Quantifying Individual-Level Inaccuracy in Glomerular Filtration Rate Estimation

A Cross-Sectional Study

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Background: Although the population-level differences between estimated glomerular filtration rate (eGFR) and measured glomerular filtration rate (mGFR) are well recognized, the magnitude and potential clinical implications of individual-level differences are unknown.

Objective: To quantify the magnitude and consequences of the individual-level differences between mGFRs and eGFRs.

Design: Cross-sectional study.

Setting: Four U.S. community-based epidemiologic cohort studies with mGFR.

Patients: 3223 participants in 4 studies.

Measurements: The GFRs were measured using urinary iothalamate and plasma iohexol clearance; the eGFR was calculated from serum creatinine concentration alone ($eGFR_{CR}$) and with cystatin C. All GFR results are presented as mL/min/1.73 m^2.

Results: The participants' mean age was 59 years; 32% were Black, 55% were women, and the mean mGFR was 68. The population-level differences between mGFR and $eGFR_{CR}$ were small; the median difference (mGFR − eGFR) was −0.6 (95% CI, −1.2 to −0.2); however, the individual-level differences were large. At an $eGFR_{CR}$ of 60, 50% of mGFRs ranged from 52 to 67, 80% from 45 to 76, and 95% from 36 to 87. At an $eGFR_{CR}$ of 30, 50% of mGFRs ranged from 27 to 38, 80% from 23 to 44, and 95% from 17 to 54. Substantial disagreement in chronic kidney disease staging by mGFR and $eGFR_{CR}$ was present. Among those with $eGFR_{CR}$ of 45 to 59, 36% had mGFR greater than 60 whereas 20% had mGFR less than 45; among those with $eGFR_{CR}$ of 15 to 29, 30% had mGFR greater than 30 and 5% had mGFR less than 15. The eGFR based on cystatin C did not provide substantial improvement.

Limitation: Single measurement of mGFR and serum markers without short-term replicates

Conclusion: A substantial individual-level discrepancy exists between the mGFR and the eGFR. Laboratories reporting eGFR should consider including the extent of this uncertainty to avoid misinterpretation of eGFR as an mGFR replacement.

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G lomerular filtration rate (GFR) is the standard metric for assessing and monitoring kidney function. Directly measured GFR (mGFR), the gold standard for assessing GFR, involves injecting a filtration marker and measuring plasma or urinary clearance by serial blood and urine sampling under standardized conditions. As direct GFR measurement is not practical for every patient, GFR is assessed indirectly by the serum concentrations of creatinine in routine clinical practice. However, many factors besides GFR determine serum creatinine concentrations, and formulas to calculate the measured GFR attempt to account for these factors. Clinical laboratories now routinely calculate and report an estimated GFR (eGFR) as a single number adjacent to measured serum creatinine concentration. Unfortunately, the natural tendency for clinicians and patients is then to assume that eGFR accurately reflects a person's mGFR and to use eGFR in clinical decision making, not realizing that eGFR is a prediction, not a direct measurement.

The eGFR reported for a patient is the predicted average mGFR of the people included in the formula derivation cohorts, with the patient's values for serum creatinine, age, and sex. Evaluations of the reliability of the eGFR in assessing the mGFR must consider both the average population differences between the mGFR and the eGFR and the individual-level differences (1–3). The average population difference between mGFR and eGFR is clinically negligible; among a group of people with eGFRs of, say, 60 mL/min/1.73 m^2, we expect that the average mGFR of the group will be close to that value. Unfortunately, the individual-level differences between the mGFR and the eGFR are high. For clinical decision making, clinicians need to understand the magnitude of these individual-level differences between the mGFR and the eGFR and how they apply to each patient. For example, if a person's eGFR is 60 mL/min/1.73 m^2, is their mGFR in the 59 to 61 mL/min/1.73 m^2 range, the 55 to 65 mL/min/1.73 m^2 range, or the 40 to 90 mL/min/1.73 m^2 range? However, this information is not provided with the eGFR and cannot be calculated using the estimated equations' reported accuracy metric, the P30, which is the

See also:

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percentage of eGFRs within 30% of the mGFR. When only the eGFR is available in clinical settings, P30 is uninterpretable as the mGFR is not available.

The goal of our study was to rigorously quantify the magnitude and consequences of the individual-level differences between the mGFR and the eGFR, using data from 4 U.S. community-based epidemiologic cohort studies that simultaneously assessed mGFR and eGFR.

METHODS

Data Sources

We used data from 4 U.S. prospective cohort studies. The GENOA (Genetic Epidemiology Network of Arteriopathy) study (1996 to 2011) was designed to explore the genetics of essential hypertension and associated target-organ damage among siblings with at least 2 members with hypertension. The GFR was measured in a subset of GENOA participants ($n = 1008$) in Jackson, Mississippi, and Rochester, Minnesota, from 2006 to 2011 (4). The ECAC (Epidemiology of Coronary Artery Calcification) cohort study (1984 to 2011) was designed to examine coronary artery calcification risk factors in persons without cardiovascular disease; participants were recruited from Olmsted County, Minnesota, and the GFR was measured for 406 participants during the third study visit from 2006 to 2011 (4). The ALTOLD (Assessing Long Term Outcomes in Living Kidney Donors) study (2006 to 2011) was a multicenter study designed to understand the effects of nephrectomy in living kidney donors. In ALTOLD, 200 pairs of donors and matched healthy control participants were recruited. Data on the mGFR were available for 386 participants (5). The CRIC (Chronic Renal Insufficiency Cohort) study is an ongoing prospective cohort study to examine risk factors and outcomes of patients with chronic kidney disease (CKD), enrolling participants at 7 clinical centers from 2003 to 2008 and measuring the GFR in a subcohort comprising 1423 participants (6). In the GENOA, ECAC, and ALTOLD studies, participants were not selected based on known CKD, whereas in the CRIC study, participants with known CKD were recruited. All studies were approved by the institutional review boards of the respective institutions, and all participants provided written informed consent.

