Kidney Medicine

Discordance Between Creatinine-Based and Cystatin C–Based Estimated GFR: Interpretation According to Performance Compared to Measured GFR

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Rationale & Objective: Use of cystatin C in addition to creatinine to estimate glomerular filtration rate (estimated glomerular filtration rate based on cystatin C [eGFRcys] and estimated glomerular filtration rate based on creatinine [eGFRcr], respectively) is increasing. When eGFRcr and eGFRcys are discordant, it is not known which is more accurate, leading to uncertainty in clinical decision making.

Study Design: Cross-sectional analysis.

Setting & Participants: Four thousand fifty participants with measured glomerular filtration rate (mGFR) from 12 studies in North America and Europe.

Exposures: Serum creatinine and serum cystatin C.

Outcome(s): Performance of creatinine-based and cystatin C–based glomerular filtration rate estimating equations compared to mGFR.

Analytical Approach: We evaluated the accuracy of eGFRcr, eGFRcys, and the combination (eGFRcr-cys) compared to mGFR according to the magnitude of the difference between eGFRcr and eGFRcys (eGFRdiff). We used CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations to estimate glomerular filtration rate. eGFRdiff was defined as eGFRcys minus eGFRcr and categorized as less than −15, −15 to <15, and ≥15 mL/min/1.73 m^2 (negative, concordant, and positive groups, respectively). We compared bias (median of mGFR minus eGFR) and the percentage of eGFR within 30% of mGFR.

Results: Thirty percent of participants had discordant eGFRdiff (21.0% and 9.6% negative and positive eGFRdiffs, respectively). In the concordant eGFRdiff group, all equations displayed similar accuracy. In the negative eGFRdiff groups, eGFRcr had a large overestimation of mGFR (−13.4 [−14.5 to −12.2] mL/min/1.73 m^2) and eGFRcys had a large underestimation (9.9 [9.1-11.2] mL/min/1.73m^2), with opposite results in the positive eGFRdiff group. In both negative and positive eGFRdiff groups, eGFRcr-cys was more accurate than either eGFRcr or eGFRcys. These results were largely consistent across age, sex, race, and body mass index.

Limitations: Few participants with major comorbid conditions.

Conclusions: Discordant eGFRcr and eGFRcys are common. eGFR using the combination of creatinine and cystatin C provides the most accurate estimates among persons with discordant eGFRcr or eGFRcys.

Visual Abstract included

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Accurate assessment of glomerular filtration rate (GFR) is essential in clinical practice, research, and public health. Serum creatinine is measured routinely in clinical practice as part of basic metabolic panels, but estimated GFR based on creatinine (eGFRcr) is not sufficiently accurate in all clinical settings. Current guidelines for GFR evaluation therefore recommend eGFRcr as the initial test and estimated GFR from cystatin C (eGFRcys) or in combination with creatinine (eGFRcr-cys) as confirmatory tests in settings where creatinine is known to be less accurate or where a more accurate GFR estimate is required for clinical decision making.[1,2] Recent recommendations from 2 US national kidney disease organizations recommend race-free GFR estimating equations and more frequent use of equations using cystatin C because there are smaller differences between race groups using GFR estimates that include cystatin C than GFR estimates that use creatinine alone.[3] With more frequent use of cystatin C, clinicians will commonly encounter discordance between eGFRcr and eGFRcys, and how these discordances should be interpreted is not well appreciated.[4–6]

A large difference between eGFRcr and eGFRcys (eGFRdiff) indicates a large error in either eGFRcr, eGFRcys or both and is due to the presence of factors other than GFR that affect serum creatinine or cystatin C. These factors often reflect the health of the individual and include muscle or fat mass, activity level, or chronic inflammation.[1,7–16] Studies in multiple cohorts demonstrate that lower levels of eGFRcys relative to those of eGFRcr are associated with increased risk of frailty, heart failure hospitalizations, cardiovascular disease events, kidney failure, and mortality.[17–29] Thus, a discordance between eGFRcr and eGFRcys provides valuable prognostic information about various health outcomes, which can inform care for an individual patient in a clinical encounter. Measured GFR (mGFR) was not available in those studies. Thus, in settings of discordance between eGFRcys and eGFRcr, where it is known that eGFRcys is a better prognostic indicator

PLAIN-LANGUAGE SUMMARY

Glomerular filtration rate (GFR) estimation using both creatinine and cystatin C together is the most accurate. It is not known whether this is true when there is a large difference between estimates based on each marker alone. To evaluate this gap in clinical knowledge, we used existing data from studies conducted in North America and Europe. We grouped all participants based on the difference between GFR estimated using creatinine and cystatin C alone. We found that ~30% of all participants had large differences between the 2 estimates. We observed that GFR estimated using both markers was the most accurate, even in the group with large differences between estimates using each marker alone. This finding supports recommendations to measure cystatin C more frequently.

than eGFRcr, it remains unknown whether or not eGFRcys is a more accurate estimate for mGFR. The answer to this question is necessary for optimal GFR-based clinical decision making.

In this study, we evaluated the accuracy of eGFRcr, eGFRcys and eGFRcr-cys compared with mGFR, stratified by concordance or discordance between eGFRcr and eGFRcys in the overall study population as well as in key subgroups. Our hypothesis was that eGFRcr-cys would be more accurate than either eGFRcr or eGFRcys irrespective of the magnitude or direction of the difference between them.

METHODS

Study Design, Population, and Laboratory Methods

This was a cross-sectional analysis of the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 external validation dataset, which included 4,050 participants from 12 studies (Table S1; Item S1).[30] The studies represent diverse populations of ambulatory individuals across a broad range of age and mGFR, with and without chronic kidney disease (CKD), diabetes, and infection with human immunodeficiency virus. Importantly, these are different studies than those in which the CKD-EPI equations were developed, thus allowing for unbiased evaluation. All studies have been previously reported.[31-43]

As previously described, GFR was measured using plasma or urinary clearance of exogenous filtration markers (Table S1).[30] The serum creatinine assays were either calibrated or measured on the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd), traceable to National Institute Standardized Technology creatinine standard reference material 96712. Serum cystatin C assays were calibrated or measured using methods traceable to International Federation for Clinical Chemists Working Group for the Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements certified reference materials.

