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GFR Estimation in Potential Living Kidney Donors: Race- and Nonrace-based Equations and Measured GFR

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Rationale & Objective: Recent studies evaluated and proposed new race-neutral, creatinine-based glomerular filtration rate (GFR) estimation equations. The performance of these equations in diverse potential living kidney donors requires study.

Study Design: Cross-sectional study.

Setting & Participants: 637 potential living kidney donors from one tertiary hospital with serum creatinine concentration measurement and GFR measurement by iohexol plasma clearance between October 2016 and December 2020.

Exposure: Creatinine-based estimation of GFR by Chronic Kidney Disease Epidemiology Collaboration (2009, CKDEPI09; 2021, CKDEPI21) and Modification of Diet in Renal Disease equations with and without inclusion of race coefficient, where applicable.

Outcomes: Equation bias, precision, accuracy, and accurate classification of GFR as equal to and above or below 80 mL/min/1.73 m^2.

Analytical Approach: GFR estimation equation performance compared to measured GFR (mGFR) by iohexol clearance.

Results: The median bias of the CKDEPI21 equation underestimated mGFR by 2.8 mL/min/1.73 m^2. The bias in the Black subgroup underestimated mGFR by 9.0 mL/min/1.73 m^2. Compared to CKDEPI09 with and without race adjustment, the accuracy of CKDEPI21 increased across all subgroups. On average, 3.9% of individuals were misclassified by CKDEPI21 as having a GFR greater than, and 8.9% misclassified less than, 80 mL/min/1.73 m^2, compared to 3.1% and 13.2% for CKDEPI09 with race adjustment, respectively. Total misclassification (either above or below 80 mL/min/1.73 m^2) was 16.3% for CKDEPI21 and 16.0% for CKDEPI09 (with race adjustment).

Limitations: Limited sample of individuals identifying as Black. Lack of cystatin C data.

Conclusions: In our potential living donor sample, GFR estimation by creatinine-based CKDEPI21 is less biased and more accurate than previous creatinine-based estimated GFR equations. When evaluated by race, this summative improvement remains in individuals identifying as Asian, Hispanic, or White. More external validation is needed to assess whether the new equation is an improvement over the previous CKDEPI equation with a race coefficient.

Complete author and article information provided before references.

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The accurate assessment of kidney function is essential to the practice of medicine, playing a critical role in medication and chemotherapy prescribing and dosing, nephrology referral decisions, initiation of kidney replacement therapy, referral for kidney transplantation and identification of potential kidney donors. Although the use of exogenous filtration markers (ie, inulin, ^{51}Cr-EDTA, iohexol) is the gold standard for measurement of glomerular filtration rate (GFR), direct measurement of kidney function remains time-intensive, costly, and too complex for routine use in the clinical setting. Instead, GFR is routinely estimated using equations that rely on serum measures of endogenous creatinine.

Creatinine-based equations to estimate GFR include demographic information to increase accuracy by accounting for non-GFR determinates of serum creatinine levels. Equations that rely on the inclusion of a race coefficient (Black vs non-Black) have been the guideline-recommended and predominant approach for initial kidney function testing.[1] This approach resulted from the observation that in the datasets used for equation development, Black individuals had higher measured GFR (mGFR) compared to non-Black individuals for a given level of serum creatinine.[2,3] Though serum creatinine is thought to reflect the balance between muscle production and renal excretion, these observed differences between Black and non-Black patients are not well understood and may reflect non-GFR determinants of creatinine not captured during creation of the equations.[4]

In 2020, the National Kidney Foundation and American Society of Nephrology created a joint task force to address the role of a race variable in estimated GFR (eGFR) equations. Race was recognized both as social construct and, when included as a coefficient in GFR estimation, a potential source of systematic error that could exacerbate health inequities. Already, Black individuals bear a disproportionate burden of kidney disease in America, have a more rapid decline in kidney function, have higher rates of incident kidney disease, are less likely to receive early care from a nephrologist, and are less likely to be waitlisted for transplant.[5-9]

Recommendations by nephrology professional societies strongly encourage race-neutral GFR estimating equations given the lack of biologic rationale for inclusion of race in the estimation of kidney function.[10,11] In 2021, the Chronic Kidney Disease Epidemiology Collaboration

PLAIN-LANGUAGE SUMMARY

Accurate creatinine-based estimation of glomerular filtration rate (GFR) is integral to the practice of medicine and evaluating kidney donor candidacy. Historically, estimation equations included a race coefficient. In an effort to reduce systematic bias and increase the accuracy of GFR estimation equations, a new GFR estimation equation has been developed that does not include a race coefficient. In this study, we use a gold standard measure of kidney function to compare the performance of the new Chronic Kidney Disease Epidemiology Collaboration 2021 estimation equation to the performance of previously developed creatinine-based estimation equations in a cohort of potential living kidney donors. We found that the new estimation equation performed better in all race groups except among Black individuals; however, our study is limited by a small sample of Black individuals.