GFR Measurements and Other Participant Characteristics

The GFR was directly measured using urinary clearance of nonradiolabeled iothalamate in GENOA and ECAC, radiolabeled iothalamate in CRIC, and plasma clearance of iohexol in ALTOLD (see the **Supplement**, available at Annals.org, for details). Measurement of the GFR by urinary iothalamate clearance is reliable across the entire range of GFRs, whereas the plasma iohexol clearance protocol used in the ALTOLD study of kidney donors is valid for the higher range of GFR (>60 mL/min/1.73 m^2) (7). The mGFRs from all studies were calculated in milliliters per minute and indexed to 1.73 m^2 of body surface area, calculated using the Dubois formula (8). All studies had serum creatinine and cystatin C measurements concurrent with mGFRs. Creatinine measurement

was standardized, and cystatin C was calibrated in all studies. Urine albumin and urine creatinine were available for GENOA, ALTOLD, and CRIC. Details of mGFR protocols and laboratory measurements are described in the **Supplement** Methods (available at Annals.org). Measurements of height and weight were standardized. Age, sex, race, and history of smoking were self-reported. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications. Diabetes was based on self-report, use of oral glucose–lowering medications, a fasting plasma glucose concentration of 6.99 mmol/L (126 mg/dL) or more, or random plasma glucose concentration of 11.10 mmol/L (200 mg/dL) or more. Coronary heart disease was defined as prior myocardial infarction or coronary revascularization. We did not have data from ECAC participants on diabetes, hypertension, cardiovascular disease, smoking, and urinary albumin–creatinine ratio.

eGFR Equations

We calculated the eGFR from serum creatinine (eGFR$_{CR}$) using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2021 race-free equation (9) and the European Kidney Function Consortium (EKFC) equation (3). We calculated the eGFR from serum cystatin C (eGFR$_{CYS}$) and from serum creatinine and serum cystatin C (eGFR$_{CR-CYS}$) using the CKD-EPI 2012 and 2021 equations, respectively (2, 9). The CKD-EPI equation was recently recommended for use by the American Society of Nephrology (ASN) and the National Kidney Foundation (NKF) joint task force (10). The CKD-EPI equation is only valid for adults, whereas the EKFC equation can be used for any person aged 2 years or older (3, 9).

Statistical Analysis

We summarized the characteristics of participants in each cohort, describing the frequency count (percentage) for categorical variables and the mean (minimum to maximum) values for continuous variables. We evaluated the reliability of the eGFR in estimating the mGFR at an individual level using 3 different approaches. First, we assessed the distribution of the mGFR at any given eGFR by modeling the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles of the mGFR, adjusted for cohort, by separate quantile regressions of the mGFR on the eGFR, using the qreg program in Stata (see **Supplement** Methods for details) (11). Compared to ordinary least-squares (linear) regression, which models just the mean, quantile regression can model any quantile, makes no assumptions about the distribution of the mGFR, and is less influenced by outlying values (11). From each quantile regression model, we calculated the distributions of the mGFR at guideline-defined eGFR cut points (15, 30, 45, 60, and 90 mL/min/1.73 m^2) and displayed them graphically. We defined the 95% prediction interval (PI) as the range that is expected to include approximately 95% (2.5th to 97.5th percentiles) of the mGFR values from persons with a given eGFR (12). The interpretation of 95% PI is that if there are 100 persons with a given

eGFR, 95 of them, on average, will have mGFR values that will fall within the 95% PI for that eGFR. The 95% PI of the eGFR is distinct from the 95% CI of the mean eGFR. The 95% CI of the eGFR is the range expected to contain the population-level mean eGFR 95 times if the study is repeated 100 times. We assessed the width of the 95% PI (97.5th minus 2.5th percentile) overall and by race, sex, and age subgroups. Second, we assessed the probability of large estimation errors at guideline-defined eGFR cut points. We defined large errors as individual-level differences between the mGFR and the eGFR on an absolute scale (more than ±5, ±10, and ±15 mL/min/1.73 m^2) and a relative scale (more than ±5%, ±10%, and ±15%). The absolute difference is more intuitive clinically, whereas the relative difference remains constant across the range of eGFRs. We assessed the probability that the mGFR was outside of these absolute and relative thresholds at each eGFR cut point, using separate logistic regression models of the large error (binary variable) on the eGFR, adjusted for cohort. We also explored whether any cohort characteristics were associated with extreme error, defined as the mGFR exceeding ±15% of the eGFR, using multivariable logistic regression. Finally, we assessed the effect of individual-level differences in the mGFR and the eGFR on CKD staging by comparing agreement in CKD categorization by mGFR and eGFR (13) and by displaying the distribution of the mGFR in each CKD category defined by the eGFR.

Our primary analysis compared the individual-level differences between the mGFR and the eGFR$_{CR}$. In secondary analyses, we compared the mGFR to the eGFR$_{CR-CYS}$, the eGFR$_{CYS}$, and the EKFC eGFR. To assess the effect of the recent recommendations for the routine use of cystatin C eGFR in patients with CKD (14), we identified people with eGFRs less than 60 mL/min/1.73 m^2 by both eGFR$_{CR}$ and eGFR$_{CR-CYS}$ and assessed the agreement in CKD categorization by mGFR and eGFR$_{CR}$ in this subgroup. We also report population-level differences in mGFR and eGFR (bias or median difference), precision (interquartile range of the bias), and error metrics, P10 and P30, corresponding to the percentage of eGFRs less than 10% and 30% different from mGFRs, respectively (1–3). We used bootstrapping with 2000 replacements and