Informed consent was waived as this study was a secondary analysis of existing deidentified data. The institutional review boards at all participating institutions approved each study, and the institutional review board at Tufts Medical Center approved the overall analyses (IRB #10533).

Estimated GFR Equations and Definition of eGFRdiff

Estimated GFR (eGFR) was calculated using the race-free 2021 CKD-EPI creatinine equation (eGFRcr), 2012 cystatin C equation (eGFRcys), and 2021 creatinine-cystatin C equation (eGFRcr-cys).[30,44] In sensitivity analysis, we also computed the average of eGFRcr and eGFRcys equations. For purposes of comparison for countries outside of the United States, where many continue to use the 2009 CKD-EPI creatinine and 2012 creatinine-cystatin C equations omitting the Black race coefficient in computation of the GFR, we also included these equations with the eGFR computed in this manner.[44-46]

The difference between eGFRcr and eGFRcys was expressed on both the raw and percent scales. The raw difference can be easily computed in a clinical setting, whereas the percent difference allows for comparison to prior studies and allows for a more stable impact across the range of GFR.[6] On the raw scale, eGFR difference (eGFRdiff) was defined as eGFRcys minus eGFRcr, where a positive value indicated a higher eGFRcys and a negative value indicated a lower eGFRcys, relative to the eGFRcr. eGFRdiff was categorized as "concordant" and "discordant" if it was −15 to <15 mL/min/1.73 m^2 or not, respectively, and "negative" or "positive" if it was less than −15 mL/min/1.73m^2 or ≥15 mL/min/1.73 m^2, respectively. The threshold was selected to be consistent with thresholds defined previously and consistent with 1 standard deviation of the difference in our dataset.[18] The concordant group was used as the reference. Percent eGFRdiff was calculated as ([eGFRcys − eGFRcr]/eGFRcr) × 100% and categorized as "negative" less than −20%, "concordant" −20% to 20%, and "positive" ≥20%, consistent with previously defined thresholds and corresponding approximately to thresholds on the raw scale at the mean level of GFR in our dataset.[4-6,47]

Statistical Analysis

The goal of our analyses was to compare the performance of eGFRcr and eGFRcys compared with mGFR stratified by groups of eGFRdiff.

The baseline characteristics of participants were compared between negative and positive eGFRdiff categories using a 2-sample *t* test (for means) or χ^2 test (for proportions), as appropriate. Lowess curves were used to describe the associations between eGFRdiff and percent eGFRdiff versus level of eGFRcr, eGFRcys, eGFRcr-cys, and mGFR.

The performance of eGFR equations was assessed using metrics of bias (systematic error), precision, accuracy, and agreement between eGFR and mGFR categories.[30,44] Bias was expressed as the median difference in mGFR minus eGFR, with positive values indicating an underestimation of mGFR.[48] Precision was assessed using the interquartile range (IQR) of the differences between mGFR and eGFR. Accuracy combines both bias and precision and was assessed by the percentage of participants with eGFR within 30% of mGFR (P_{30}). Agreement was assessed between eGFR and mGFR categories (<30, 30-59, 60-89 and ≥90 mL/min/1.73 m^2). P_{30} from 75%-80% to 90% has been considered to be adequate for decision making in many clinical circumstances; P_{30} >90% is considered optimal.[1] In past studies, agreement between GFR categories of 60%-70% corresponds approximately to P_{30} of 80%-90% and agreement of more than 70% corresponds approximately to P_{30} of >90%, respectively.[2,44,46] An improvement in bias IQR was indicated by a smaller value, and an improvement in P_{30} and concordance was indicated by a larger value. Confidence intervals were calculated by bootstrap methods using 2,000 replicating samples.

The performance was evaluated in subgroups of age (<40, 40-<65, ≥65 years), sex (male and female), race (Black and non-Black) and body mass index (BMI) (<20, 20-<25, 25-<30, ≥30 kg/m^2) using the metrics of bias and P_{30}. Differential bias within subgroups leads to lesser accuracy in the overall study population. Analyses were conducted using SAS 9.4 (SAS Institute, Inc) and R version 3.6.1 (R Foundation for Statistical Computing).

RESULTS

In the pooled dataset, the mean age was 57.0 ± 17.4 (standard deviation) years, 38.4% were female, 33.5% had diabetes, the mean BMI was 26.9 ± 5.0 kg/m^2, and the mean mGFR was 76.4 ± 29.6 mL/min/1.73 m^2 (Fig S1; Table 1).

In the overall cohort, the mean eGFRdiff was −3.8 ± 15.3 mL/min/1.73 m^2. A total of 2,811 (69.4%) participants had concordant eGFRcr and eGFRcys (reference group), 851 (21.0%) had lower eGFRcys compared with eGFRcr (negative eGFRdiff group), and 388 (9.6%) had higher eGFRcys compared with eGFRcr (positive eGFRdiff group) (Table 1). The mean eGFRdiff in the concordant and negative and positive groups was −1.3 ± 7.7, 24.5 ± 8.8, and 24.0 ± 7.7 mL/min/1.73 m^2, respectively (Fig 1). In the overall cohort, the mean percent eGFRdiff was −3.8% ± 21.5%. A total of 66.5%, 21.9%, and 11.7% participants had concordant, negative, and positive percent eGFRdiff, respectively (Table S2).

Compared with the concordant group, participants in the negative eGFRdiff group were older, had a higher BMI, and were less likely to be Black individuals. Participants in the positive eGFRdiff group were younger, were more likely to be Black individuals, and were less likely to have diabetes (Table 1). As expected, individuals with higher versus lower levels of eGFRcr were more likely to have a negative eGFRdiff whereas individuals with higher versus lower levels of eGFRcys were more likely to have a positive eGFRdiff (Fig S2; Table 1). Similar results were observed when using percent eGFRdiff categories (Fig S3; Table S2).