(CKD-EPI) published new creatinine-based GFR estimation equations without race using 10 developmental data sets including 8,254 participants, of which 31% were Black (CKDEPI21).[12]

Classifying the kidney function of potential living kidney donors is an important step in ensuring successful transplantation, both for the donor and recipient.[13] There are no consensus guidelines regarding the best process for assessing donor eligibility; screening is often performed with creatinine-based estimates of GFR. Studies of creatinine-based estimation as an initial assessment of kidney function in potential donors have yielded mixed results.[14,15]

The purpose of this study is to expand the understanding of creatinine-based GFR estimation equation performance in a diverse population of potential living kidney donors. To our knowledge, this study is the first to evaluate the novel CKDEPI21 equation in this population, in conjunction with the most used eGFR equations. Using plasma iohexol clearance as a gold standard measure of GFR, we compare CKDEPI21 to previously developed creatinine-based estimation equations with and without the inclusion of race coefficients.

METHODS

Setting and Participants

We performed a cross-sectional study measuring the GFR of potential live kidney donors evaluated at the University of California, Davis Medical Center. All potential donors over the age of 18 with at least one GFR measurement by iohexol plasma clearance between October 2016 and December 2020 were included in this analysis. At our center, only individuals who meet initial eligibility criteria undergo iohexol GFR measurement; by default, individuals with any center-specific exclusions to living kidney donation would not enter the cohort (see Table S1 for full list of initial exclusions). For those who had 2 iohexol GFR measurements, only the initial measurement was used. Individuals missing dates of serum creatinine measurement or race data were excluded from the analysis.

Individuals who self-identified as a race or ethnicity other than Asian, Hispanic, Black or White, including individuals self-identifying as bi-/multiracial, were excluded from analysis (because the heterogeneity of this group precluded meaningful aggregation). These individuals included at least 10 unique self-identified multiracial identities (eg, Black and Native American, Asian and White, etc), as well as individuals who declined to provide further race information or did not identify with one of the larger categories. The largest subgroup was 14 individuals who self-identified as both Hispanic and White.

This study was approved by the Institutional Review Board of the University of California, Davis (#1436710-2). Need for informed consent was waived because of deidentified information.

GFR Measurement and Estimation

GFR was measured by plasma iohexol clearance. Participants were administered 640 mg of iohexol intravenously and serum concentration of iohexol was checked 180 minutes later. All serum iohexol measurements were performed at the Mayo Clinic Laboratory. The coefficient of variation of the iohexol assay used is 4%. The single iohexol plasma measurement method is an accurate, low-cost alternative to inulin clearance.[16-18]

Serum creatinine measurements were obtained from the electronic medical record. If multiple measurements were available, measurements with the least time difference from iohexol GFR measurement were selected. Serum creatinine measurements were performed at Quest, LabCorp, or University of California, Davis laboratories. Measurements collected at University of California, Davis laboratories were isotope dilution mass spectrometry-traceable.

Estimates of GFR were generated using 3 GFR estimation equations: (1) Modification of Diet in Renal Disease (MDRD), (2) Chronic Kidney Disease Epidemiology Collaboration 2009 (CKDEPI09), and (3) Chronic Kidney Disease Epidemiology Collaboration 2021 (CKDEPI21) (Table S2).[2,3,12] The MDRD and CKDEPI09 equations were evaluated with and without the Black race coefficient (nonrace equations identified as MDRD-NB and CKDEPI09-NB). The CKDEPI09 equation with the race coefficient removed has been considered as an alternative to relying on the inclusion of race in estimation equations.

GFR estimation equations generate estimates that assume a standard body surface area (BSA) of 1.73 m^2. Measured GFR was normalized to this standard BSA by multiplying measured values by the ratio of 1.73 m^2 to subject BSA (ie, mGFR × (1.73 m^2/BSA), where BSA is calculated by the DuBios equation.[14,19,20] To generate

Table 1. Characteristics of Potential Living Kidney Donors

	Total	Asian	Hispanic	Black	White
Count (% of total)[a]	637 (100.0%)	86 (13.5%)	186 (29.2%)	37 (5.8%)	328 (51.5%)
Female (% of group)	413 (64.8%)	55 (64.0%)	122 (65.6%)	20 (54.1%)	216 (65.9%)
Age, y, mean (SD)	42.5 (13.1)	39.7 (12.6)	39.4 (12.0)	40.4 (10.9)	45.9 (13.3)
BMI, kg/m^2, mean (SD)	27.3 (4.1)	26.4 (3.6)	27.6 (4.1)	29.1 (4.7)	27.2 (4.1)
BSA, m^2, mean (SD)	1.9 (0.2)	1.8 (0.2)	1.8 (0.2)	2.0 (0.2)	1.9 (0.2)
Serum Cr, mean (SD)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	1.0 (0.2)	0.9 (0.2)
Days, mean (SD)[b]	57.9 (72.0)	64.1 (87.1)	55.2 (55.7)	53.7 (60.6)	58.2 (77.0)
Iohexol mGFR[c] (SD)	102.9 (16.1)	108.9 (14.7)	110.2 (16.4)	99.7 (14.7)	97.6 (14.2)
Iohexol mGFR-NN[c] (SD)	110.5 (21.8)	111.6 (22.0)	115.7 (22.4)	114.3 (20.7)	106.9 (20.9)
CKDEPI21 eGFR[c] (SD)	99.9 (15.9)	106.2 (13.7)	108.1 (14.1)	91.7 (14.5)	94.5 (14.9)
CKDEPI09 eGFR[c] (SD)	97.1 (16.5)	102.7 (14.3)	104.8 (15.0)	102.1 (16.7)	90.6 (15.2)
CKDEPI09-NB eGFR[c] (SD)	96.3 (16.5)	102.7 (14.3)	104.8 (15.0)	88.1 (14.4)	90.6 (15.2)
MDRD eGFR[c] (SD)	89.6 (18.5)	94.8 (16.6)	98.2 (19.9)	95.6 (16.3)	82.6 (15.6)
MDRD-NB eGFR[c] (SD)	88.6 (18.5)	94.8 (16.6)	98.2 (19.9)	78.9 (13.5)	82.6 (15.6)