Table 1. Characteristics of Study Participants by Cohort

Characteristics	Overall *n* = 3223 (100%)	GENOA *n* = 1008 (31%)	ECAC *n* = 406 (13%)	ALTOLD *n* = 386 (12%)	CRIC *n* = 1423 (44%)
Mean age (min–max), *y*	59 (19–86)	65 (38–86)	66 (39–86)	43 (19–71)	56 (21–75)
Race/Ethnicity, *n (%)*					
Non-Hispanic White	1876 (58)	519 (51)	406 (100)	366 (95)	585 (41)
Non-Hispanic Black	1021 (32)	489 (49)	0 (0)	7 (2)	525 (37)
Hispanic	215 (7)	0 (0)	0 (0)	1 (0)	214 (15)
Other	111 (3)	0 (0)	0 (0)	12 (3)	99 (7)
Sex: Female, *n (%)*	1760 (55)	677 (67)	210 (52)	253 (66)	620 (44)
CVD, *n (%)*	437 (16)	191 (19)	–*	1 (0)	245 (17)
Diabetes, *n (%)*	867 (31)	179 (18)	–	2 (1)	686 (48)
Hypertension, *n (%)*	1966 (70)	741 (74)	–	12 (3)	1213 (85)
Current smoker, *n (%)*	302 (11)	94 (9)	–	48 (13)	160 (11)
Mean height (min–max), *cm*	170 (122–201)	168 (140–201)	168 (147–201)	170 (122–198)	170 (142–196)
Mean weight (min–max), *kg*	87 (40–195)	90 (44–191)	82 (41–140)	78 (46–142)	89 (40–195)
Mean body surface area (min–max), *m²*	1.99 (1.29–3)	1.96 (1.39–2.75)	1.92 (1.39–2.45)	1.93 (1.38–2.74)	2.04 (1.29–3)
Mean BMI (min–max), *kg/m²*	31 (15–71)	32 (18–58)	29 (16–54)	27 (18–43)	31 (15–71)
Mean urine albumin–creatinine ratio (min–max), *mg/g*	51 (0–1917)	34 (2–1917)	–	6 (1–53)	70 (0–1541)
Mean serum creatinine concentration (min–max)					
μmol/L	114.9 (35.4–424.3)	79.6 (35.4–256.3)	70.7 (44.2–168.0)	70.7 (44.2–114.9)	159.1 (53.0–424.3)
mg/dL	1.3 (0.4–4.8)	0.9 (0.4–2.9)	0.8 (0.5–1.9)	0.8 (0.5–1.3)	1.8 (0.6–4.8)
Mean serum cystatin C (min–max), *mg/L*	1.1 (0.2–3.8)	0.9 (0.2–2.9)	0.9 (0.6–2.1)	0.7 (0.3–1.1)	1.5 (0.5–3.8)
mGFR, *mL/min/1.73 m²*					
Mean (min–max)	68 (9–208)	80 (20–162)	79 (20–208)	96 (12–152)	48 (9–167)
Categories, *n (%)*					
≥120	89 (3)	45 (4)	11 (3)	29 (8)	4 (0)
90–119	675 (21)	285 (28)	103 (25)	242 (63)	45 (3)
60–89	1160 (36)	516 (51)	231 (57)	111 (29)	302 (21)
45–59	537 (17)	105 (10)	46 (11)	3 (1)	383 (27)
30–44	477 (15)	45 (4)	12 (3)	0 (0)	420 (30)
15–29	267 (8)	12 (1)	3 (1)	0 (0)	252 (18)
<15	18 (1)	0 (0)	0 (0)	1 (0)	17 (1)
Mean eGFR (min–max), *mL/min/1.73 m²*					
CKD-EPI creatinine	69 (11–134)	83 (19–116)	88 (35–117)	102 (56–134)	44 (11–112)
CKD-EPI creatinine–cystatin C	74 (12–164)	88 (19–151)	89 (34–119)	113 (61–164)	51 (12–118)
CKD-EPI cystatin C	75 (13–184)	85 (18–170)	82 (26–116)	114 (61–184)	55 (13–146)
EKFC creatinine	63 (11–123)	74 (19–112)	78 (30–114)	95 (50–123)	42 (11–107)

ALTOLD = Assessing Long Term Outcomes in Living Kidney Donors; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRIC = Chronic Renal Insufficiency Cohort; CVD = cardiovascular disease; ECAC = Epidemiology of Coronary Artery Calcification; eGFR = estimated glomerular filtration rate; EKFC = European Kidney Function Consortium; GENOA = Genetic Epidemiology Network of Arteriopathy; max = maximum; mGFR = measured glomerular filtration rate; min = minimum.
* An en dash indicates information not available in the ECAC data set.

