P, Ebert N, Melsom T *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. https://doi.org/10.1093/ckj/sfw070
29. Delanaye P, Flamant M, Dubourg L *et al.* Single- versus multiple-sample method to measure glomerular filtration rate. *Nephrol Dial Transplant* 2018;**33**:1778–85. https://doi.org/10.1093/ndt/gfx345
30. Grubb A, Blirup-Jensen S, Lindstrom V *et al.* First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med* 2010;**48**:1619–21. https://doi.org/10.1515/CCLM.2010.318
31. Karger AB, Long T, Inker LA *et al.* Improved performance in measurement of serum cystatin C by laboratories participating in the College of American Pathologists 2019 CYS Survey. *Arch Pathol Lab Med* 2022;**146**:1218–23. https://doi.org/10.5858/arpa.2021-0306-CP
32. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
33. Bjork J, Grubb A, Sterner G *et al.* Revised equations for estimating glomerular filtration rate based on the Lund-Malmo Study cohort. *Scand J Clin Lab Invest* 2011;**71**:232–9. https://doi.org/10.3109/00365513.2011.557086
34. Inker LA, Schmid CH, Tighiouart H *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;**367**:20–9. https://doi.org/10.1056/NEJMoa1114248
35. Grubb A, Horio M, Hansson LO *et al.* Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. *Clin Chem* 2014;**60**:974–86. https://doi.org/10.1373/clinchem.2013.220707
36. http://www.statistikdatabasen.scb.se/sq/117607.
37. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–266.
38. R CoreTeam. *R: a Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2021. https://www.R-project.org/.
39. Hsu CY, Yang W, Go AS *et al.* Analysis of estimated and measured glomerular filtration rates and the CKD-EPI equation race coefficient in the chronic renal insufficiency cohort study. *JAMA Netw Open* 2021;**4**:e2117080. https://doi.org/10.1001/jamanetworkopen.2021.17080.
40. Levey AS, Inker LA. GFR as the "gold standard": estimated, measured, and true. *Am J Kidney Dis* 2016;**67**:9–12. https://doi.org/10.1053/j.ajkd.2015.09.014
41. Delanaye P, Jouret F, Le Goff C *et al.* Concordance between iothalamate and iohexol plasma clearance. *Am J Kidney Dis* 2016;**68**:329–30. https://doi.org/10.1053/j.ajkd.2016.01.007
42. Seegmiller JC, Burns BE, Schinstock CA *et al.* Discordance between iothalamate and iohexol urinary clearances. *Am J Kidney Dis* 2016;**67**:49–55. https://doi.org/10.1053/j.ajkd.2015.08.020
43. Levey AS, Titan SM, Powe NR *et al.* Kidney disease, race, and GFR estimation. *Clin J Am Soc Nephrol* 2020;**15**:1203–12. https://doi.org/10.2215/CJN.12791019
44. Bukabau JB, Yayo E, Gnionsahé A *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. https://doi.org/10.1016/j.kint.2018.11.045
45. Moodley N, Hariparshad S, Peer F *et al.* Evaluation of the CKD-EPI creatinine based glomerular filtration rate estimating equation in Black African and Indian adults in KwaZulu-Natal, South Africa. *Clin Biochem* 2018;**59**:43–9. https://doi.org/10.1016/j.clinbiochem.2018.06.014
46. Fabian J, Kalyesubula R, Mkandawire J *et al.* Measurement of kidney function in Malawi, South Africa, and Uganda: a multicentre cohort study. *Lancet Glob Health* 2022;**10**:e1159–69. https://doi.org/10.1016/S2214-109X(22)00239-X
47. Delanaye P, Vidal-Petiot E, Björk J *et al.* Performance of creatinine-based equations to estimate glomerular filtration rate in white and black populations in Europe, Brazil and Africa. *Nephrol Dial Transplant* 2023;**38**:106–18. https://doi.org/10.1093/ndt/gfac241
48. Teo BW, Zhang L, Guh JY *et al.* Glomerular filtration rates in Asians. *Adv Chronic Kidney Dis* 2018;**25**:41–8. https://doi.org/10.1053/j.ackd.2017.10.005
49. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! *Nephron* 2017;**136**:302–08. https://doi.org/10.1159/000469669
50. Delanaye P, Cavalier E, Cristol JP *et al.* Calibration and precision of serum creatinine and plasma cystatin C measurement: impact on the estimation of glomerular filtration rate. *J Nephrol* 2014;**27**:467–75. https://doi.org/10.1007/s40620-014-0087-7
51. Nyman U, Grubb A, Larsson A *et al.* The revised Lund-Malmo GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. *Clin Chem Lab Med* 2014;**52**:815–24. https://doi.org/10.1515/cclm-2013-0741
52. Levey AS, Tighiouart H, Simon AL *et al.* Comparing newer GFR estimating equations using creatinine and cystatin C to the CKD-EPI equations in adults. *Am J Kidney Dis* 2017;**70**:587–89. https://doi.org/10.1053/j.ajkd.2017.04.012
53. Levey AS, Tighiouart H, Inker LA. Improving glomerular filtration rate estimation-across the age and diversity spectrum. *Ann Intern Med* 2021;**174**:265–67. https://doi.org/10.7326/M20-6983
54. Nyman U, Bjork J, Berg U *et al.* The modified CKiD study estimated GFR equations for children and young adults under 25 years of age: performance in a European multicenter cohort. *Am J Kidney Dis* 2022;**80**:807–10. https://doi.org/10.1053/j.ajkd.2022.02.018
55. Pottel H, Hoste L, Dubourg L *et al.* An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant* 2016;**31**:798–806. https://doi.org/10.1093/ndt/gfv454
56. Pottel H, Vrydags N, Mahieu B *et al.* Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. *Clin Chim Acta* 2008;**396**:49–55. https://doi.org/10.1016/j.cca.2008.06.017

Received: July 1, 2023; Editorial decision: September 4, 2023