The performance of the 3 eGFR equations according to eGFRdiff is presented in Tables 2, S3, and S4. As previously reported, in the overall group, eGFRcr and eGFRcys had

Table 1. Baseline Characteristics Stratified by eGFRdiff (eGFRcys − eGFRcr) Groups

		eGFRdiff Group (eGFRcys-eGFRcr)			
	Overall	Negative (Less Than −15) (eGFRcr Higher)	Concordant (−15 to <15)	Positive (≥15) (eGFRcys Higher)	*P* value
Participants, N	4,050 (100%)	851 (21.0%)	2,811 (69.4%)	388 (9.6%)	
Age, y	57.0 ± 17.4	60.4 ± 17.3	57.1 ± 17.5	48.7 ± 13.8	<0.001
Female	1,557 (38.4%)	314 (36.9%)	1,111 (39.5%)	132 (34.0%)	0.9
Race (Black)	579 (14.3%)	78 (9.20%)	359 (12.8%)	142 (36.6%)	<0.001
Smoking (Yes)	430 (10.6%)	136 (16.0%)	258 (9.20%)	36 (9.3%)	0.70
BMI, kg/m^2	26.9 ± 5.0	27.6 ± 5.6	26.8 ± 4.7	26.6 ± 4.8	0.004
Weight, kg	79.0 ± 16.5	80.6 ± 17.9	78.5 ± 16.1	79.6 ± 15.8	0.35
Diabetes	1,357 (33.5%)	279 (32.8%)	980 (34.9%)	98 (25.3%)	0.09
mGFR	76.4 ± 29.6	74.2 ± 23.4	75.3 ± 31.8	89.1 ± 20.8	<0.001
eGFRcr	78.8 ± 27.3	86.8 ± 19.7	76.5 ± 29.9	78.3 ± 17.2	<0.001
eGFRcys	75.0 ± 29.4	62.3 ± 18.5	75.1 ± 30.8	102.4 ± 17.7	<0.001
eGFRcr-cys	78.4 ± 28.7	73.8 ± 19.3	77.7 ± 31.5	93.3 ± 18.1	<0.001
eGFRdiff	−3.8 ± 15.3	−24.5 ± 8.8	−1.3 ± 7.7	24.0 ± 7.7	NA
%eGFRdiff	−3.8 ± 21.5	−29.1 ± 9.5	−1.3 ± 14.7	32.9 ± 15.9	NA

Note: Data are presented as mean ± standard deviation or n (%). *P* value for positive eGFRdiff versus negative eGFRdiff. Missing values: smoking, 1,878; BMI, 6; weight, 3; diabetes, 434. Units for eGFRcr, eGFRcys, eGFRcr-cys and mGFR are mL/min/1.73 m^2.
Abbreviations and definitions: BMI, body mass index; mGFR, measured glomerular filtration rate; eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcys, estimated glomerular filtration rate based on cystatin C; eGFRcr-cys, estimated glomerular filtration rate based on creatinine and cystatin C; NA, not applicable; eGFRdiff, difference between estimated glomerular filtration rate based on creatinine and estimated glomerular filtration rate based on cystatin C.