Abbreviations: BMI, body mass index; BSA, body surface area; CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, creatinine; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; NB, non-Black; NN, nonnormalized; SD, standard deviation.
[a]Race is based on participant reporting. Multiracial individuals were not included in analyses because of the heterogeneity of the group.
[b]Absolute value of the difference between date of measured iohexol clearance and measurement of serum creatinine in days.
[c]mGFR and eGFR are measured in mL/min/1.73 m^2 unless noted to be NN (nonnormalized), at which time the units are mL/min. Iohexol mGFR denotes measured GFR by iohexol. The term eGFR denotes estimated GFR by the creatinine-based equation with which it is referenced. NB (Non-Black) refers to equations in which the Black race coefficient was omitted; thus, for non-Black subpopulations, estimates are unchanged.

nonnormalized estimates of GFR from normalized estimates, these estimates were multiplied by the ratio of BSA to 1.73 m^2 (ie, eGFR × (BSA/1.73 m^2)).[21]

Analytical Approach

Bias (systematic error), precision, accuracy, and agreement between GFR categories (and donor eligibility) were used to assess performance of creatinine-based GFR estimation equations. For individuals identifying as Black, estimation equations were used with and without race coefficients. The bias was expressed as the median difference between measured GFR (mGFR) and estimated GFR (eGFR) (mGFR-eGFR), so that a positive number reflects an underestimation of GFR by an estimation equation. Confidence intervals were estimated using bootstrap estimation methods (1,000 repetitions). Precision was expressed as the interquartile range (from the 25th percentile to 75th percentile) of the difference between mGFR and eGFR. Accuracy was expressed as the P30, which is the percent of eGFR values that are at or within 30% of the mGFR. For the estimation of GFR, a P30 value >90% is preferred whereas >75% is generally accepted.[22,23]

GFR of greater than or equal to 80 mL/min/1.73 m^2 was used as a marker of theoretical donor eligibility, which is the GFR cutoff for many transplant programs.[24]

Statistical Analysis

Descriptive statistics were calculated to summarize our patient sample: means and standard deviations for continuous variables and counts and percentages for categorical variables. Data were graphed to evaluate for the normality of continuous data and assess for outliers or influential data. Analysis of variance was used to compare continuous variables across groups; the χ^2 and Fisher exact tests were used to compare categorical variables. Univariate linear regression was used to isolate individual levels of significance, with White as the reference subgroup. Data were represented graphically as scatter plots comparing eGFR and mGFR with locally weighted scatterplot smoothing lines. All statistical analyses were performed using Stata/IC 15.1.

RESULTS

Participants

A total of 698 individuals were reviewed for inclusion, of which 3 individuals were excluded because of not indicating a race, 48 were excluded because of self-identifying as a minor race group (n < 8) or multiracial (n = 34), and 10 were excluded because of missing serum creatinine measurement date. This resulted in a total of 637 individuals included for analysis. Individuals self-identified as White (51.5%), Hispanic (29.2%), Asian (13.5%), or Black (5.8%) (Table 1).

The majority of individuals were female (65.2%), with a mean age of 42.8 years. Mean body mass index and BSA were 27.3 kg/m^2 and 1.9 m^2, respectively; the Black subgroup's body mass index and BSA at 29.1 kg/m^2 (P = 0.007) and 2.0 m^2 (P = 0.01), respectively, were significantly higher than the body mass indices and BSAs of the remaining subgroups. On average, serum creatinine and plasma iohexol measurement were 41 days apart (standard deviation, 83 days) without significant differences between groups (P = 0.81).

The average mGFR, not normalized to a BSA of 1.73 m^2, was 110.5 mL/min, and was lowest in the White

subgroup (106.93 mL/min) and highest in the Hispanic subgroup (115.7 mL/min). Average mGFR, after normalization to a BSA of 1.73 m^2, was 102.9 mL/min/1.73 m^2 and ranged from a low of 97.6 mL/min/1.73 m^2 in the White subgroup to a high of 110.2 mL/min/1.73 m^2 in the Hispanic subgroup.

Equation Performance

After normalization to a BSA of 1.73 m^2, the median bias of the CKDEPI21 equation is an underestimation of mGFR by 2.8 mL/min/1.73 m^2 (Table 2). The CKDEPI21 equation underestimates mGFR in the Black subgroup by 9.0 mL/min/1.73 m^2; this is different from the CKDEPI09 equation with race modification, which overestimates Black GFR by 1.2 mL/min/1.73 m^2. Among the Asian, Hispanic, and White subgroups, the CKDEPI21 equation also underestimates mGFR by 2.3, 1.9, and 2.9 mL/min/1.73 m^2, respectively. For the Asian, Hispanic, and White subgroups, the CKDEPI09 equation underestimates mGFR by 5.6, 5.6, and 6.4 mL/min/1.73 m^2, respectively. The MDRD estimation equations underestimated mGFR to a still greater degree than any of the CKDEPI equations for the Asian, Hispanic and White subgroups. When bias is assessed without normalizing GFR estimates or measurements to BSA, the above patterns persist; moreover, the absolute values of the bias among the Black subgroup is marginally increased (Tables S3-S5).