Table 2. Bias and Inaccuracy of Estimating Equations

Subgroup	Systematic Difference or Bias: mGFR − eGFR (95% CI),* mL/min/1.73 m^2	Inaccuracy: Width of 95% Prediction Interval (95% CI),† mL/min/1.73 m^2
CKD-EPI creatinine		
Overall	−0.6 (−1.2 to −0.2)	55.2 (54.7 to 55.9)
Race/Ethnicity: Black	3.7 (3.0 to 4.4)	50.4 (49.6 to 52.0)
Race/Ethnicity: White	−2.9 (−3.5 to −2.1)	56.7 (56.1 to 57.2)
Sex: Female	−1.7 (−2.6 to −0.8)	58.1 (57.4 to 58.6)
Sex: Male	0.4 (−0.2 to 1.5)	50.8 (49.9 to 51.8)
Age <65 y	−0.4 (−1.0 to 0.3)	53.2 (52.6 to 54.0)
Age ≥65 y	−1.1 (−2.3 to −0.3)	58.3 (57.6 to 59.4)
CKD-EPI creatinine–cystatin C		
Overall	−5.5 (−6.0 to −5.1)	50.8 (50.1 to 51.7)
Race/Ethnicity: Black	−3.5 (−4.3 to −2.7)	53.1 (50.8 to 54.4)
Race/Ethnicity: White	−6.5 (−7.1 to −5.9)	50.3 (49.5 to 51.2)
Sex: Female	−6.6 (−7.3 to −5.8)	54.4 (53.6 to 55.5)
Sex: Male	−4.6 (−5.2 to −3.9)	47.1 (46.5 to 48.2)
Age <65 y	−6.1 (−6.6 to −5.5)	47.9 (47.2 to 48.5)
Age ≥65 y	−4.6 (−5.5 to −3.8)	58.7 (57.7 to 59.8)
CKD-EPI cystatin C		
Overall	−5.9 (−6.7 to −5.3)	52.9 (51.9 to 54.1)
Race/Ethnicity: Black	−6.5 (−8.0 to −5.3)	59.9 (57.3 to 62.8)
Race/Ethnicity: White	−5.6 (−6.6 to −4.9)	51.2 (50.6 to 52.1)
Sex: Female	−6.3 (−7.4 to −5.3)	58.9 (57.5 to 60.3)
Sex: Male	−5.7 (−6.6 to −4.8)	49.1 (48.5 to 49.8)
Age <65 y	−8.2 (−9.0 to −7.5)	48.6 (47.8 to 49.1)
Age ≥65 y	−2.5 (−3.4 to −1.5)	66.6 (65.2 to 67.2)
EKFC creatinine		
Overall	4.5 (4.1 to 5.0)	54.0 (53.5 to 54.5)
Race/Ethnicity: Black	8.1 (7.1 to 9.0)	49.9 (48.6 to 51.0)
Race/Ethnicity: White	2.9 (2.3 to 3.5)	55.6 (54.9 to 56.0)
Sex: Female	4.2 (3.5 to 4.7)	56.4 (55.7 to 57.2)
Sex: Male	4.9 (4.3 to 5.6)	50.3 (49.7 to 50.9)
Age <65 y	3.7 (3.0 to 4.3)	53.0 (52.2 to 53.6)
Age ≥65 y	5.8 (5.1 to 6.4)	55.4 (54.5 to 56.2)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; EKFC = European Kidney Function Consortium; mGFR = measured glomerular filtration rate.
* The population-level systematic difference or bias is the median of the differences between mGFR and eGFR for each individual in the sample; note that the median of the differences (mGFR − eGFR) for each individual in the sample is different from the difference in the median eGFR and the median mGFR in the sample. The CI of the differences was calculated using the percentile method after bootstrapping with 2000 replacements.
† The width of the 95% prediction interval (PI) is a metric for individual-level differences between mGFR and eGFR. It was calculated as the median of the difference between the 97.5th and the 2.5th percentiles of mGFR, each predicted from separate quantile regression models, adjusted for cohort. The CI of the differences was calculated using the percentile method after bootstrapping with 2000 replacements.

the percentile method to calculate the 95% CIs. We used Stata 17 for these analyses.

Role of the Funding Source

RESULTS

Participant Characteristics

The mean age of the participants was 59 years, and 55% were women (**Table 1**). Non-Hispanic Black persons comprised 49% of GENOA and 37% of CRIC participants; ECAC had no non-Hispanic Black participants, and ALTOLD had 7 non-Hispanic Black participants. The mean mGFR was 68 mL/min/1.73 m^2; 764 participants (24%) had an mGFR greater than 90 mL/min/1.73 m^2 and 285 participants (9%) had an mGFR less than 30 mL/min/1.73 m^2. The mean eGFR$_{CR}$ was 69 mL/min/1.73 m^2 overall, and 83, 88, 102, and 44 mL/min/1.73 m^2 in GENOA, ECAC, ALTOLD, and CRIC, respectively.

Individual-level Differences Between the mGFR and the eGFR$_{CR}$

In the overall sample, eGFR$_{CR}$ was higher than the mGFR, with a median difference (mGFR − eGFR$_{CR}$) of −0.6 mL/min/1.73 m^2 (**Table 2**), but the pattern varied across the cohorts (**Supplement Table 1**, available at Annals.org). In contrast to this small population-level difference (systemic differences), the individual-level difference between the mGFR and the eGFR was large. The median width of 95% PI was 55 mL/min/1.73 m^2 in the

overall sample, and this pattern was seen across all of the race, age, and sex subgroups (**Table 2**). At eGFR$_{CR}$ thresholds used to define CKD stages, the distribution of the percentiles of mGFR was wide, and the 95% PI crossed 1 or more CKD stage cutoffs (**Figure 1**). For example, at an eGFR$_{CR}$ of 60 mL/min/1.73 m^2, 50% of mGFRs ranged from 52 to 67 mL/min/1.73 m^2, 80% from 45 to 76 mL/min/1.73 m^2, and 95% from 36 to 87 mL/min/1.73 m^2. The wide PI contrasts with the much narrower CI of the mean population-level difference between mGFR and eGFR$_{CR}$ (**Supplement Figure 1**, available at Annals.org). **Supplement Table 2** (available at Annals.org) provides the quantile regression coefficients used to calculate the distributions of the mGFR at a given eGFR. An online calculator is available at https://mindset.umc.edu/shiny/PredictionInterval/.

Probability of Large Differences Between the mGFR and the eGFR$_{CR}$

The large individual-level differences in mGFR and eGFR$_{CR}$ resulted in a large proportion of the participants with an mGFR outside of the ±5, ±10, and ±15 mL/min/1.73 m^2 of the eGFR$_{CR}$ (**Figure 2**, *top*).

