

## ORIGINAL ARTICLE

# Race, Genetic Ancestry, and Estimating Kidney Function in CKD

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## ABSTRACT

**BACKGROUND**

The inclusion of race in equations to estimate the glomerular filtration rate (GFR) has become controversial. Alternative equations that can be used to achieve similar accuracy without the use of race are needed.

**METHODS**

In a large national study involving adults with chronic kidney disease, we conducted cross-sectional analyses of baseline data from 1248 participants for whom data, including the following, had been collected: race as reported by the participant, genetic ancestry markers, and the serum creatinine, serum cystatin C, and 24-hour urinary creatinine levels.

**RESULTS**

Using current formulations of GFR estimating equations, we found that in participants who identified as Black, a model that omitted race resulted in more underestimation of the GFR (median difference between measured and estimated GFR, 3.99 ml per minute per 1.73 m<sup>2</sup> of body-surface area; 95% confidence interval [CI], 2.17 to 5.62) and lower accuracy (percent of estimated GFR within 10% of measured GFR [P<sub>10</sub>], 31%; 95% CI, 24 to 39) than models that included race (median difference, 1.11 ml per minute per 1.73 m<sup>2</sup>; 95% CI, -0.29 to 2.54; P<sub>10</sub>, 42%; 95% CI, 34 to 50). The incorporation of genetic ancestry data instead of race resulted in similar estimates of the GFR (median difference, 1.33 ml per minute per 1.73 m<sup>2</sup>; 95% CI, -0.12 to 2.33; P<sub>10</sub>, 42%; 95% CI, 34 to 50). The inclusion of non-GFR determinants of the serum creatinine level (e.g., body-composition metrics and urinary excretion of creatinine) that differed according to race reported by the participants and genetic ancestry did not eliminate the misclassification introduced by removing race (or ancestry) from serum creatinine-based GFR estimating equations. In contrast, the incorporation of race or ancestry was not necessary to achieve similarly statistically unbiased (median difference, 0.33 ml per minute per 1.73 m<sup>2</sup>; 95% CI, -1.43 to 1.92) and accurate (P<sub>10</sub>, 41%; 95% CI, 34 to 49) estimates in Black participants when GFR was estimated with the use of cystatin C.

**CONCLUSIONS**

The use of the serum creatinine level to estimate the GFR without race (or genetic ancestry) introduced systematic misclassification that could not be eliminated even when numerous non-GFR determinants of the serum creatinine level were accounted for. The estimation of GFR with the use of cystatin C generated similar results while eliminating the negative consequences of the current race-based approaches. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others.)

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\*A full list of the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CONSIDERATION OF RACE IN CLINICAL decision making has recently come under much scrutiny and criticism. In particular, the use of indicators for Black race in equations that are widely used to estimate the glomerular filtration rate (GFR) from the serum creatinine level has been questioned.<sup>1-8</sup>

Adults who identify as Black have higher serum creatinine levels on average, independent of age, sex, and GFR, than those who do not identify as Black. Thus, equations that have been developed to estimate the GFR from the serum creatinine level have generally incorporated information on race.<sup>9-11</sup> It has been argued that the race coefficient should be removed from these equations, in part because its inclusion suggests that race is a biologic rather than primarily a social construct.<sup>3,12,13</sup> However, concerns have also been raised about possible misclassification of the estimated GFR that would ensue after removing the race coefficient from current equations.<sup>4,14-16</sup>

Consequently, we analyzed data from a large national study involving adults with chronic kidney disease (CKD).<sup>17,18</sup> The purpose of our analysis was to gain insights into the relationships among race, genetically derived ancestry, the serum creatinine level, and the serum cystatin C level in order to identify strategies for accurately estimating the GFR without reliance on racial classifications.