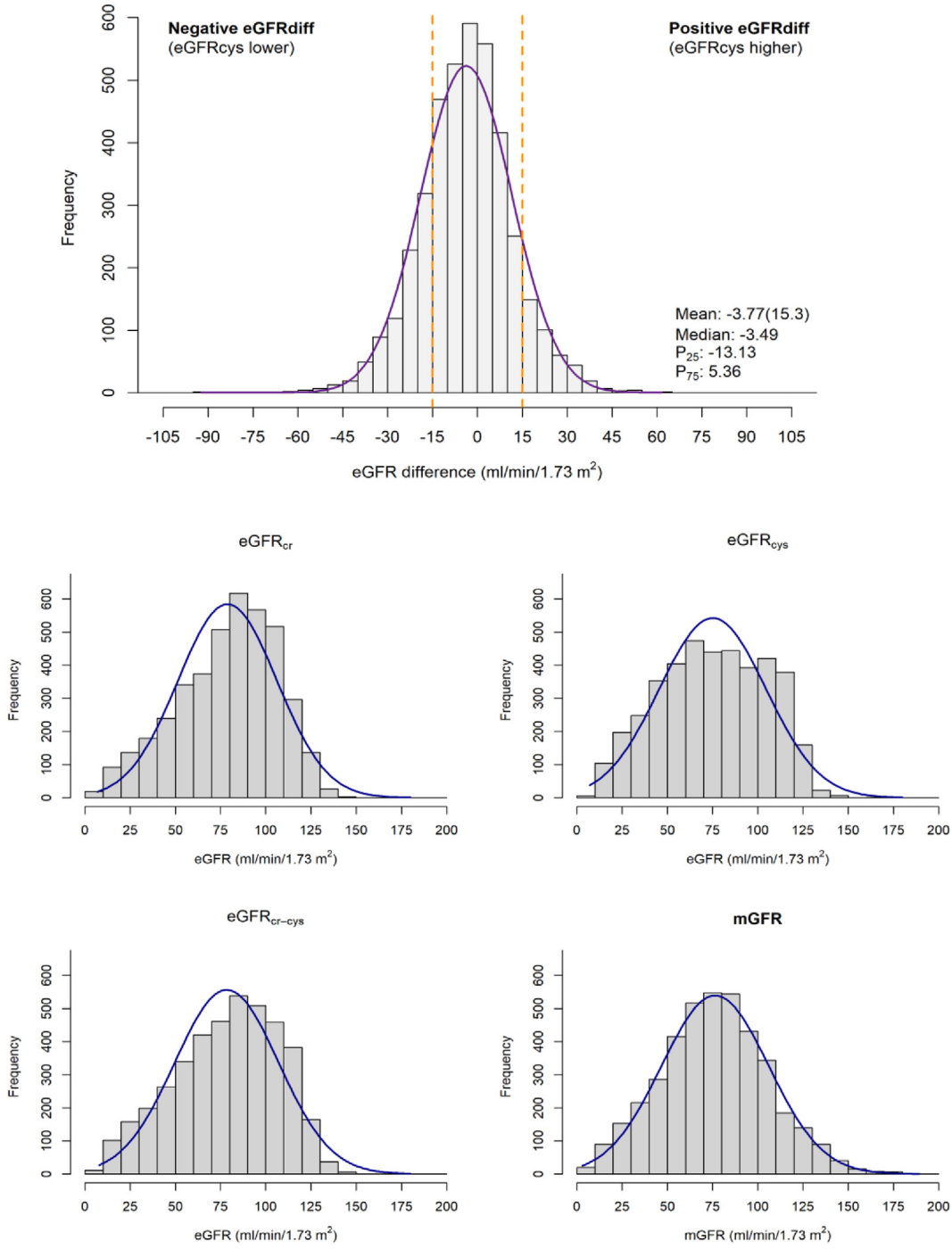

Figure 1. Distribution of difference between eGFRcr and eGFRcys. Top panel shows distribution of eGFR difference (eGFRdiff) on the raw scale, computed as eGFRcys − eGFRcr. Orange dashed lines at −15 and 15 mL/min/1.73 m^2 indicate the cutoff points for eGFR difference categories. Bottom panels show distribution of eGFRcr, eGFRcys, eGFRcr-cys, and mGFR in the study population. The eGFRcr and eGFRcr-cys correspond to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 equations, and eGFRcys to the CKD-EPI 2012 equation. Abbreviations and definitions: eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, estimated glomerular filtration rate based on cystatin C; eGFRcys, estimated glomerular filtration rate based on cystatin C; eGFRdiff, estimated glomerular filtration rate difference; mGFR, measured glomerular filtration rate.

similar performance compared with mGFR, whereas eGFRcr-cys was more accurate than either eGFRcr or eGFRcys.[30] In the concordant group, the performance of eGFRcr, eGFRcys, and eGFRcr-cys equations was similar, with bias of −2.0, −0.5 and −2.7 mL/min/1.73 m^2 and IQR of 15, 16 and 15 mL/min/1.73 m^2, respectively. The P_{30} was 91% and agreement was 74% for the 3 eGFR equations (Table 2; Table S4).

Table 2. Comparison the Performances of GFR Estimating Equations in Comparison with Measured GFR Stratified by eGFRdiff (eGFRcys − eGFRcr) Groups

		eGFRdiff Group (eGFRcys − eGFRcr)		
	Overall Population	Negative (Less Than −15) (eGFRcr Higher)	Concordant (−15 to <15)	Positive (≥15) (eGFRcys Higher)
Participants, N	4,050 (100%)	851 (21.0%)	2,811 (69.4%)	388 (9.6%)
eGFRcr				
Bias	−3.1 (−3.5 to −2.6)	−13.4 (−14.5 to −12.2)	−2.0 (−2.5 to −1.5)	8.6 (7.2 to 10.7)
IQR	17.5 (16.7 to 18.1)	16.2 (14.5 to 17.5)	14.9 (14.0 to 15.5)	19.1 (16.4 to 21.3)
P_{30}	87 (85 to 88)	70 (67 to 73)	91 (90 to 92)	88 (85 to 91)
Agreement	70 (69 to 72)	58 (54 to 61)	76 (74 to 77)	58 (53 to 63)
eGFRcys				
Bias	0.6 (0.1 to 1.0)	9.9 (9.1 to 11.2)	−0.5 (−1.0 to −0.1)	−13.4 (−15.3 to −11.9)
IQR	18.0 (17.2 to 18.7)	17.3 (15.9 to 18.7)	15.7 (14.8 to 16.4)	18.6 (15.7 to 20.7)
P_{30}	88 (87 to 89)	83 (80 to 85)	91 (90 to 92)	77 (73 to 81)
Agreement	71 (70 to 72)	58 (55 to 62)	76 (74 to 77)	64 (59 to 68)
eGFRcr-cys				
Bias	−2.5 (−2.9 to −2.1)	−0.8 (−1.7 to 0.1)	−2.7 (−3.1 to −2.2)	−5.1 (−6.8 to −3.7)
IQR	15.8 (15.2 to 16.4)	16.6 (15.4 to 18.4)	15.2 (14.5 to 16.0)	18.1 (16.2 to 21.0)
P_{30}	91 (90 to 92)	88 (86 to 91)	91 (90 to 92)	92 (89 to 94)
Agreement	74 (73 to 76)	71 (68 to 74)	76 (74 to 78)	69 (64 to 74)

Note: Bias (median difference, 95% confidence interval) was expressed as the median difference between measured GFR and estimated GFR. A negative bias indicates overestimation of the measured GFR, and a positive bias indicates underestimation of the measured GFR. Accuracy (P_{30}, 95% confidence interval) was defined as the percentage of individuals with estimated GFRs within 30% of measured GFR. Agreement was defined between measured and estimated GFR categories. Units for bias are mL/min/1.73 m^2 and are percent for P_{30} and agreement.

Abbreviations and definitions: eGFRdiff, estimated glomerular filtration rate difference; eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcys, estimated glomerular filtration rate based on cystatin C; eGFRcr-cys, estimated glomerular filtration rate based on creatinine and cystatin C; GFR, glomerular filtration rate; P_{30}, estimated glomerular filtration rate within 30% of the measured glomerular filtration rate; IQR, interquartile range.

By contrast, and as expected, performance varied widely for the 3 eGFR equations in the negative and positive eGFRdiff groups. In the negative eGFRdiff group, the eGFRcr equation had a large overestimation of mGFR (−13.4 [−14.5 to −12.2] mL/min/1.73 m^2) and the eGFRcys equation had a large underestimation of mGFR (9.9 [9.1-11.2] mL/min/1.73 m^2). The opposite pattern was seen in the positive eGFRdiff group; the eGFRcr equation had a large underestimation of mGFR (8.6 [7.2-10.7] mL/min/1.73 m^2) and the eGFRcys equation had a large overestimation of mGFR (−13.4 [−15.3 to −11.8] mL/min/1.73 m^2). For both eGFRcr and eGFRcys equations, P_{30} and concordance were lower in the negative and positive eGFRdiff groups compared with the concordant group (Table 2; Table S4). For example, in the negative eGFRdiff group, P_{30} for eGFRcr and eGFRcys equations was 70% (67%-73%) and 83% (80%-85%), respectively; whereas in the positive eGFRdiff group, the opposite pattern was observed, where P_{30} for eGFRcr equation was 88% (85%-91%) and P_{30} for eGFRcys equation was 77% (73%-81%).