For example, at an eGFR$_{CR}$ of 45 mL/min/1.73 m^2, 15% of the participants had an mGFR outside of the range of 30 to 60 mL/min/1.73 m^2, 30% had an mGFR outside of 35 to 45 mL/min/1.73 m^2, and 57% had an mGFR outside of 40 to 50 mL/min/1.73 m^2. A similar pattern was seen with the differences on a relative scale, and approximately half of the participants had extreme errors (exceeding ±15%) between the mGFR and the eGFR$_{CR}$ (**Figure 2**, *bottom*). The individual-level inaccuracy was also reflected in the low P10 values, which showed that in the overall sample, only 37% of eGFR$_{CRS}$ were within ±10% of mGFRs (**Supplement Table 1**). In an exploratory multivariable-adjusted model of patient characteristics associated with extreme errors (**Supplement Table 3**, available at Annals.org), non-Hispanic Black race/ethnicity was the only factor associated with extreme errors in GFR estimation (probability of extreme error, 54%).

Agreement in CKD Staging by mGFR and eGFR$_{CR}$

Substantial misclassification was noted in CKD categorization by mGFR compared with eGFR$_{CR}$ (**Table 3**). The agreement in CKD staging by mGFR and eGFR$_{CR}$ was 58% in the overall sample. Of the 42% misclassified, 22% were in a lower, and 20% were in a higher, eGFR$_{CR}$ category; the majority (39%) were misclassified by 1 category. The prevalence of the 45 to 59 mL/min/1.73 m^2 category was similar by eGFR$_{CR}$ (16%) and mGFR (17%). However, the agreement between the eGFR$_{CR}$ and mGFR categories was only 44%. Among those with eGFR$_{CR}$ in the 45 to 59 mL/min/1.73 m^2, 36% had an mGFR greater than 60 mL/min/1.73 m^2 and 20% had an mGFR less than 45 mL/min/1.73 m^2. Similarly, among those with an eGFR$_{CR}$ of 15 to 29 mL/min/1.73 m^2, 30% had an mGFR greater than 30 mL/min/1.73 m^2 and 5% had an mGFR less than 15 mL/min/1.73 m^2. The distribution of mGFR within each category of eGFR$_{CR}$ was wide

(**Figure 3**), with an overlapping distribution of mGFR between non-Hispanic Black and non-Black persons.

Other eGFR Equations

The eGFR equations using cystatin C had a narrower range of distribution of mGFR than eGFR$_{CR}$ (**Supplement Figures 2** and **3**, available at Annals.org), but the PI was still quite wide overall and in subgroups (**Table 2**). The probability of large errors (**Supplement Figures 4** and **5**, available at Annals.org) and agreement with CKD staging by mGFR (**Table 3**; **Supplement Table 4**, available at Annals.org) using cystatin C equations were not substantially different from eGFR$_{CR}$. Findings were similar using the EKFC creatinine equation (**Table 2**; **Supplement Table 4** and **Supplement Figures 6** and **7**, available at Annals.org).

Other Analyses

To assess the role of simultaneous serum creatinine and cystatin C testing, we identified a subgroup of 1089

Figure 1. Distribution of mGFR at selected eGFR$_{CR}$ thresholds in 3223 participants of 4 cohort studies.
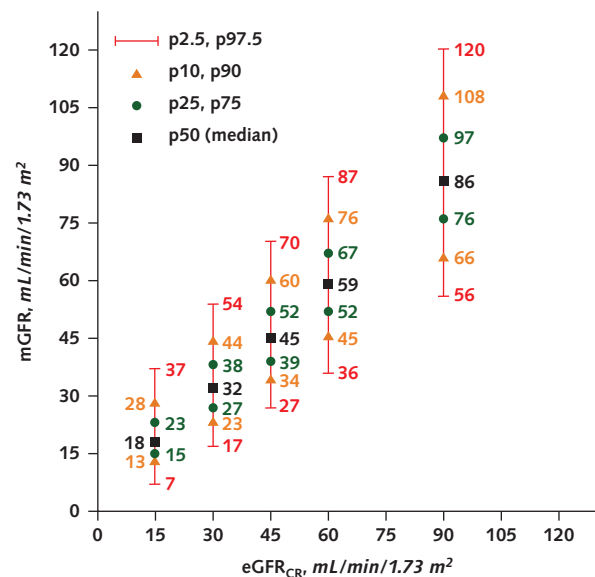
The eGFR$_{CR}$ is calculated from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) race-free creatinine equation, and the selected values (15, 30, 45, 60, and 90 mL/min/1.73 m^2) correspond to the guideline-recommended thresholds for chronic kidney disease (CKD) staging. The 4 cohorts with mGFR are GENOA (Genetic Epidemiology Network of Arteriopathy), ALTOLD (Assessing Long Term Outcomes in Living Kidney Donors), ECAC (Epidemiology of Coronary Artery Calcification), and CRIC (Chronic Renal Insufficiency Cohort). The symbols in the figure identify the percentiles of mGFR at a given eGFR$_{CR}$. Each percentile value is from a separate quantile (2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th) regression model of mGFR on eGFR$_{CR}$, adjusted for cohort, followed by calculation of the corresponding percentile of mGFR for the eGFR$_{CR}$ thresholds. The interpretation of the percentiles is that at a given eGFR, 50% of mGFRs range from the 25th to 75th percentiles, 80% from the 10th to 90th percentiles, and 95% from the 2.5th to 97.5th percentiles. Conversely, at a given eGFR, 50% of the mGFR are outside of the 25th to 75th percentiles range, 20% are outside of the 10th to 90th percentiles range, and 5% are outside of the 2.5th to 97.5th percentiles range. eGFR$_{CR}$ = glomerular filtration rate estimated from serum creatinine; mGFR = measured glomerular filtration rate.