## METHODS

### STUDY SAMPLE

Participants were enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study, a multicenter, prospective, observational study of racially and ethnically diverse patients with CKD in the United States. In this study, which began in 2003, the initial cohort of 3939 patients included a purposive sample of adults with a broad range of types and severities of CKD.<sup>17-19</sup> In order to be representative of key components of the U.S. population with CKD, the protocol specified that the cohort should be composed of approximately 40% of participants who identified as Black, approximately 50% women, approximately 50% persons with diabetes, and approximately 15% who identified as Hispanic. We randomly selected a subgroup of 1423 participants from the CRIC study to undergo direct measurement of GFR through urinary <sup>125</sup>I-iothalamate clearance. This

approach involved stratified sampling to ensure representation across strata of diabetes status, stages of CKD, age, sex, race, and participating clinical centers.<sup>17-19</sup> Our analytic sample included 1248 of these participants for whom the following data had also been collected: race as reported by the participant, genetic ancestry markers, and serum creatinine, serum cystatin C, and 24-hour urinary creatinine levels (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The CRIC study was approved by the institutional review boards at the participating sites. All the participants provided written informed consent, which included consent to participate in secondary analyses such as the current study.

### STUDY DESIGN AND OVERSIGHT

The overall goals of our study were to determine whether we could accurately estimate GFR without including race. We considered three alternatives (Fig. S2). First, we examined whether we could replace race with a quantitative measure of genetic ancestry in GFR estimation. Second, we evaluated whether we could replace race in GFR estimation by accounting for determinants of serum creatinine that are unrelated to GFR and that vary according to race. Third, we assessed whether we could eliminate the need to consider race — and genetic ancestry, given findings from our first set of analyses — in GFR estimation by replacing the use of serum creatinine with serum cystatin C as the glomerular filtration marker.

The manuscript was written by the CRIC study investigators without external assistance. The study was designed by the CRIC steering committee. Data were collected by the seven CRIC clinical centers, and data analysis was performed at the Kaiser Permanente Northern California–University of California, San Francisco CRIC Clinical Center and the CRIC Scientific and Data Coordinating Center at the University of Pennsylvania. The decision to submit the manuscript for publication was made by all the authors and approved by the CRIC publication executive committee and steering committee. The authors had complete access to the data.

### STUDY VARIABLES

Variables that were used in this analysis included race reported by the participant, demographic characteristics, the percentage of genetic African ancestry, body-composition metrics (body-mass



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index [BMI], height, weight, body-surface area, bioelectrical impedance analysis phase angle, and bioelectrical impedance analysis–quantified fat-free mass), reported and calculated daily dietary protein intake, 24-hour urinary excretion of creatinine, estimates of tubular secretion of creatinine calculated from the creatinine clearance and measured GFR, serum creatinine level, serum cystatin C level, and measured GFR level. Specific assays and collection methods for all measurements, including a detailed description of assignment of genetic ancestry, are provided in Table S1 and the Supplementary Methods section in the Supplementary Appendix.

#### STATISTICAL ANALYSIS

All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute) at Kaiser Permanente Northern California (Oakland) and independently replicated at the University of Pennsylvania (Philadelphia). We used standardized differences (Cohen's D statistic for continuous and binary variables and Cramér's V statistic for categorical variables) to compare distributions of African or European ancestry and other characteristics among participants who identified as Black or non-Black. We then conducted a series of analyses to address the three alternatives to estimate GFR without including race. Measured GFR was log-transformed when it was the outcome of the model; therefore, coefficients for race or ancestry were exponentiated and reported as percent changes for interpretability on the original scale of the outcome. In addition, the serum creatinine level and the cystatin C level were log-transformed in all models.

First, to examine the potential usefulness of genetic ancestry in GFR estimation, we used random sampling to categorize the data into development (67%) and validation (33%) data sets within each race or ethnic group category as reported by the participants (Black, White, or other race or ethnic group). We then combined the data sets to form one final development data set and one validation data set with equal distributions of race or ethnic group as reported by the participants. For our analyses, we combined the White and "other race or ethnic group" categories into a "non-Black" category because of the relatively small number of participants with other race or ethnic group. As a sensitivity analysis, we also performed the analyses using 10-fold cross-

validation of the full sample. We first used the development data set to derive GFR estimating equations with linear regression for measured GFR with the serum creatinine level, age, and sex (i.e., the variables in the widely used Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]<sup>10</sup> and Modification of Diet in Renal Disease [MDRD] study equations<sup>11</sup>). Race and African ancestry were then added individually in separate models. We then applied all derived equations to the validation data set to estimate GFR, and we compared performance using the root-mean-square error (RMSE) calculated in the original GFR scale, the difference between measured and estimated GFR (i.e., statistical bias) and its interquartile range (i.e., precision), and the proportion of estimated GFRs within 10% of measured GFR (termed  $P_{10}$ ) and within 30% of measured GFR (termed  $P_{30}$ ) (i.e., accuracy). We constructed 95% confidence intervals using the 2.5th and 97.5th percentiles from 1000 bootstrapped samples of the validation data set. We also explored the possible added value of interaction terms between race or African ancestry and the serum creatinine level.