In both negative and positive eGFRdiff groups, the eGFRcr-cys equation had better performance than the eGFRcr and eGFRcys equations, as indicated by a smaller bias, higher P_{30}, and agreement. The eGFRcr-cys equation had minimal overestimation in the negative eGFRdiff group (−0.8 [−1.7 to 0.1] mL/min/1.73 m^2) and a small overestimation in the positive eGFRdiff group (−5.1 [−6.8 to −3.7] mL/min/1.73 m^2). P_{30} and agreement were stable across eGFRdiff groups and were substantially higher than for the eGFRcr and eGFRcys equations within each group (P_{30} of 88% [86%-91%] and 92% [89%-94%], respectively, and agreement of 71% [68%-74%] and 69% [64%-74%], respectively).

Results were similar when using the average of eGFRcr and eGFRcys equations, when using percent eGFRdiff groups (Fig S4; Table S4) and when using the 2009 eGFRcr and 2012 eGFRcr-cys equations (Table S5). Results were also similar across the range of eGFR (Fig 2), subgroups of sex and BMI, and for participants less than 65 years of age (Fig 3; Tables S6 and S7). For those older than 65 years of age, eGFRcr was the least biased in the eGFRdiff positive group, with approximately equivalent P_{30} for the eGFRcr-cys and eGFRcr equations, similar to the overall population (Fig 3; Table S8). For non-Black individuals, both the 2021 and 2012 eGFRcr-cys equations led to equivalent or higher P_{30} regardless of the direction of eGFRdiff (Tables S9 and S10). For Black individuals, the 2021 but not the 2012 eGFRcr-cys, led to a higher P_{30}.

DISCUSSION

Creatinine is routinely measured as part of the basic metabolic panel and reported as eGFRcr, informing many clinical decisions such as the detection and management of acute kidney disease and CKD, interpretation of symptoms

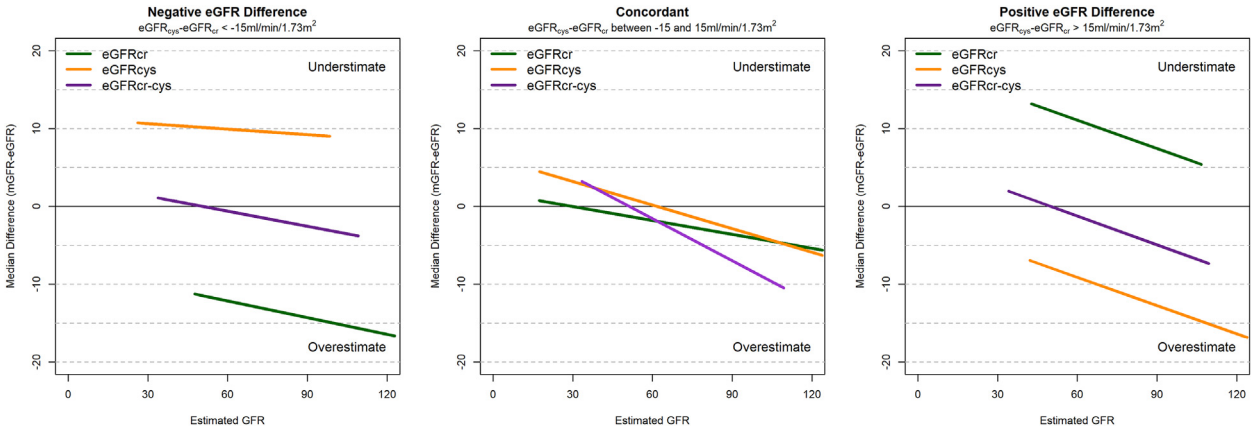

Figure 2. Systematic error in GFR estimating equations by level of estimated GFR according to eGFR difference group. Left panel shows the systematic error (median difference) between measured and estimated GFR for the negative eGFR difference group (eGFRcys − eGFRcr less than −15 mL/min/1.73 m^2). Middle panel shows the systematic error (median difference) between measured and estimated GFRs when the eGFR difference is concordant (eGFRcys − eGFRcr −15 to 15 mL/min/1.73 m^2). Right panel shows the median difference between measured and estimated GFRs for the positive eGFR difference group eGFRcys − eGFRcr > 15 mL/min/1.73 m^2. Green, orange, and purples lines are the smoothed regression lines for eGFRcr, eGFRcys, and eGFRcr-cys, respectively. The eGFRcr and eGFRcr-cys correspond to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 equations, and eGFRcys to the CKD-EPI 2012 equation. The regression lines are drawn using the lowess smoothing function in R, excluding lowest and highest 2.5% of estimated GFR values. A positive sign indicates underestimation of measured GFR and a negative sign indicates overestimation of measured GFR. The x axis is the eGFR for the specific equation and thus varies across the 3 regression lines. Abbreviations and definitions: eGFR, estimated glomerular filtration rate; eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, estimated glomerular filtration rate based on cystatin C; eGFRcys, estimated glomerular filtration rate based on cystatin C; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate.

that may be due to kidney disease, and assignment of drug dosage. Cystatin C is increasingly being used in clinical practice and reported as eGFRcys. In the absence of mGFR, clinicians may not know how to best determine the level of GFR for patients in whom there is a discrepancy between eGFRcr and eGFRcys. Indeed, because eGFR from cystatin C is referred to as a confirmatory test, it is often assumed that in settings of large differences, eGFRcys provides the most accurate estimate. Our study provides guidance as to how to interpret discordant eGFRcr and eGFRcys in ambulatory adults. We found that discordant eGFRcr and eGFRcys were common, with ∼30% of participants having a difference between eGFRcys and eGFRcr greater than 15 mL/min/1.73 m^2, and that most of these participants had higher eGFRcr than eGFRcys. We noted that when eGFRcr and eGFRcys were concordant, there was similar accuracy among all 3 eGFR equations. However, importantly, when eGFRcr and eGFRcys were discordant, regardless of the direction of the difference, eGFRcr-cys provided the most accurate estimate of mGFR, and provided estimates of GFR that approached those of eGFRcr or eGFRcys in the concordant group. These findings were largely consistent across subgroups of age, sex, and BMI when discordant eGFRcr and eGFRcys were defined as a percentage greater than 20% rather than on the raw scale as greater than 15 ml/min/1.73 m^2; when the average of eGFRcr and eGFRcys was used rather than eGFRcr-cys; and when using the 2009 eGFRcr and 2012 eGFRcr-cys equations, which include race. These results have implications for recommendations for the measurement of cystatin C and how to use cystatin C in GFR estimation.