The precision of the CKDEPI21 estimation equation in the total sample is 20.1 mL/min/1.73 m^2, which compares to the precision of the CKDEPI09 equation with race adjustment of 19.6 mL/min/1.73 m^2 and the precision of the MDRD equation with race adjustment of 21.1 mL/min/1.73 m^2 (Table 2). Across all subgroups, the precision of estimates generated by CKDEPI21 compared to other methods is improved, except for the White subgroup, where the CKDEPI21 estimate is less precise than the CKDEPI09 equation estimates.(Table 2).

Across all subgroups and the total sample, the accuracy of CKDEPI21 is an improvement from the accuracy of CKDEPI09 with and without race adjustment. Ninety-six percent of the total sample estimates of GFR were within 30% of measured GFR; subgroup accuracy ranged from 92% of Black estimates to 97% of White estimates within 30% of mGFR.

Donation Eligibility

The percent of mGFR that was lower than 80 mL/min/1.73 m^2 was 7.2% in the total sample but ranged from 3.2% to 10.4% across subgroups (Table 3; Figs 1-4). Nearly all GFR estimation equations underestimated mGFR, erroneously indicating that a higher percent of each subgroup had GFR less than 80 mL/min/1.73 m^2 than actually did; notable exceptions were that CKDEPI21 underestimated the percent of Asian subjects with mGFR less than 80 mL/min/1.73 m^2, and CKDEPI09 with a race coefficient very closely estimated the number of Black individuals with mGFR less than 80 mL/min/1.73 m^2. These trends are evident in Figure 1, where data points shift upward along the x-axis (eGFR) as the method of estimation changes from CKDEPI09 to CKDEPI21. The Black subgroup had a large difference between measured and estimated percentage of the sample categorized as ineligible to donate based on a GFR cutoff of 80 mL/min. Using the CKDEPI21 and CKDEPI09 (with race adjustment) methods, 24.3% and 10.8%, respectively, of Black individuals were classified as having a GFR less than 80 mL/min/1.73 m^2, compared to the actual value of 8.1% with a mGFR less than 80 mL/min/1.73 m^2.

An average of 3.9% of individuals were misclassified by CKDEPI21 as having a GFR greater than 80 mL/min/1.73 m^2, compared to 3.1% for CKDEPI09 (with race adjustment) (Table 3). Total misclassification (either above or below 80 mL/min/1.73 m^2) was 12.9% and 16.3% for CKDEPI21 and CKDEPI09 (with race adjustment), respectively. On average, MDRD tended to misclassify individuals as below cutoff; although it overall misclassified 29.8% of all individuals, only 1.6% of individuals were misclassified as having a GFR greater than 80 mL/min/1.73 m^2.

When BSA normalization to 1.73 m^2 was removed and GFR was reported as mL/min, misclassification was reduced. A total of 8.5%, 11%, and 21% of individuals were misclassified as above or below 80 mL/min/1.73 m^2 by CKDEPI21, CKDEPI09, or MDRD, respectively. Specifically, fewer Black and White participants were incorrectly classified as having a GFR <80 mL/min, whereas there was little difference for Hispanic participants, and the number of Asian participants misclassified increased from 4.7% to 8.1% (Table S4).

DISCUSSION

The National Kidney Foundation and American Society of Nephrology created a task force to reassess the inclusion of a race coefficient in past creatinine-based eGFR equations (CKDEPI09), which has resulted in the development of new equations that are modeled and refit without a race variable (CKDEPI21). How this change may affect evaluation of potential living kidney donors, particularly in a diverse population, has not yet been evaluated.

Our data suggest that in the aggregate, the GFR estimates generated by the CKDEPI21 equation are less biased and more accurate than earlier estimates of GFR function in the potential living donor population. Precision is slightly reduced compared to previous estimates, but the difference is likely clinically insignificant. The superiority of the CKDEPI21 GFR estimates is reflected in measures of bias and accuracy that are maintained regardless of whether or not estimates are normalized to a BSA of 1.73 m^2.

The MDRD estimation equation performed worst; it is known that the MDRD performs more poorly than the CKDEPI09 equation in non-CKD populations such as with this potential donor cohort.[14,25,26] This observation holds in diverse populations.[27] Nevertheless, this remains a