Second, to assess whether non-GFR determinants of serum creatinine were independently associated with race or genetic ancestry, we used the full sample to perform multivariable linear regression to separately examine the association of race or African ancestry with measures of body composition, dietary protein intake, 24-hour urinary excretion of creatinine, and tubular secretion of creatinine, with adjustment for age, sex, and measured GFR level. Models of tubular secretion of creatinine were not adjusted for measured GFR because estimates of secretion relied on measured GFR in their calculation. We then assessed whether any of these non-GFR determinants of serum creatinine that differed according to race or ancestry could replace Black race or African ancestry in estimating GFR. We did this by evaluating the degree to which these factors attenuated the strength of association of the Black race or African ancestry coefficient in linear models for measured GFR that included the serum creatinine level, Black race or African ancestry, age, and sex. We evaluated individually each non-GFR determinant of serum creatinine that differed according to race as reported by the participants, and we also evaluated all possible combinations to obtain a final model that maxi-

mized the attenuation of the Black race or African ancestry coefficient.

Third, we repeated analyses using serum cystatin C as an alternative marker of glomerular filtration. We first used the full sample to examine the independent associations of Black race and African ancestry with serum cystatin C, after adjustment for age, sex, and measured GFR. Next, we used the same development and validation data sets described above first to derive (in the development data set) GFR estimating equations with cystatin C, age, sex, and either a term for Black race or African ancestry and then to evaluate model performance (in the validation data set).

## RESULTS

### **BASELINE CHARACTERISTICS OF THE PARTICIPANTS**

Among the 1248 CRIC participants in our study, 458 (37%) identified as Black or Black and multiracial; the median percentage of African ancestry was 82.6% (interquartile range, 74.5 to 88.3) in participants who identified as Black and 0.2% (interquartile range, 0.1 to 2.0) in those who identified as non-Black (Table 1 and Fig. S3). Standardized differences between Black and non-Black participants with respect to age, sex, and measured GFR were low (<0.01, 0.04, and 0.06, respectively). Black participants had higher mean serum creatinine levels (standardized difference, 0.33), but they did not have higher mean cystatin C levels (standardized difference, 0.06) (Table 1). Characteristics of the 844 participants in the development data set and of the 404 participants in the validation data set are shown in Table S2.

### **ESTIMATING GFR WITH RACE OR GENETIC ANCESTRY**

In Black participants, the estimated GFR calculated on the basis of the serum creatinine level, age, and sex alone underestimated the measured GFR by a median of 3.99 ml per minute per 1.73 m<sup>2</sup> of body-surface area (95% confidence interval [CI], 2.17 to 5.62) in the validation data set. In non-Black participants, the median difference between measured and estimated GFR was -0.92 ml per minute per 1.73 m<sup>2</sup> (95% CI, -2.29 to 0.55), indicating statistical bias in Black participants when a race or an ancestry term was not used (Table 2 and Fig. S4). Inclusion of race as reported by the participants (Black or non-Black) or percentage of African ancestry yielded no sys-

tematic differences between the measured and estimated GFR in both Black and non-Black participants (Table 2). Models that included a race or an ancestry term were correspondingly more accurate for Black participants with respect to P<sub>10</sub> (42%; 95% CI, 34 to 50) than models that did not include such a term (31%; 95% CI, 24 to 39) (Table 2). Both RMSE and precision (Table S3) were also better when a race or an ancestry term was included, whereas P<sub>30</sub> was unchanged (86% in all models) (Table 2). Results calculated with the use of 10-fold cross-validation showed similar patterns (Table S4). Interaction terms between race or ancestry and serum creatinine level did not meaningfully improve model performance in the validation data set (Table S5).