A large difference between eGFRcr and eGFRcys indicates a large error compared with mGFR in eGFRcr, eGFRcys, or both. In principle, these errors are caused by the presence of clinical conditions that affect the level of creatinine or cystatin C independent of GFR (known as non-GFR determinants) and that, on average, differ from conditions that were present in participants in the studies in which the GFR estimating equations were developed.[1] Non-GFR determinants include generation, tubular reabsorption or secretion, or extra-renal elimination of creatinine or cystatin C. Previous studies have demonstrated that muscle wasting, inactivity, and malnutrition are associated with lower levels of serum creatinine, causing a higher eGFRcr relative to mGFR, while obesity, smoking, chronic inflammation as indicated by insulin resistance, higher levels of C-reactive protein and tumor necrosis factor, or lower levels of serum albumin, have been associated with higher levels of serum cystatin C, causing a lower eGFRcys relative to mGFR.[7-16] Because these same conditions also serve as risk factors for adverse outcomes, a large difference between eGFRcr and eGFRcys would indicate the presence of larger non-GFR determinants of creatinine or cystatin C, providing prognostic information. Indeed, multiple epidemiological

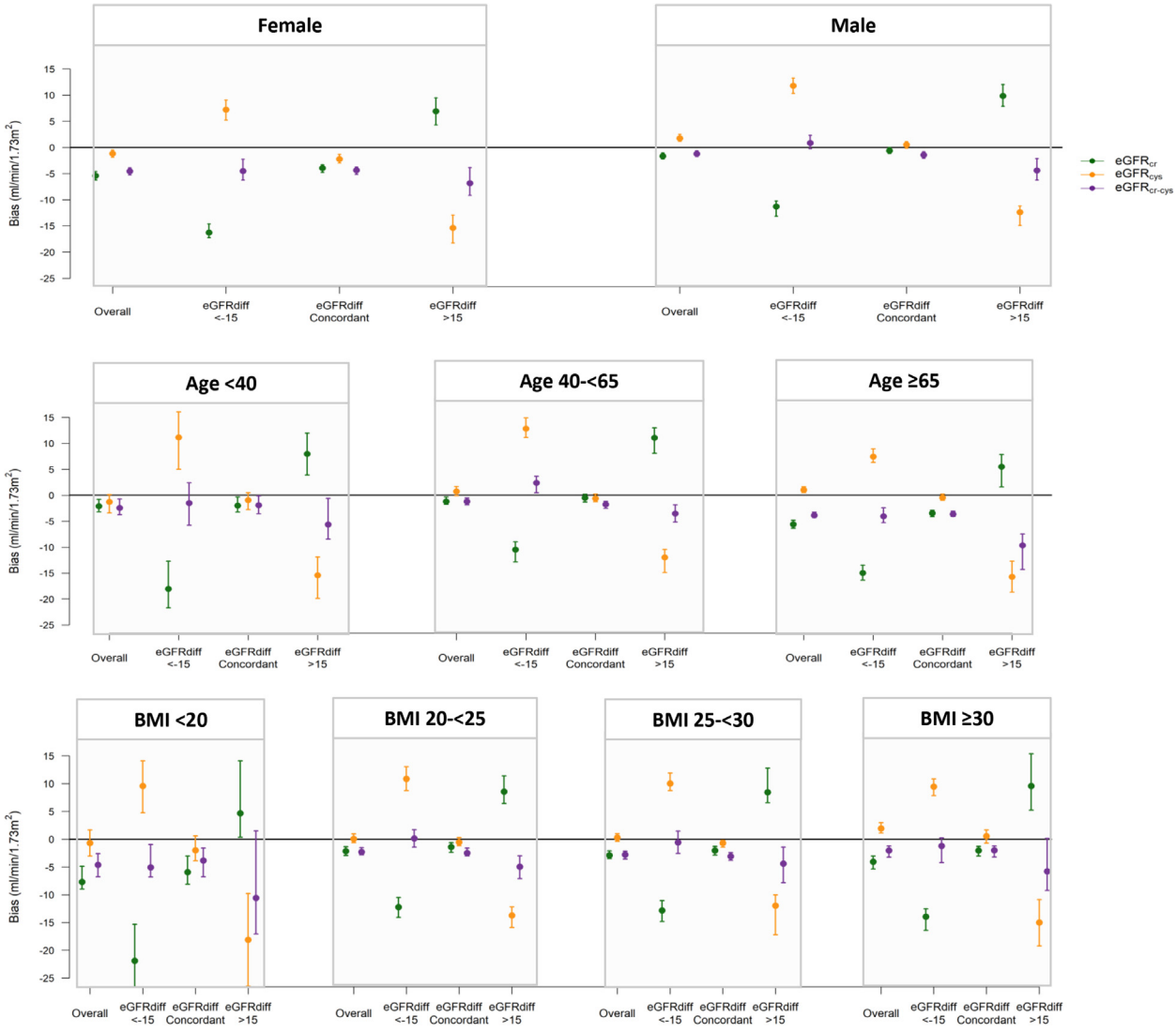

Figure 3. Performance of eGFRcr, eGFRcys, and eGFRcr-cys stratified by estimated glomerular filtration rate (eGFR) difference group and sex, age, and BMI groups. All panels show systematic error (median difference) between measured and estimated glomerular filtration rate stratified by eGFR difference group for subgroups of demographic or clinical characteristics. Green, orange, and purples lines show the data for eGFRcr, eGFRcys and eGFRcr-cys, respectively. The eGFR difference group defined as negative less than −15, concordant −15 to 15, and positive >15 mL/min/1.73 m^2. The eGFRcr and eGFRcr-cys correspond to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 equations, and eGFRcys to the CKD-EPI 2012 equation. Top panel: sex groups. Middle panel: age groups defined as <40, 40 - <65, and ≥65 years. Bottom panel: BMI groups defined as <20, 20 to <25, 25 to <30, and ≥30 kg/m^2. Abbreviations and definitions: BMI, body mass index; eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, estimated glomerular filtration rate based on cystatin C; eGFRcys, estimated glomerular filtration rate based on cystatin C; eGFRdiff, estimated glomerular filtration rate difference.