Figure 2. Probability of discrepancy between mGFR and eGFR$_{CR}$ at selected eGFR$_{CR}$ thresholds.
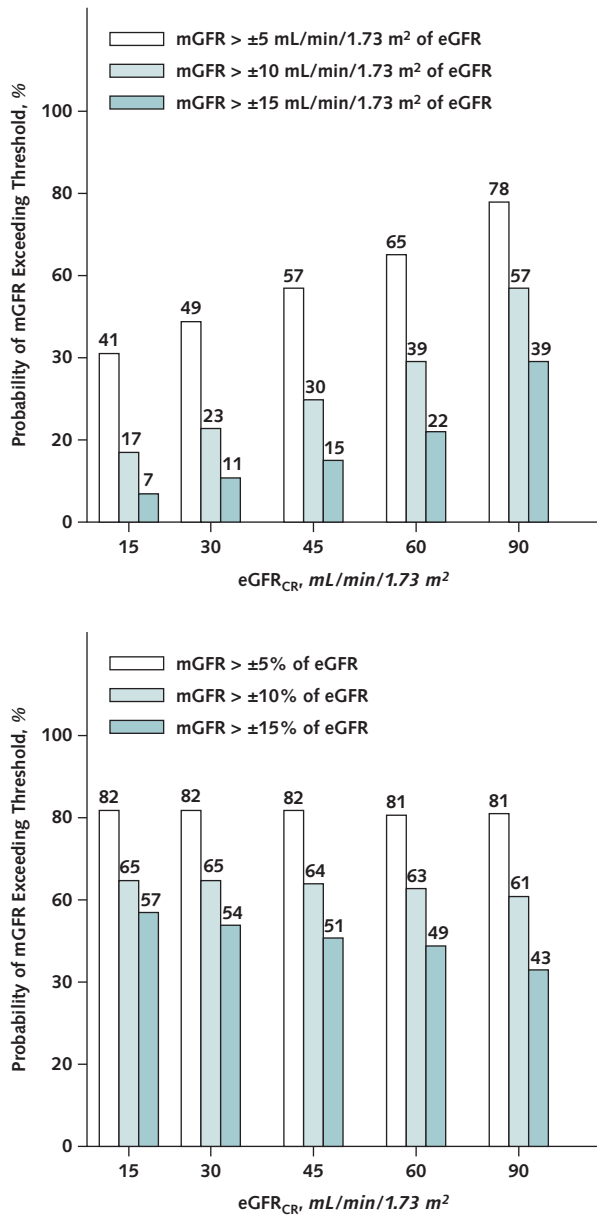
The eGFR$_{CR}$ is calculated from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) race-free creatinine equation, and the selected values (15, 30, 45, 60, and 90 mL/min/1.73 m^2) correspond to the guideline-recommended thresholds for CKD staging. eGFR$_{CR}$ = glomerular filtration rate estimated from serum creatinine; mGFR = measured glomerular filtration rate. Each vertical bar corresponds to the probability that mGFR exceeds the eGFR$_{CR}$ plus or minus a certain range on an absolute scale (*top*) or a relative scale (*bottom*). A difference greater than ±5 mL/min/1.73 m^2 implies that at a given eGFR, the mGFR is outside of a 10 mL/min/1.73 m^2 range of the eGFR value; ±10 corresponds to a range of 20 mL/min/1.73 m^2 and ±15 to a range of 30 mL/min/1.73 m^2. On the relative scale, the percent difference remains constant across the range of eGFRs. However, the same absolute difference, say 10 mL/min/1.73 m^2, is a much smaller percent difference at a higher eGFR (for example, eGFR of 60 mL/min/1.73 m^2) than at a lower eGFR (for example, eGFR of 30 mL/min/1.73 m^2).

persons with both eGFR$_{CR}$ and eGFR$_{CR-CYS}$ less than 60 mL/min/1.73 m^2 (**Supplement Table 4**). However, the agreement in CKD staging by mGFR versus eGFR$_{CR}$ was not substantially higher even in this subset.

DISCUSSION

In this study of 3223 persons with a broad spectrum of mGFRs, our key finding is the substantial individual-level differences between the mGFR and the eGFR. These differences are underappreciated by focusing on only the population-level differences (bias) and are not considered when the eGFR is reported as a single number and substituted for the mGFR in clinical decision making. For example, at an eGFR$_{CR}$ of 60 mL/min/1.73 m^2, the median mGFR was 59 mL/min/1.73 m^2, a clinically insignificant population-level difference. However, for a person with an eGFR$_{CR}$ of 60 mL/min/1.73 m^2, 95% of the directly measured GFRs are expected to range from as low as 36 mL/min/1.73 m^2 to as high as 87 mL/min/1.73 m^2, values ranging from stage 3B CKD to no CKD. These differences between the mGFR and the eGFR resulted in only approximately 50% agreement between CKD stages based on the mGFR versus the eGFR. Individual-level differences between the mGFR and the eGFR did not improve substantially with cystatin C.

Several factors contribute to the considerable differences between mGFR and eGFR noted in our study. First, the key inputs in the eGFR calculations, creatinine and cystatin C, have non-GFR factors influencing their serum concentration. Serum creatinine concentration is influenced by muscle mass, cooked meat intake, and fasting status, and both serum creatinine and cystatin C concentrations are influenced by obesity (15–17). Second, variability in the mGFR can result from normal physiology and measurement error from mGFR markers (for example, hepatic clearance of iothalamate or iohexol) or mGFR technique (for example, bladder emptying) (17–19). Third, as GFR estimation in mL/min/1.73 m^2 models the ratio, mGFR/body surface area × 1.73, as a function of serum markers, it incorporates errors in mGFR and errors in body surface area estimation from height and weight. A combination of these factors, which may vary from patient to patient, likely contributes to the large individual-level differences in mGFR and eGFR noted in our study.