### **NON-GFR DETERMINANTS OF CREATININE AND THEIR USE IN CREATININE-BASED EQUATIONS**

Independent of age, sex, and measured GFR, Black race was associated with a 10.7% (95% CI, 8.8 to 12.7) higher serum creatinine level than non-Black race. In addition, every 10% increase in the percentage of African ancestry was associated with an increase of 1.3% (95% CI, 1.1 to 1.6) in the serum creatinine level in the full study sample.

Non-GFR determinants of serum creatinine that differed according to Black (as compared with non-Black) race and higher percentage of African ancestry included higher BMI, body-surface area, height, weight, bioelectrical impedance analysis phase angle, bioelectrical impedance analysis-quantified fat-free mass, and 24-hour urinary excretion of creatinine (Table S6). Neither Black race nor a higher percentage of African ancestry was associated with tubular secretion of creatinine, but both were associated with lower dietary protein intake as assessed by the Diet History Questionnaire.<sup>20</sup>

The coefficient in the base model of measured GFR (including serum creatinine level, age, and sex) for Black race was 12.8% (95% CI, 9.7 to 15.9). This association was only slightly attenuated after consideration of height, bioelectrical impedance analysis phase angle, bioelectrical impedance analysis-quantified fat-free mass, or urinary excretion of creatinine (which had coefficients of 12.0%, 10.5%, 12.4%, and 10.7%, respectively) (Table 3). Results were similar with respect to an increased percentage of African

<b>Table 1. Baseline Characteristics of the Analytic Cohort, According to Race as Reported by the Participants.*</b>				
Characteristic	Overall (N=1248)	Race		Standardized Difference
		Black (N=458)	Non-Black (N=790)	
Age — yr	55.9±12.1	55.9±11.8	55.8±12.3	<0.01
Sex — no. (%)				0.04
Male	709 (56.8)	247 (53.9)	462 (58.5)	
Female	539 (43.2)	211 (46.1)	328 (41.5)	
Race or ethnic group — no. (%) †				0.99
American Indian or Alaska Native	8 (0.6)	0	8 (1.0)	
Asian	60 (4.8)	0	60 (7.6)	
Native Hawaiian or other Pacific Islander	5 (0.4)	0	5 (0.6)	
Black	447 (35.8)	447 (97.6)	0	
White	603 (48.3)	0	603 (76.3)	
Multiracial	21 (1.7)	11 (2.4)	10 (1.3)	
Unknown or not reported	104 (8.3)	0	104 (13.2)	
Highest educational attainment — no. (%)				0.34
6th grade or less	55 (4.4)	3 (0.7)	52 (6.6)	
7th to 12th grade, no high-school diploma	158 (12.7)	103 (22.5)	55 (7.0)	
High-school graduate or equivalent	241 (19.3)	112 (24.5)	129 (16.3)	
Technical or vocational school degree	61 (4.9)	26 (5.7)	35 (4.4)	
Some college education but degree not completed	287 (23.0)	124 (27.1)	163 (20.6)	
College graduate	265 (21.2)	54 (11.8)	211 (26.7)	
Professional or graduate degree	181 (14.5)	36 (7.9)	145 (18.4)	
Genetic ancestry — % of genetic makeup				
African	30.7±38.5	79.9±12.2	2.2±6.5	7.95
Median (IQR)	2.4 (0.1–77.7)	82.6 (74.5–88.3)	0.2 (0.1–2.0)	
European	56.1±38.6	17.7±11.6	78.4±30.4	2.64
Median (IQR)	56.0 (16.0–96.7)	15.0 (9.8–23.1)	95.7 (63.7–97.6)	
Serum creatinine level — mg/dl	1.7±0.6	1.8±0.6	1.6±0.5	0.33
Median (IQR)	1.5 (1.3–2.0)	1.6 (1.4–2.1)	1.5 (1.3–1.9)	
iGFR — ml/min/1.73 m <sup>2</sup>	48±20	47±19	49±20	0.07
Median (IQR)	46 (34–60)	45 (33–60)	47 (34–60)	
Urinary creatinine excretion — mg/24 hr	1378±590	1470±632	1325±558	0.24
Median (IQR)	1289 (973–1701)	1370 (1057–1830)	1238 (917–1655)	
Creatinine clearance — ml/min/1.73 m <sup>2</sup>	52±26	51±27	53±25	0.09
Median (IQR)	49 (35–65)	48 (32–63)	49 (36–67)	
Ratio of creatinine clearance and iGFR	1.13±0.46	1.11±0.48	1.14±0.45	0.07
Difference between creatinine clearance and iGFR — ml/min/1.73 m <sup>2</sup>	4.0±20.3	3.4±21.9	4.4±19.3	0.05
Serum cystatin C level — mg/liter	1.45±0.51	1.47±0.54	1.44±0.50	0.06
Median (IQR)	1.35 (1.09–1.71)	1.36 (1.08–1.72)	1.34 (1.09–1.70)	
Median urinary protein level (IQR) — g/24 hr	0.2 (0.1–1.1)	0.3 (0.1–1.2)	0.2 (0.1–0.9)	0.04
Missing data — no. (%)	3 (0.2)	0	3 (0.4)	