studies have shown that individuals with a large negative eGFRdiff (with eGFRcys lower than eGFRcr) have a higher risk of multiple adverse health outcomes compared with individuals with a small difference between eGFR and eGFRcys.[17-29] An alternative hypothesis for the cause of large differences between eGFRcr and eGFRcys is that eGFRcys is falsely low owing to selective damage to large pores in the glomerular capillary wall responsible for filtration of cystatin C ("shrunken pore syndrome"), and occurs in conditions associated with higher risk for cardiovascular disease.[25,49] Additional investigations would be necessary to distinguish between these hypothesized causal mechanisms.

We found that even in circumstances of large negative and positive differences, eGFRcr-cys was more accurate than or as accurate as, either eGFRcr or eGFRcys. Indeed, in settings with large negative differences between eGFRcr and eGFRcys, use of eGFRcr-cys led to reductions in large errors in eGFR from 30% (P_{30} of 70%) to 12% (P_{30} of 88%), a reduction in larger errors of 60%. Our observations contrast

with an often-made assumption that in the setting of discordant eGFRcr and eGFRcys, eGFRcys yields a more accurate estimate of mGFR compared to eGFRcr, especially in cases of lower eGFRcys than eGFRcr (negative eGFRdiff). Our findings are consistent with prior studies demonstrating the higher accuracy of eGFRcr-cys or the average of eGFRcr and eGFRcys in general population or CKD cohorts, and one recent study in a large community-based study in Sweden with a wider range of comorbid conditions, which showed higher accuracy with eGFRcr-cys even with discordance between eGFRcr and eGFRcys, providing evidence for the generalizability of these findings in outpatient settings.[17,18,30,50,51,52] Importantly, our findings were consistent in subgroups of individuals with BMI less than 20 kg/m^2, among whom inaccuracy of eGFRcr is often a concern owing to low muscle mass, or malnutrition, and supported by prior studies, which also demonstrated greater accuracy of eGFRcr-cys in those who are liver transplant recipients.[53-55] The findings in the older age group are mostly consistent in that eGFRcr-cys provides a more accurate estimate when eGFRcys is lower than eGFRcr (negative eGFRdiff) and a similarly accurate estimate when eGFRcys is higher than eGFRcr (positive eGFRdiff), and this was also seen in the community-based cohort in Sweden.[56] Using a smaller magnitude of discordance, a recent paper describing results from a research study of older adults in Germany concluded that the lower of eGFRcr or eGFRcys was more accurate than eGFRcr-cys when eGFRcr and eGFRcys were discordant.[57] It is possible that the higher prevalence of CKD in this older adult cohort leads to a lower eGFR regardless of filtration marker, and thus the eGFR that provides the lower eGFR is more likely to be correct. Future studies should explore the causes of these findings.

We found that 30% of participants had differences between eGFRcr and eGFRcys of greater than 15 mL/min/1.73 m^2, confirming prior studies, which similarly reported high rates of large differences ranging from 25% to 33%.[17-19,21] Our study extends these results as we demonstrate that eGFRcr alone is not optimal for estimating GFR, as 30% of this subgroup had large errors compared to mGFR (ie, P_{30} of only 70%). Our results reinforce the need for more frequent cystatin C measurements in clinical settings where the level of GFR would inform clinical decisions, such as confirmation of diagnosis of CKD or decisions regarding kidney replacement therapy or dosing of medications with narrow therapeutic or toxic ranges.[2,3] Serum cystatin C is much less commonly measured than serum creatinine, limiting identification of patients with large errors in eGFRcr.[3,58] Current clinical practice guidelines only contain general recommendations that clinicians measure cystatin C in clinical settings where eGFRcr is thought to be less accurate or where a highly accurate assessment of GFR is required.[59] The lack of specific indications for the measurement of cystatin C has limited adoption. The results of our study might suggest that an alternative recommendation might be for routine measurement of cystatin C in patients with suspected CKD. If eGFRcys and eGFRcr are similar, then both are correct, and repeat measurement of cystatin C could be done less frequently, for example, on an annual basis. However, if a large difference is observed, then cystatin C should be measured more frequently, depending on the clinical situation. Although the cost of cystatin C measurement is higher than that of creatinine,[60] it is less costly than other routine laboratory tests (such as troponin, brain natriuretic peptide, parathyroid hormone, or vitamin D) and is far less expensive than mGFR testing.[52,61]

Two US national kidney organizations, the National Kidney Foundation and American Society of Nephrology, recently recommended the use of the 2021 CKD-EPI race-free creatinine and creatinine-cystatin C eGFR equations.[3] The 2021 creatinine equation is slightly less accurate than the 2009 creatinine equation; therefore, the National Kidney Foundation and American Society of Nephrology also recommended more frequent measurement of cystatin C.[3,30,62] European Federation of Clinical Chemistry and Laboratory Medicine continues to support the use of CKD-EPI 2009 equation without reporting the value for Black individuals because of the fewer Black individuals in European countries but also recommends increased use of cystatin C because of its independence from race.[45] Our finding that, regardless of the equation, eGFRcr-cys provides similar or greater accuracy in both groups with discordant or concordant eGFRcr and eGFRcys supports additional cystatin C testing for all individuals.