The individual-level differences between the mGFR and the eGFR are well recognized (12, 15, 20, 21) but have not been rigorously analyzed. In clinical practice, the only reason to calculate the eGFR is to assess the GFR, and thus the expected range of the mGFR at a calculated eGFR has direct relevance to patient care. Unfortunately, the commonly reported eGFR metrics, bias, precision, and P30 do not provide this information. Both bias and precision are population-level metrics and cannot be translated readily for individual patients. The accuracy metric P30 is uninterpretable in the clinical setting where the mGFR is unavailable. In this context, our study provides a rigorous analysis of the individual-level differences between the mGFR and the eGFR. We describe the distribution of the mGFR at clinically relevant thresholds and provide options to calculate the possible ranges of the mGFR at a given eGFR.

Our findings have implications for individualized patient care (precision medicine) and population health. From a patient care perspective, we noted that the errors in eGFR included both underestimation and overestimation. Underestimation (eGFR is lower than mGFR) may exclude patients from receiving optimal therapies, such as guideline-directed medical therapy for heart failure and anticancer drugs (22, 23). Conversely, overestimation (eGFR is higher than mGFR) may result in patients experiencing more hyperkalemia from mineralocorticoid antagonists and toxicity from renally cleared chemotherapy. Similarly, living donor nephrectomy based on eGFR alone can be problematic. Stage 3A CKD without albuminuria (albumin–creatinine ratio <30 mg/g), with a U.S. prevalence of 7.5 million adults, is defined solely based on an $eGFR_{CR}$ between 45 and 59 mL/min/1.73 m^2. In our study, 36% of the people with an $eGFR_{CR}$ of 45 to 59 mL/min/1.73 m^2 had an mGFR greater than 60 mL/min/1.73 m^2. The use of the $eGFR_{CR-CYS}$ did not lead to a substantial change in misclassification. Thus, using only the eGFR to classify people as CKD 3A needs to be reexamined (20, 24). From a population health perspective, the eGFR is an excellent metric, providing many opportunities for population health interventions (25). Given the considerable individual-level difference between the mGFR and the eGFR, it might be worth redefining the eGFR as a population health metric, such as the "population average GFR (paGFR)," to continue its use in population health strategies without implying that it is a replacement for the mGFR. This approach will be consistent with the recent U.S. Food and Drug Administration (FDA) recommendation to use "Glucose Management Indicator," or GMI, instead of estimated A_{1c} for A_{1c} calculated from continuous glucose-monitoring data (26).

The issues with the inclusion of race in eGFR while making individual treatment decisions have been intensely debated. In our study, the population-level racial differences between the mGFR and the $eGFR_{CR}$ were minor (<5 mL/min/1.73 m^2) compared with the sizeable individual-level differences (95% PI, >50 mL/min/1.73 m^2), suggesting that the differences among people in each race group far exceed differences between groups. These findings suggest that making the mGFR widely available should be considered a priority as race, sex, age, and socioeconomic factors should not cause errors in GFR measurement.

Some limitations of our study deserve mention. First, we had a single measurement of the mGFR and serum markers without short-term replicate measurements, so we cannot quantify the different sources of variability contributing to the individual-level estimation error. Second, data from CRIC—but not ALTOLD, GENOA, or ECAC—were previously used for CKD-EPI equation development. This could minimize the observed differences, and the discrepancy between the mGFR and the eGFR may be even larger in clinical settings. However, these limitations are counterbalanced by several notable strengths of our study, including selection of diverse, community-based research cohorts with the mGFR, participants with and without CKD, and a wide range of mGFRs.

Our findings highlight the need to make direct GFR measurements available to patients who need them. Advances in nonisotopic (nonradiolabeled) GFR measurement techniques have made GFR measurement a simple and highly feasible outpatient procedure (27, 28). These measurements have been extensively used in thousands of people and have an excellent safety profile. Thus, the adage that "GFR

Table 3. Agreement Between CKD Staging by mGFR and eGFR

| eGFR	mGFR, mL/min/1.73 m^2 (%)						
	≥90	60–89	45–59	30–44	15–29	<15	Total*
$eGFR_{CR}$, mL/min/1.73 m^2†							
≥90	**579 (59)‡**	360 (37)	29 (3)	6 (1)	–§	–	974 (30)
60–89	179 (19)	**592 (64)‡**	126 (14)	20 (2)	4 (0.4)	1 (0.1)	922 (29)
45–59	6 (1)	177 (35)	**220 (44)‡**	89 (18)	8 (2)	1 (0.2)	501 (16)
30–44	–	29 (5)	159 (30)	**284 (53)‡**	66 (12)	–	538 (17)
15–29	–	2 (1)	3 (1)	78 (28)	**185 (65)‡**	15 (5)	283 (9)
<15	–	–	–	–	4 (80)	**1 (20)‡**	5 (0.2)
Total*	764 (24)	1160 (36)	537 (17)	477 (15)	267 (8)	18 (1)	3223 (100)
$eGFR_{CR-CYS}$, mL/min/1.73 m^2†							
≥90	**658 (58)‡**	435 (38)	27 (2)	10 (1)	1 (0.1)	1 (0.1)	1132 (35)
60–89	82 (9)	**615 (67)‡**	197 (21)	20 (2)	5 (1)	–	919 (29)
45–59	3 (1)	88 (19)	**227 (49)‡**	140 (30)	8 (2)	1 (0.2)	467 (15)
30–44	–	13 (3)	82 (18)	**271 (60)‡**	85 (19)	1 (0.2)	452 (14)
15–29	–	1 (0.5)	1 (0.5)	35 (16)	**165 (76)‡**	14 (6)	216 (7)
<15	–	–	–	–	2 (67)	**1 (33)‡**	3 (0.1)
Total*	743 (23)	1152 (36)	534 (17)	476 (15)	266 (8)	18 (1)	3189 (100)

CKD = chronic kidney disease; eGFR = estimated GFR; $eGFR_{CR}$ = eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation; $eGFR_{CR-CYS}$ = eGFR calculated using the CKD-EPI creatinine and cystatin C equation; GFR = glomerular filtration rate; mGFR = measured GFR.
* The percent values (%) in the Total row and column correspond to the cell value as a percentage of the total participant *n*.
† The *n* and percent values (%) for each eGFR category (rows) correspond to the row percent corresponding to the mGFR category in the columns. For example, there are 501 participants with $eGFR_{CR}$ 45–59 mL/min/1.73 m^2, and 220/501 (44%) had mGFR in the same category as $eGFR_{CR}$.
‡ These values, presented diagonally, represent agreement in CKD staging by mGFR and $eGFR_{CR}$.
§ An en dash indicates zero participants.