**Table 1. (Continued.)**

Characteristic	Overall (N = 1248)	Race		Standardized Difference
		Black (N = 458)	Non-Black (N = 790)	
Fat-free mass — kg	60.0±15.3	62.3±15.9	58.6±14.7	0.24
Missing data — no. (%)	22 (1.8)	5 (1.1)	17 (2.1)	
Bioelectrical impedance analysis phase angle — degrees	6.7±2.5	7.1±3.5	6.5±1.6	0.25
Missing data — no. (%)	17 (1.4)	2 (0.4)	15 (1.9)	
Body-mass index†	31.2±6.7	33.0±6.5	30.2±6.5	0.42
Height — cm	169.1±9.6	169.7±9.4	168.7±9.7	0.11
Weight — kg	89.4±20.4	95.1±20.2	86.2±19.9	0.44
Body-surface area — m <sup>2</sup>	2.0±0.3	2.1±0.3	2.0±0.3	0.42
Dietary protein intake				
Determined from Diet History Questionnaire — g/day‡	72.6±36.9	71.7±39.4	73.1±35.4	0.04
Median (IQR)	64.9 (47.2–88.5)	62.1 (47.0–87.5)	65.8 (47.7–89.8)	
Missing data — no. (%)	265 (21.2)	101 (22.1)	164 (20.8)	
Determined from 24-hr urinary level — g/24 hr	72.9±27.8	69.7±26.2	74.7±28.6	0.18
Median (IQR)	68.0 (54.2–87.1)	66.6 (52.7–83.1)	69.1 (54.9–90.9)	
Missing data — no. (%)	9 (0.7)	2 (0.4)	7 (0.9)	

\* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. The abbreviation iGFR denotes <sup>125</sup>I-iothalamate glomerular filtration rate, and IQR interquartile range.

† Race or ethnic group was reported by the participants.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The Diet History Questionnaire is a freely available food frequency questionnaire that was developed by the National Cancer Institute for adults who are 19 years of age or older.

ancestry (Table 3). In the final model that included several of these non-GFR determinants of serum creatinine, the race coefficients were not fully attenuated and there remained 8.7% (95% CI, 5.8 to 11.7) higher measured GFR in Black participants than in non-Black participants and 1.1% (95% CI, 0.8 to 1.5) higher measured GFR per 10% increase in the percentage of African ancestry (Table 3).

#### USE OF CYSTATIN C TO ESTIMATE GFR

With adjustment for age, sex, and measured GFR, Black race was not associated with the cystatin C level — the difference comparing Black with non-Black participants in the full study sample was 0.03% (95% CI, –2.12 to 2.11). African ancestry was also not independently associated with the cystatin C level (0.02% per 10% increase in the percentage of African ancestry; 95% CI, –0.25 to 0.28). Models with cystatin C, age, and sex alone derived from the development data set yielded GFR estimates that were very close to the

measured GFR in Black participants (median difference between measured and estimated GFR, 0.33 ml per minute per 1.73 m<sup>2</sup>; 95% CI, –1.43 to 1.92) and in non-Black participants (0.29 ml per minute per 1.73 m<sup>2</sup>; 95% CI, –0.84 to 1.36) (Table 4). As compared with equations using the serum creatinine level, age, sex, and race or percentage of African ancestry, this estimating equation also resulted in approximately equal accuracy in Black participants (Tables 2 and 4). There was no meaningful improvement in the statistical bias or accuracy in the model when a race term or an ancestry term was included in a cystatin C–based equation (Table 4).