Table 2. Comparison of Equations for Estimating GFR

	CKDEPI21	CKDEPI09	CKDEPI09-NB	MDRD	MDRD-NB
Bias: median difference between measured GFR and estimated GFR (95% CI), by subpopulation[a]					
Total	2.8 (1.2-4.4)	5.9 (4.2-7.6)	6.4 (4.6-8.1)	14.2 (12.3-16.0)	15.1 (13.3-16.9)
Asian	2.3 (-2.2 to 6.9)	5.6 (0.3-11.0)	5.6 (0.3-11.0)	16.4 (12.8-19.9)	16.4 (12.8-19.9)
Hispanic	1.9 (-2.0 to 5.8)	5.6 (1.7-9.5)	5.6 (1.7-9.5)	13.0 (8.4-17.5)	13.0 (8.34 17.5)
Black	9.0 (0.9-17.1)	−1.2 (−10.0 to 7.7)	12.3 (4.5-20.1)	6.3 (−2.6 to 15.2)	22.9 (14.0-31.7)
White	2.9 (1.0-4.8)	6.4 (4.4-8.3)	6.4 (4.4-8.3)	15.1 (13.0-17.2)	15.1 (13.0-17.2)
Precision: interquartile range of the difference between measured GFR and estimated, IQR (P25, P75), by subpopulation					
Total	20.1 (−7.6, 12.4)	19.6 (−4.1, 15.6)	19.9 (−3.9, 16.0)	21.1 (3.1, 24.2)	21.6 (3.5, 25.2)
Asian	18.6 (−8.1, 10.5)	19.8 (−4.7, 15.1)	19.8 (−4.7, 15.1)	22.6 (1.7, 24.3)	22.6 (1.7, 24.3)
Hispanic	19.9 (−8.5, 11.3)	20.1 (−4.6, 15.5)	20.1 (−4.6, 15.5)	22.2 (0.7, 23.0)	22.2 (0.7, 23.0)
Black	25.7 (−6.1, 19.6)	29.4 (−172, 12.2)	25.4 (−1.8, 23.6)	27.2 (−9.3, 17.8)	23.3 (9.1, 32.4)
White	19.7 (−7.1, 12.6)	19.4 (−3.0, 16.5)	19.4 (−3.0, 16.5)	19.7 (5.4, 25.0)	19.7 (5.4, 25.0)
Accuracy: P30, the percent of estimated GFR within 30% of measured GFR (95% CI), by subpopulation					
Total	96.4% (94.9%-97.8%)	94.7% (92.9%-96.4%)	94.2% (92.4%-96.1%)	88.7% (86.3%-91.1%)	86.8% (83.9%-89.3%)
Asian	96.5% (90.1%-100.0%)	93.0% (87.6%-98.4%)	93.0% (87.6%-98.4%)	88.4% (79.7%-94.3%)	88.4% (79.7%-94.3%)
Hispanic	96.2% (93.6%-98.9%)	95.7% (92.8%-98.6%)	95.7% (92.8%-98.6%)	90.9% (85.8%-94.6%)	90.9% (85.8%-94.6%)
Black	91.9% (83.2%-100.0%)	89.2% (79.4%-99.0%)	81.1% (68.1%-94.1%)	91.9% (78.1%-98.3%)	59.5% (42.1%-75.3%)
White	97.0% (94.5%-98.5%)	95.1% (92.8%-97.5%)	95.1% (92.8%-97.5%)	87.2% (83.1%-90.6%)	87.2% (83.1%-90.6%)

Notes: All units of GFR in mL/min/1.73 m^2. Estimates in this table are normalized to a body surface area of 1.73 m^2. The term eGFR denotes estimated GFR by the creatinine-based equation with which it is referenced. NB (Non-Black) refers to equations in which the Black race coefficient was omitted; thus, this equation is only applicable to Black participants. Race is based on participant reporting. Total values do not include multiracial individuals. Abbreviations: CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; NB, non-Black.

[a]Positive values indicate underestimation of mGFR by eGFR; negative values indicate overestimation of mGFR by eGFR.

Table 3. Count of Inappropriate Classification Above or Below 80 mL/min/1.73 m^2 for Each Estimation Equation, by Subpopulation

	Total (N = 637)	Asian (n = 86)	Hispanic (n = 186)	Black (n = 37)	White (n = 328)
mGFR, n (%)	46 (7.2%)	3 (3.5%)	6 (3.2%)	3 (8.1%)	34 (10.4%)
CKDEPI21, n (%)					
misclass. above	25 (3.9%)	2 (2.3%)	6 (3.2%)	2 (5.4%)	15 (4.6%)
misclass. below	57 (8.9%)	2 (2.3%)	8 (4.3%)	8 (21.6%)	39 (11.9%)
total misclass	82 (12.9%)	4 (4.7%)	14 (7.5%)	10 (27.0%)	54 (16.5%)
CKDEPI09, n (%)					
misclass. above	20 (3.1%)	2 (2.3%)	4 (2.2%)	3 (8.1%)	11 (3.4%)
misclass. below	84 (13.2%)	6 (7.0%)	10 (5.4%)	4 (10.8%)	64 (19.5%)
total misclass	104 (16.3%)	8 (9.3%)	14 (7.5%)	7 (18.9%)	75 (22.9%)
CKDEPI09-NB, n (%)					
misclass. above	19 (3.0%)	2 (2.3%)	4 (2.2%)	2 (5.4%)	11 (3.4%)
misclass. below	90 (14.1%)	6 (7.0%)	10 (5.4%)	10 (27.0%)	64 (19.5%)
total misclass	109 (17.1%)	8 (9.3%)	14 (7.5%)	12 (32.4%)	75 (22.9%)
MDRD, n (%)					
misclass. above	10 (1.6%)	2 (2.3%)	3 (1.6%)	2 (5.4%)	3 (0.9%)
misclass. below	180 (28.2%)	14 (16.3%)	29 (15.6%)	7 (18.9%)	130 (39.6%)
total misclass	190 (29.8%)	16 (18.6%)	32 (17.2%)	9 (24.3%)	133 (40.5%)
MDRD-NB, n (%)					
misclass. above	10 (1.6%)	2 (2.3%)	3 (1.6%)	2 (5.4%)	3 (0.9%)
misclass. below	194 (30.5%)	14 (16.3%)	29 (15.6%)	21 (56.8%)	130 (39.6%)
total misclass	204 (32.0%)	16 (18.6%)	32 (17.2%)	23 (62.2%)	133 (40.5%)