Our results have implications for eGFR reporting. In Sweden, cystatin C has been included in routine clinical practice since 1995. In recognition of the greater accuracy of the combination of eGFRcr and eGFRcys, the average of eGFRcr and eGFRcys is used when the eGFRcys/eGFRcr ratio is less than 0.8 or greater than 1.2 analogous to our definition of discordant eGFRcr and eGFRcys using the threshold for percent difference of 20%.[4-6,47,56] Consistent with this practice, the Laboratory Engagement Group of the National Kidney Foundation recommends reporting all 3 values (eGFRcr, eGFRcys, and eGFRcr-cys) when both creatinine and cystatin C are measured.[58] We support this recommendation as it facilitates the interpretation of the level of GFR, prognosis, and clinical conditions associated with non-GFR factors affecting creatinine and cystatin C.

The strengths of the study are the inclusion of GFR measurements from 12 different studies capturing a diverse ambulatory population, which increases the generalizability of our results. In addition, we used both eGFRdiff and percent eGFRdiff to examine differences between eGFRcr and eGFRcys and observed similar results. Nevertheless, some limitations merit consideration. First, this is a cross-sectional study, and we did not have repeated measurements. Random errors are inevitable, and we could not assess whether eGFRdiff is consistent over time. Second, study participants included ambulatory patients without severe comorbid conditions. The proportion of patients with large negative eGFRdiff might be expected to be higher among ambulatory patients with

more extensive comorbid conditions as well as among hospitalized patients where the relative impacts of non-GFR determinants on creatinine and cystatin C could differ from our study,[63-65] although the recent studies in general population samples provide support for these findings in the general clinical population.[56] Future studies in large community-based populations and in clinical populations, with more extensive burden of co-morbidity, including hospitalized patients, can provide more specific information for indications for cystatin C measurement.

In conclusion, within this large, diverse population with mGFR, discordant eGFRcr and eGFRcys were frequent, with eGFRcys lower than eGFRcr being most common. For both concordant and discordant eGFRcr and eGFRcys, the GFR estimate based on both filtration markers (eGFRcr-cys) was as or more accurate than eGFR using either filtration marker alone, across sex, age, BMI, and race subgroups. Our data, in conjunction with the prior information that the difference between eGFRcys and eGFRcr provides important prognostic information, supports recommendations to measure cystatin C more frequently. Future work should evaluate the accuracy of eGFR using creatinine, cystatin C, or both compared with mGFR in populations at higher risk of adverse outcomes according to eGFRdiff.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Distribution of percent eGFRdiff total population (n=4,050).

Figure S2: Linear regression analysis between eGFRdiff (eGFRcys-eGFRcr) and eGFRcr, eGFRcys, and eGFRcr-cys in the total population (n=4,050).

Figure S3: Linear regression analysis between percent eGFRdiff (eGFRcys-eGFRcr)/eGFRcr and eGFRcr, eGFRcys, and eGFRcr-cys in the total population (n=4,050).

Figure S4: Bias of eGFRcr, eGFRcys, and eGFRcr-cys in comparison to measured GFR by percent eGFRdiff categories.

Item S1: Funding for studies included in analysis.

Table S1: GFR Measurement Method and Characteristics of Studies Included in 2021 External Validation Dataset.

Table S2: Baseline Characteristics Stratified by eGFRdiff Percent (eGFRcys-eGFRcr)/eGFRcr Groups.

Table S3: Agreement to mGFR Categories (<30, 30-<60, 60-<90, ≥90 mL/min/1.73 m^2) for eGFRcr, eGFRcys, eGFRcr-cys by eGFRdiff Groups.

Table S4: Comparison of the Performance of CKD-EPI 2021 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff Percent (eGFRcys-eGFRcr)/eGFRcr Groups.

Table S5: Comparison of the Performance of CKD-EPI 2009 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff (eGFRcys-eGFRcr) Groups.

Table S6: Comparison of the Performance of CKD-EPI 2021 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff (eGFRcys-eGFRcr) and Sex Groups.

Table S7: Comparison of the Performance of CKD-EPI 2021 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff (eGFRcys-eGFRcr) and BMI Groups.

Table S8: Comparison of the Performance of CKD-EPI 2021 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff (eGFRcys-eGFRcr) and Age Groups.

Table S9: Comparison of the Performance of CKD-EPI 2021 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff (eGFRcys-eGFRcr) and Race Groups.

Table S10: Comparison of the Performance of CKD-EPI 2009 and 2012 GFR Estimating Equations vs Measured GFR Stratified by eGFRdiff (eGFRcys-eGFRcr) and Race Groups.

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Discordance between creatinine and cystatin C-based eGFR: interpretation according to performance compared to mGFR

Kidney Medicine

Cross-sectional analysis
North America & Europe

N = 4,050 participants with measured GFR (mGFR)

CKD-EPI equations for estimating GFR

eGFRdiff = eGFRcys - eGFRcr

- **<-15: negative** (eGFRcr higher)
- **-15 to 15: concordant**
- **≥15: positive** (eGFRcys higher)

Comparison of GFR estimating equations with mGFR

Bias expressed as median difference between mGFR and eGFR, 95% CI

Participant group by eGFRdiff	Negative 851	Concordant 2,811	Positive 388
2021 eGFRcr	-13.4 (-14.5, -12.2)	-2.0 (-2.5, -1.5)	8.6 (7.2, 10.7)
2012 eGFRcys	9.9 (9.1, 11.2)	-0.5 (-1.0, -0.1)	-13.4 (-15.3, -11.9)
2021 eGFRcr-cys	-0.8 (-1.7, 0.1)	-2.7 (-3.1, -2.2)	-5.1 (-6.8, -3.7)

Small bias indicates **bias between -5 to 5 mL/min/1.73 m²**
Positive bias indicates **underestimation of mGFR >5 mL/min/1.73 m²**
Negative bias indicates **overestimation of mGFR <-5 mL/min/1.73 m²**

Conclusion: Discordant eGFRcr and eGFRcys results are common. Estimation of GFR using the combination of creatinine and cystatin C is more accurate among persons with discordant eGFRcr or eGFRcys. When concordant, eGFRcr, eGFRcys and eGFRcr-cys are all accurate.

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