#### DISCUSSION

In this diverse, multicenter sample of adults with CKD, GFR estimating equations that were based only on the serum creatinine level, age, and sex without consideration of race resulted in greater systematic underestimation of GFR among

**Table 2. Comparison of Model Performance and Race Coefficients from GFR Estimating Equations Based on Serum Creatinine Using Black Race as Reported by the Participants or Percentage of African Ancestry.\***

Model Covariates	Median Difference between iGFR and eGFR (95% CI)		P <sub>30</sub> (95% CI)		P <sub>10</sub> (95% CI)		Percent Higher iGFR for Black Race or 10% Increase in Percentage of African Ancestry (95% CI)
	Black	Non-Black	Black	Non-Black	Black	Non-Black	
Serum creatinine, age, and sex	3.99 (2.17 to 5.62)	-0.92 (-2.29 to 0.55)	86 (81 to 92)	81 (76 to 86)	31 (24 to 39)	34 (29 to 40)	—
Serum creatinine, age, sex, and race as reported by the participants	1.11 (-0.29 to 2.54)	1.01 (-0.54 to 2.47)	86 (80 to 91)	82 (77 to 86)	42 (34 to 50)	37 (31 to 43)	13.6 (9.9 to 17.3) †
Serum creatinine, age, sex, and percentage of African ancestry	1.33 (-0.12 to 2.33)	1.07 (-0.51 to 2.28)	86 (80 to 91)	83 (78 to 88)	42 (34 to 50)	37 (31 to 43)	1.6 (1.2 to 2.1) †

\* African ancestry information can be used to replace Black race as reported by the participants in equations that rely on serum creatinine, and a serum creatinine–based equation without race or African ancestry is statistically biased in Black participants. Models were derived from a development subgroup of 844 participants (68%), and performance was reported on a validation data set of 404 participants (32%). All 95% confidence intervals correspond to the 2.5th and 97.5th percentile values from 1000 bootstrapped samples of the validation data set. The abbreviation eGFR denotes estimated glomerular filtration rate, GFR glomerular filtration rate, P<sub>30</sub> percent of estimated GFR within 30% of <sup>125</sup>I-iothalamate GFR, and P<sub>10</sub> percent of estimated GFR within 10% of <sup>125</sup>I-iothalamate GFR.

† The percent difference was obtained by exponentiating the coefficient for Black race or percentage of African ancestry in models derived from the development data set (844 participants).

adults who identified as Black than of those who identified as non-Black. When a race coefficient was included, differences in the statistical bias and accuracy of GFR estimates between Black and non-Black participants were eliminated. The direction and size of the included race coefficient in the CRIC study sample (12.8%) was similar to that observed in the CKD-EPI equation<sup>21</sup> (15.9%) and smaller than that in the MDRD equation (21.2%).<sup>11</sup> This 12.8% difference is sufficient to affect clinical decision making under certain conditions (e.g., timing of termination of metformin use, initiation of sodium–glucose cotransporter 2 inhibitors, withholding of procedures involving contrast agents, and initiation of renal-replacement therapies).<sup>4,14-16</sup> Although estimation of GFR based on the serum creatinine level can be imprecise at an individual patient level,<sup>10,11,21,22</sup> our data do not support removing the race coefficient from serum creatinine–based GFR estimating equations because this would add systematic misclassification and further degrade the accuracy of GFR estimates, in particular among persons who identify as Black.

We found that when the serum creatinine level was used to estimate the GFR, incorporation of genetic ancestry provided estimates of GFR similar to those based on race as reported by the participants. One advantage of using genetic ancestry information<sup>8</sup> is avoidance of highlighting of race-based categorization that may exacerbate systemic discrimination in health care. Furthermore, it rids GFR estimation of categorical characterizations of race (“Black” and “non-Black”) that do not reflect ancestry admixture.