Notes: mGFR and eGFR are measured in mL/min/1.73 m^2. Iohexol mGFR denotes measured GFR by iohexol. The term eGFR denotes estimated GFR by the creatinine-based equation with which it is referenced. NB (Non-Black) refers to equations in which the Black race coefficient was omitted; thus, this equation is only applicable to Black participants. Race is based on participant reporting.
Abbreviations: CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; NB, non-Black.

critical observation because as of 2020, a majority of North American clinical laboratories still report eGFR based on MDRD equations.[28]

One approach to race-neutral GFR estimation considered by some institutions has been to omit the Black race coefficient from pre-existing creatinine-based equations that had been fit with a race term, thus, treating all individuals as non-Black.[28-30] Our findings suggest that, among the Black subgroup, removal of the race coefficient (CKDEPI09-NB, MDRD-NB) produces GFR estimates with more bias than when race coefficients are included. This is consistent with previous analyses.[12,31,32] However, separate studies of Black populations outside of the United States, in South Africa, Brazil, and Congo, found increased

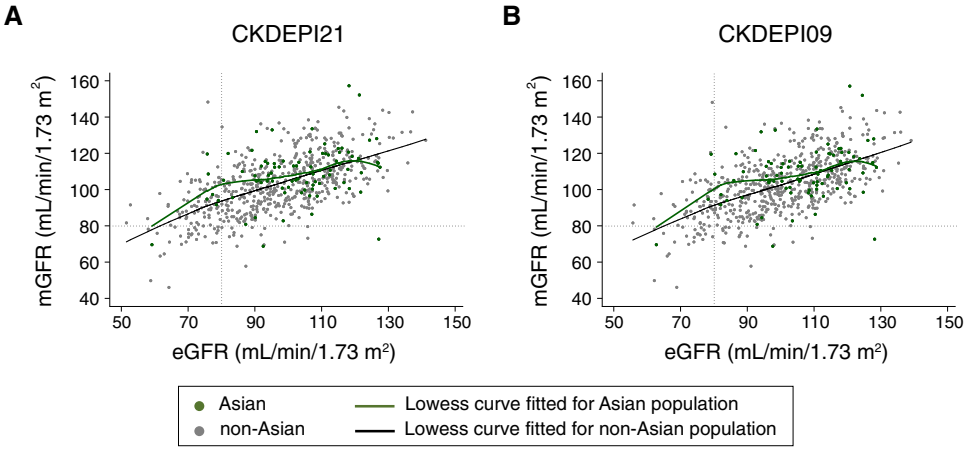

Figure 1. Comparison of measured GFR (mGFR) and estimated GFR (eGFR) by CKDEPI21 or CKDEPI09 among the Asian subgroup. Each graph compares mGFR and eGFR, estimated either by CKDEPI21 or CKDEPI09, for the Asian subgroup. Solid lines represent LOWESS curves. Dashed lines at mGFR = 80 and eGFR = 80 represent theoretical thresholds below which kidney donation eligibility is lost. Abbreviations: CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LOWESS, locally weighted scatterplot smoothing; mGFR, measured glomerular filtration rate.

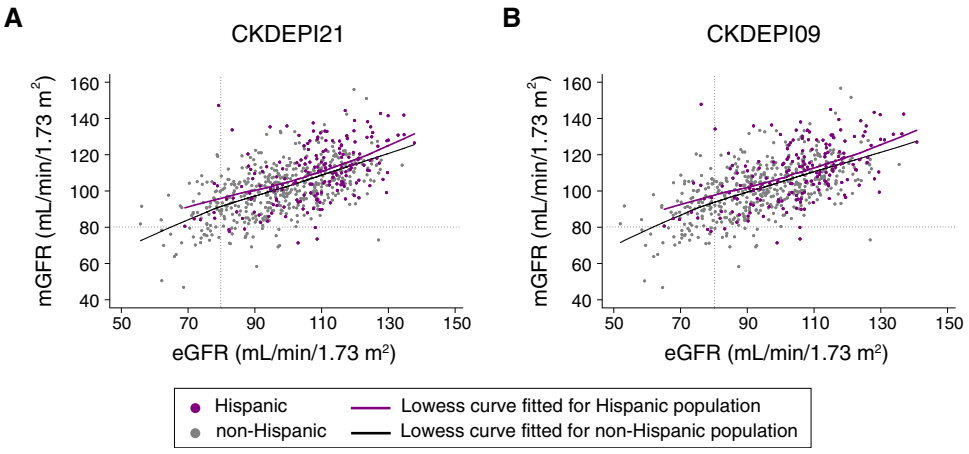

Figure 2. Comparison of measured GFR (mGFR) and estimated GFR (eGFR) by CKDEPI21 or CKDEPI09 among the Hispanic subgroup. Each graph compares mGFR and eGFR, estimated either by CKDEPI21 or CKDEPI09, for the Hispanic subgroup. Solid lines represent LOWESS curves. Dashed lines at mGFR = 80 and eGFR = 80 represent theoretical thresholds below which kidney donation eligibility is lost. Abbreviations: CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LOWESS, locally weighted scatterplot smoothing; mGFR, measured glomerular filtration rate.

systematic bias with inclusion of the race variable.[33-35] Thus, whenever possible, the best approach may be to rely on derivation cohorts from the population of interest for the creation and validation of GFR estimation equations.