Figure 3. Distribution of mGFR for people in guideline-defined eGFR categories.
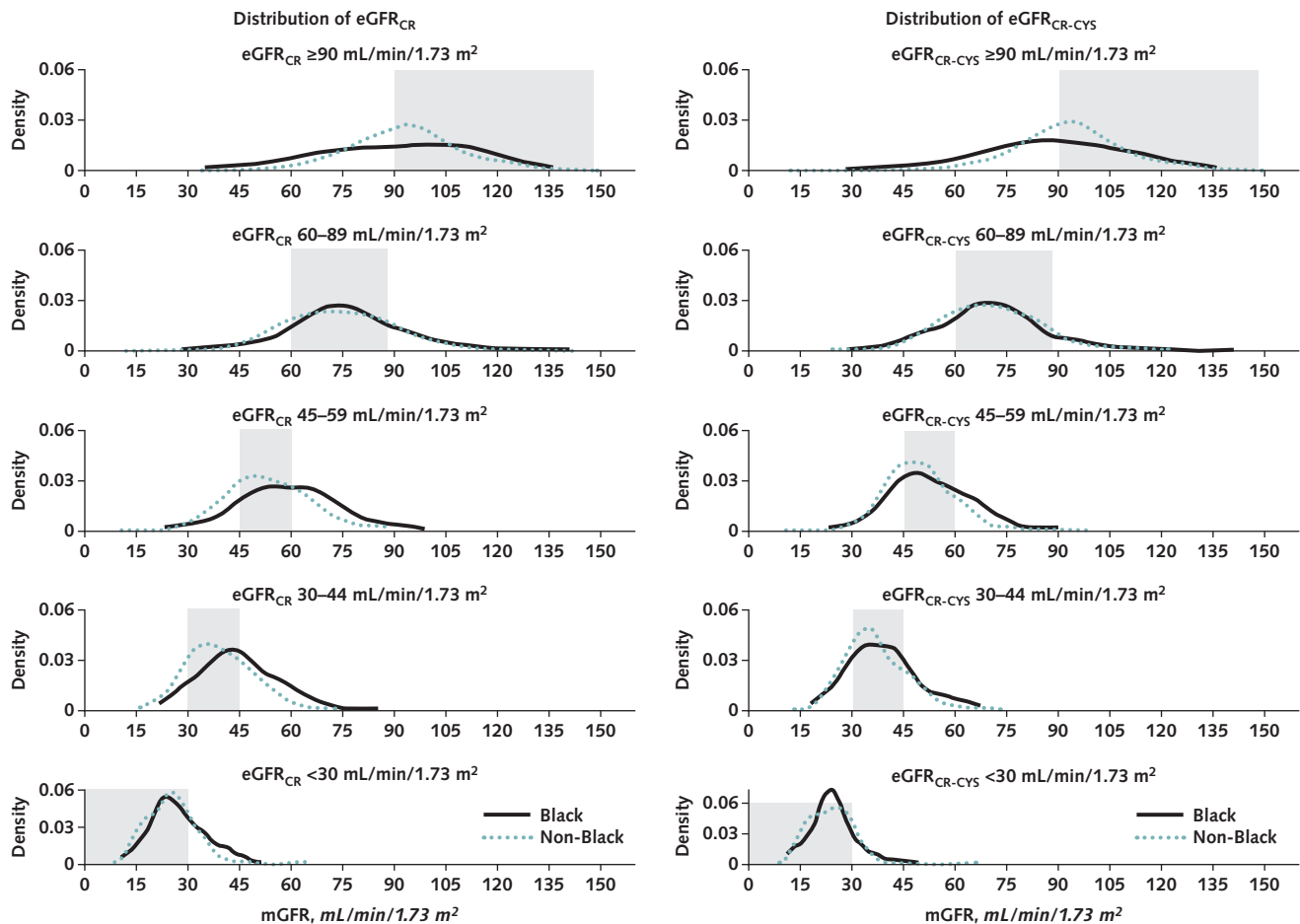
The shaded gray area represents the guideline-defined estimated glomerular filtration rate (eGFR) categories used for chronic kidney disease staging. The lines represent the distribution of mGFR for people in each eGFR category. **Left.** The distribution of eGFR$_{CR}$. **Right.** The distribution of eGFR$_{CR-CYS}$. eGFR$_{CR}$ = glomerular filtration rate estimated from serum creatinine; eGFR$_{CR-CYS}$ = eGFR from serum creatinine and serum cystatin C; mGFR = measured GFR.

measurement is a cumbersome procedure" no longer holds (29). Implementation studies are needed in this area, and research is needed to assess how the availability and use of mGFRs change clinical management.

In conclusion, we found that the individual-level differences between the mGFR and the eGFR are substantial. Laboratory reports that provide eGFR calculations should consider including the distribution of this uncertainty. Clinicians need to recognize that the eGFR is not an mGFR replacement and consider eGFR's inaccuracy while managing individual patients. Renaming the eGFR as a population average GFR (or paGFR) merits further discussion.

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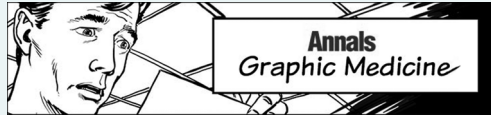
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