Our findings of an association between African ancestry and the serum creatinine level are consistent with results of previous studies, which have shown that a higher percentage of African ancestry is associated with higher serum creatinine levels.<sup>23,24</sup> However, those studies were unable to assess whether this association between ancestry and serum creatinine level was confounded by differences in underlying kidney function, which we addressed by adjusting for measured GFR. Replacing race with genetic ancestry data to estimate GFR in clinical practice, however, is limited by the need for widespread and routine genotyping that is not broadly available and that may arouse concerns related to cost, privacy, and perpetuation of the incorrect notion that race reflects a specific biologic construct.

**Table 3. Association between Black Race as Reported by the Participants or Percentage of African Ancestry and Measured GFR after Controlling for Non-GFR Determinants of Serum Creatinine.\***

Model	No. of Participants	Coefficient for Black Race vs. Non-Black Race (95% CI)	Coefficient for Percentage of African Ancestry, per 10% Increase (95% CI)
		% higher iGFR	
<b>Base model</b>			
$\ln(i\text{GFR}) = [\text{race or African ancestry}] + \ln(\text{serum creatinine}) + \text{age} + \text{sex}$	1248	12.8 (9.7 to 15.9) †	1.6 (1.2 to 1.9) †
<b>Base model with potential explanatory variables considered individually</b>			
$\ln(i\text{GFR}) = [\text{race or African ancestry}] + \ln(\text{serum creatinine}) + \text{age} + \text{sex} + \text{any of the following:}$			
Body-mass index	1248	13.8 (10.7 to 17.0)	1.7 (1.3 to 2.0)
Body-surface area	1248	13.1 (9.9 to 16.3)	1.6 (1.2 to 2.0)
Height	1248	12.0 (9.0 to 15.1)	1.5 (1.1 to 1.8)
Weight	1248	13.4 (10.3 to 16.6)	1.6 (1.3 to 2.0)
$\ln(\text{bioelectrical impedance analysis phase angle})$	1231	10.5 (7.5 to 13.6)	1.3 (0.9 to 1.6)
Bioelectrical impedance analysis–quantified fat-free mass	1226	12.4 (9.2 to 15.6)	1.5 (1.2 to 1.9)
24-Hr urinary excretion of creatinine	1248	10.7 (7.7 to 13.7)	1.3 (1.0 to 1.7)
<b>Base model with several potential explanatory variables considered simultaneously</b>			
$\ln(i\text{GFR}) = [\text{race or African ancestry}] + \ln(\text{serum creatinine}) + \text{age} + \text{sex} + \text{height} + \text{fat-free mass} + \ln(\text{bioelectrical impedance analysis phase angle}) + 24\text{-hr urinary excretion of creatinine}$	1226	8.7 (5.8 to 11.7)	1.1 (0.8 to 1.5)

\* The association between Black race or African ancestry and measured GFR persists even after consideration of non-GFR determinants of serum creatinine as potential explanatory variables.

† The percent difference was obtained by exponentiating the coefficient for Black race or percentage of African ancestry in models with serum creatinine level, age, and sex in the full study sample (1248 participants).

Another potential opportunity to remove race from GFR estimating equations would come from delineating non-GFR determinants of serum creatinine that correlate with race (or ancestry) and accounting for them in estimating equations. Although previous research has suggested that Black patients with CKD have lower rates of tubular secretion of creatinine than non-Black patients,<sup>25,26</sup> we found no differences in tubular secretion of creatinine according to race (or ancestry). We observed that participants who identified as Black (or had a higher percentage of African genetic ancestry) had higher rates of 24-hour urinary excretion of creatinine, similar to observations in other studies.<sup>27</sup> It is possible that extrarenal (e.g., gut) elimination of creatinine varies according to race (or ancestry), but we did not measure this and, to our knowledge, neither have previous studies.<sup>28</sup> Even after accounting for 24-hour urinary creatinine excretion and other

variables that are not typically available in clinical practice such as bioelectrical impedance phase angle or bioelectrical impedance analysis–quantified fat-free mass, the incremental value of including race (or ancestry) to serum creatinine–based GFR estimation was not eliminated.