For individuals identifying as Asian, Hispanic, or White, the CKDEPI21 estimation equation represents an improvement over the CKDEPI09 and MDRD estimation equations. Improvements noted in bias were potentially clinically significant; changes in bias ranged from a reduction of 55% (3.5 mL/min/1.73 m^2) for White individuals to 66% (3.7 mL/min/1.73 m^2) for Hispanic individuals. These results differ from those of Inker et al,[12] who found that for non-Black individuals, the new CKDEPI21 equation produced estimates with greater bias than the CKDEPI09 equation. Remarkably, the bias of the CKDEPI21 equation is approximately equal for Asian, Hispanic, and White individuals. This is similar to work by Stevens et al[36] that found small differences in eGFR (1%-5%) across these groups for age-, sex-, and serum-creatinine-matched individuals when using the CKDEPI09 equation.

In our data, when compared to the older CKDEPI09 and MDRD equations with race adjustments included, the new CKDEPI21 equation improved accuracy and precision but introduced a greater degree of bias for Black individuals. Compared to the CKDEPI09 equation, the bias of the CKDEPI21 estimate increased from -1.2 mL/min/1.73 m^2

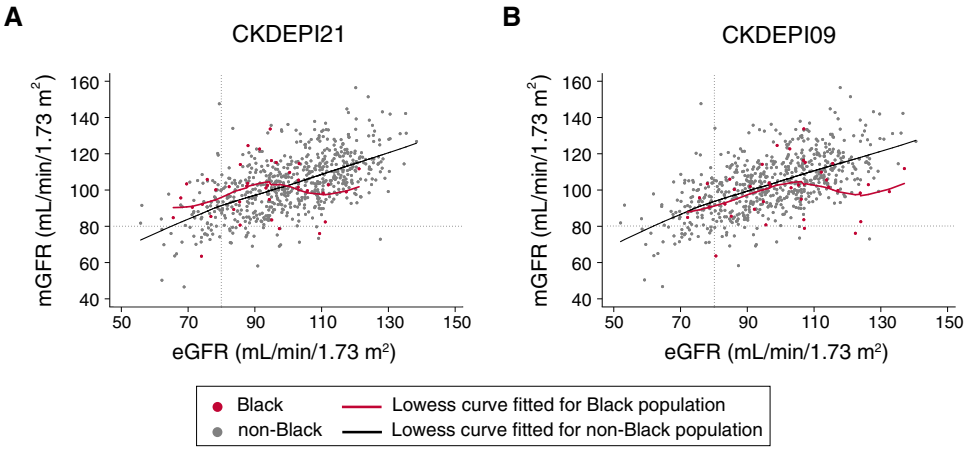

Figure 3. Comparison of measured GFR (mGFR) and estimated GFR (eGFR) by CKDEPI21 or CKDEPI09 among the Black subgroup. Each graph compares mGFR and eGFR, estimated either by CKDEPI21 or CKDEPI09, for the Black subgroup. Solid lines represent LOWESS curves. Dashed lines at mGFR = 80 and eGFR = 80 represent theoretical thresholds below which kidney donation eligibility is lost. Abbreviations: CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LOWESS, locally weighted scatterplot smoothing; mGFR, measured glomerular filtration rate.

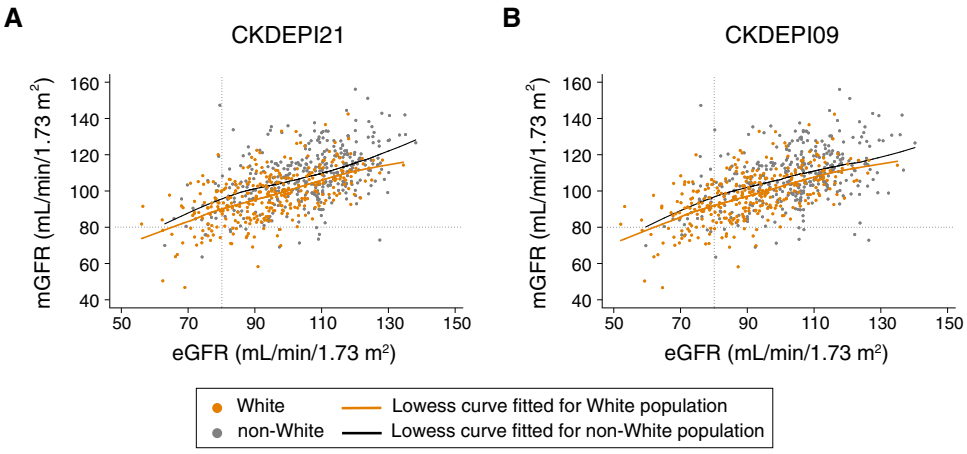

Figure 4. Comparison of measured GFR (mGFR) and estimated GFR (eGFR) by CKDEPI21 or CKDEPI09 among the White subgroup. Each graph compares mGFR and eGFR, estimated either by CKDEPI21 or CKDEPI09, for the White subgroup. Solid lines represent LOWESS curves. Dashed lines at mGFR = 80 and eGFR = 80 represent theoretical thresholds below which kidney donation eligibility is lost. Abbreviations: CDKEPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LOWESS, locally weighted scatterplot smoothing; mGFR, measured glomerular filtration rate.