We found that the precision and validity of estimation of GFR from serum cystatin C, a filtration marker that is currently available clinically, were similar to those of GFR estimation based on the serum creatinine level, without the need to consider either race or ancestry. Furthermore, estimation with the use of cystatin C was not altered or improved by including race. This finding is consistent with previous studies,<sup>10,29</sup> but we also found that genetic ancestry was not needed when cystatin C was used to estimate the GFR. As compared with serum creatinine–based GFR estimating equations that included race, we found that cystatin C–based equations without

**Table 4. Comparison of Model Performance and Race Coefficients from GFR Estimating Equations Based on Cystatin C.\***

Model Covariates	Median Difference between iGFR and eGFR (95% CI)			P <sub>30</sub> (95% CI)		P <sub>10</sub> (95% CI)		Percent Higher iGFR for Black Race or 10% Increase in Percentage of African Ancestry (95% CI)
	Black	Non-Black	ml/min/1.73 m <sup>2</sup>	Black	Non-Black	Black	Non-Black	
Cystatin C, age, and sex	0.33 (-1.43 to 1.92)	0.29 (-0.84 to 1.36)		85 (79 to 90)	83 (78 to 87)	41 (34 to 49)	39 (33 to 45)	—
Cystatin C, age, sex, and race as reported by the participants	0.85 (-1.05 to 2.51)	0.03 (-1.00 to 1.12)		85 (79 to 90)	83 (78 to 87)	42 (35 to 50)	39 (33 to 45)	-1.6 (-4.7 to 1.4)†
Cystatin C, age, sex, and percentage of African ancestry	0.90 (-1.14 to 2.34)	0.04 (-0.95 to 1.14)		85 (79 to 90)	83 (78 to 87)	42 (35 to 50)	39 (33 to 45)	-0.2 (-0.6 to 0.2)†

\* Coefficients for race as reported by the participants and genetic ancestry are not significant in GFR estimating equations that rely on cystatin C; those equations perform similarly to GFR estimating equations that rely on serum creatinine. Models were derived from a development subgroup of 844 participants (68%), and performance of estimated GFR was reported in a validation set of 404 participants (32%). All 95% confidence intervals correspond to the 2.5th and 97.5th percentile values from 1000 bootstrapped samples of the validation set. † The percentage difference was obtained by exponentiating the coefficient for Black race or the percentage of African ancestry in models derived in the development data set (844 participants).

race or ancestry performed with similar levels of statistical bias and accuracy among Black and non-Black participants. These findings suggest that using serum cystatin C instead of serum creatinine would yield equivalent GFR estimation without the need to consider race or ancestry. Challenges regarding the cost, calibration, and standardization of cystatin C measurements would have to be addressed, but we anticipate that cost reduction could occur with broad adoption over time.<sup>29,30</sup>

The strengths of this study include the analysis of concurrent race as reported by the participants, genetic ancestry, measured GFR and serum cystatin C, along with the serum creatinine level and 24-hour urinary excretion of creatinine. We were able to conduct investigations regarding correlates of creatinine generation such as body composition and dietary intake, in contrast to other studies that have had information on only height and weight.<sup>14</sup> The limitations of this study include the involvement of only research volunteers. After stratification according to race, our sample sizes were not sufficient to allow evaluation of subgroups (e.g., those reporting Hispanic ethnic group or defined according to BMI). Creatinine clearance and the <sup>125</sup>I-iothalamate glomerular filtration rate were not measured on the same day with the use of the same blood and urine collections. Because of correlation between race as reported by the participants and genetic ancestry,<sup>31</sup> observed associations may be the consequence of socioeconomic or other factors related to race. Our results do not generalize to those with higher levels of GFR or populations outside the United States. We did not use an external validation data set, because we are unaware of any other study with concurrently measured GFR, serum creatinine, cystatin C, and genetic ancestry data. Finally, we did not compare the performance of our equations with established GFR estimation equations because the purpose of this study was not to derive a new GFR estimating equation without race. The findings of a study conducted by Inker et al.,<sup>32</sup> also now published in the *Journal*, are similar to those in our analyses with respect to race and GFR estimation based on the serum creatinine level as compared with the serum cystatin C level.

Our study showed that the use of serum cystatin C rather than serum creatinine for GFR estimation produced estimates of similar validity

while eliminating the negative consequences of race-based approaches.

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#### APPENDIX

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