(overestimation of mGFR) to 9.0 mL/min/1.73 m^2 (underestimation of mGFR). These results differ from those of Inker et al,[12] who found the bias of the new equation (overestimation by 3.7 mL/min/1.73 m^2) to be equal to the previous bias (underestimation by 3.6 mL/min/1.73 m^2). However, our findings are congruent in the direction of bias change with the new CKDEPI21 equation.[12] When systematically applied to populations, the absolute differences of this degree of bias could have large implications, particularly around GFR cutoffs used clinically in drug dosing and transplant evaluation and donation.[29,37]

The clinical significance of an estimation equation can also be appreciated by examining how accurately it classifies individuals in the pool of potential live kidney donors as having a mGFR above or below 80 mL/min/1.73 m^2, the threshold used by many kidney transplant programs in the USA to exclude individuals from donation. The older CKDEPI09 equation erroneously estimates that twice as many Asian (100% more), 66.7% more Hispanic, and 88.2% more White individuals would have a mGFR less than 80ml/min/1.73m^2, which may exclude these individuals from the potential donor pool. The CKDEPI21 equation largely reduces this misclassification for Asian, Hispanic, and White individuals. However, in our donor pool, compared to the CKDEPI09 equation with a race coefficient, the new CKDEPI21 equation erroneously estimates twice as many Black individuals would have a mGFR less than 80 mL/min/1.73 m^2. Because of the small numbers of Black individuals in our cohort, this result will need to be further examined in larger cohorts or externally validated.

The large proportions of GFR underestimation highlight the importance of not relying on a single creatinine-based estimation of GFR to determine donor candidacy. Although it is common practice in transplant centers not to rely on single creatinine estimation of GFR, it is important that nonnephrologist practitioners understand the limits of creatinine-based GFR estimation and do not discourage potential living kidney donors from donation application based on eGFR alone.

Importantly, for all CKDEPI equations, 3%-4% of individuals are misclassified as having a GFR greater than 80 mL/min/1.73 m^2 when mGFR is actually lower, which can lead to the inappropriate inclusion of individuals with decreased kidney function in the donor pool. However, overinclusion is less of a problem than inappropriate donor exclusion because confirmatory mGFR testing is required at US transplant centers for all potential living donors who meet initial inclusion criteria. Interestingly, the MDRD equation reduces this misclassification by nearly half (1.6% misclassified above 80 mL/min/1.73 m^2), suggesting that checking an individual's MDRD may reduce inappropriate inclusion, though its general lack of accuracy and large bias may make it an undesirable choice for GFR estimation.

Finally, errors in GFR estimation are markedly reduced when the assumption of a normalized BSA of 1.73 m^2 of GFR is removed. One interpretation may be that assuming a standard BSA of 1.73 m^2 leads to underestimation of measured kidney function. Indeed, this observation is consistent with studies noting that BSA adjustment (ie, normalization) exacerbates underestimation of kidney function in individuals with higher BSA or higher body mass index.[21,38,39] However, it is notable that in our data, with limited exceptions, both overestimation and underestimation misclassifications are reduced when nonnormalized estimates of GFR are used (Table S6).

Our cross-sectional study set out to evaluate the degree of agreement between measured GFR by iohexol plasma

clearance and creatinine-based estimates of GFR in a diverse sample of potential living kidney donors including the recently developed CKDEPI21 and CKDEPI09 with removal of race coefficient and refitting, which have not yet been evaluated in healthy living donors. Strengths of our study include a diverse study sample with strong representation of patients self-identifying as Asian and Hispanic, as well as large samples of mGFR. However, our study is limited by its restricted geography and small representation of individuals identifying as Black. Our cohort of healthy potential living kidney donors also limits generalizability to the CKD population. We did not evaluate the CKDEPI21 creatinine and cystatin C combined equation as cystatin C was not obtained. Our "gold standard" of GFR is based on iohexol plasma clearance, which itself has inherent errors and precision limitations; however, this method of measuring GFR has been shown to perform just as well as iothalamate and nuclear medicine-based measurements when compared with inulin clearance.[40,41]

In summary, we observed that the refit CKDEPI21 equation without race coefficient demonstrates improvements in bias and accuracy of GFR estimation compared to race-neutral estimates of GFR from the CKDEPI09 and MDRD equations. However, in our study cohort with a relatively small sample of Black individuals without CKD, the new CKDEPI21 equation also appears to generate more biased estimates than the CKDEPI09 equation with a race coefficient. Still, the new CKDEPI21 equation represents an improvement over all previous equations for the measurement of glomerular filtration in White, Asian and Hispanic patients without CKD. These findings warrant further evaluation in a larger study, which ideally would include evaluation of the new CKDEPI creatinine and cystatin C based equation, as well as a larger population of Black individuals.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: UC Davis Potential Living Kidney Donor Absolute Exclusions

Table S2: Featured eGFR estimation equations

Table S3: Bias, Precision, Accuracy of GFR Estimation Equations, non-normalized estimates (ml/min): Bias: median difference between measured GFR and estimated GFR (95% CI), by subpopulation.

Table S4: Bias, Precision, Accuracy of GFR Estimation Equations, non-normalized estimates (ml/min): Precision: Interquartile Range of the difference between measured GFR and estimated GFR, IQR (p25, p75), by subpopulation.

Table S5: Bias, Precision, Accuracy of GFR Estimation Equations, non-normalized estimates (ml/min): Accuracy: P30, the percent of estimated GFR within 30% of measured GFR (95% CI), by subpopulation.

Table S6: Count of inappropriate classification above or below 80m/min for each estimation equation, by subpopulation.

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