Kidney Disease, Race, and GFR Estimation

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Abstract
Assessment of GFR is central to clinical practice, research, and public health. Current Kidney Disease Improving Global Outcomes guidelines recommend measurement of serum creatinine to estimate GFR as the initial step in GFR evaluation. Serum creatinine is influenced by creatinine metabolism as well as GFR; hence, all equations to estimate GFR from serum creatinine include surrogates for muscle mass, such as age, sex, race, height, or weight. The guideline-recommended equation in adults (the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation) includes a term for race (specified as black versus nonblack), which improves the accuracy of GFR estimation by accounting for differences in non-GFR determinants of serum creatinine by race in the study populations used to develop the equation. In that study, blacks had a 16% higher average measured GFR compared with nonblacks with the same age, sex, and serum creatinine. The reasons for this difference are only partly understood, and the use of race in GFR estimation has limitations. Some have proposed eliminating the race coefficient, but this would induce a systematic underestimation of measured GFR in blacks, with potential unintended consequences at the individual and population levels. We propose a more cautious approach that maintains and improves accuracy of GFR estimates and avoids disadvantaging any racial group. We suggest full disclosure of use of race in GFR estimation, accommodation of those who decline to identify their race, and shared decision making between health care providers and patients. We also suggest mindful use of cystatin C as a confirmatory test as well as clearance measurements. It would be preferable to avoid specification of race in GFR estimation if there was a superior, evidence-based substitute. The goal of future research should be to develop more accurate methods for GFR estimation that do not require use of race or other demographic characteristics.

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Introduction
Assessment of GFR is central to clinical practice, research, and public health (1). In clinical practice, GFR is used to interpret the symptoms, signs, and laboratory abnormalities that might signify kidney disease; to adjust drug doses; and to detect, assess risk, and manage acute kidney diseases and disorders (AKD) and CKD. In clinical research, GFR is used as an exposure, outcome, or characteristic in stratification or adjustment. In public health, GFR is used to estimate the burden of kidney disease. For these reasons, improving or worsening the accuracy of GFR assessment has implications at the individual and population levels.

AKD and CKD are worldwide public health problems, with variation in incidence, prevalence, and outcomes by race, which may reflect region, ethnicity, and ancestry and which may be the result of biologic, socioeconomic, and behavioral risk factors as well as access to and quality of health care (2–7). In particular, in the United States, blacks are at higher risk for progression of CKD, including kidney failure (7–9). Of particular importance are the large number of modifiable factors that contribute to this risk as well as the discovery of genetic susceptibility due to inheritance of high-risk APOL1 mutations (10). It is now widely accepted that race is a social rather than a biologic construct, and research has sought to understand the reasons for this disparity by exploring factors that ameliorate the association of race with kidney disease (Supplemental Box) (11–22). Importantly, some interventions directed at the underlying causes have been tested, such as in the African-American Study of Kidney Disease (AASK) (23).

Criteria for the definitions of AKD and CKD are independent of race as are methods to assess measured GFR (mGFR) and mGFR itself, although data are limited (1,24). However, eGFR from serum creatinine (eGFRcr), the initial test in GFR estimation, requires specification of race in adults, and eGFRcr is recommended by current guidelines in combination with assessment of albuminuria and cause of disease to guide prevention, detection, evaluation, and treatment of CKD (25,26). A recent article by Eneanya et al. (27) suggests that using race to guide clinical care is justified only if (1) the use confers substantial benefit; (2) the benefit cannot be achieved through other feasible approaches; (3) patients who reject race categorization are accommodated fairly; and (4) the use of race is transparent. They recommend reconsidering the use of race in eGFRcr because in their opinion, it fails to meet these criteria (27). In this feature, we will review the strengths and limitations of the use of race in GFR estimation, and we propose a way forward to overcome some of the limitations while maintaining accuracy of GFR estimation and fulfill the criteria suggested by Eneanya et al. (27).
Current Recommendations and Limitations

Current guidelines from Kidney Disease Improving Global Outcomes (KDIGO) (Box 1) recommend eGFR, as the initial step in GFR evaluation (25). Confirmatory tests include measurement of serum cystatin C for use in GFR estimation (eGFR from the combination of serum creatinine and cystatin C [eGFRcys] or eGFR from serum cystatin [eGFRcys] if eGFR is likely to be inaccurate) or a clearance measurement (using an exogenous filtration marker [mGFR] or urinary creatinine clearance if mGFR is not available). Serum creatinine is influenced by creatinine metabolism as well as GFR; hence, eGFR includes surrogates for muscle mass, such as age, sex, race, height, or weight. The guideline-recommended eGFR for adults, the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, includes a term for race (specified as black versus nonblack), which improves the accuracy by accounting for differences in non-GFR determinants of serum creatinine that differ by race (28). The recommendations were made despite an appreciation of some limitations: race can be incorrectly ascertained when inferred from physical or other attributes; variation and sometimes, inconsistency exist in how race is assigned in clinical settings and throughout the world; races other than black and country are not specified; and the entire biologic basis for the observed racial difference in non-GFR determinants of serum creatinine may not be captured by race per se. GFR estimation and clinical decisions on the basis of GFR estimation should take into account these limitations.

GFR Estimating Equations

GFR estimating equations enable assessment of GFR from serum concentrations of endogenous filtration markers without clearance measurements (1). Endogenous filtration markers include metabolites (approximately <1000 daltons; including creatinine and more recently recognized filtration markers pseudouridine, acetyltrehalose, myoinositol, phenylacetylglutamine, and tryptophan) and low molecular weight proteins (approximately 1000–20,000 daltons; including cystatin C, β-2 microglobulin, and β-trace protein).

In principle, the serum concentration of an endogenous filtration marker is inversely related to the GFR and directly related to other physiologic processes affecting the marker, termed “non-GFR determinants,” which include generation, renal tubular handling (reabsorption and secretion), and extrarenal elimination of the marker. The non-GFR determinants are difficult to measure, but they may be associated with demographic variables, such as age, sex, and race, or clinical variables, such as height and weight, which can be included as surrogates of these determinants in GFR estimating equations. To facilitate clinical practice, research, and public health, a single equation for each filtration marker or a combination of markers is selected for routine eGFR reporting.

Most GFR estimating equations are predictive models generally developed using linear regression to relate the observed mGFRs to the observed serum concentrations of the filtration marker (both on the logarithmic scale) and to observed demographic and clinical variables as surrogates for the unmeasured non-GFR determinants. By design, an estimating equation provides a more accurate estimate of mGFR than the serum concentration of the filtration marker alone. Error in a single eGFR arises from systematic or random variation in non-GFR determinants that is not accounted for by surrogates and from measurement error in serum assays and mGFR. Systematic error and random variation in mGFR methods have been underemphasized as a source of error in eGFR (1,24). eGFRcys has similar accuracy as eGFRcr, but because the non-GFR determinants of serum creatinine and cystatin C differ from each other, using the combination of both markers (eGFRcyscr) reduces systematic or random variation and is more accurate than using either marker alone (1). Other methodologic approaches have been reported, such as the Full Age Spectrum equations, which use assumed age-adjusted values for normal GFR, and sex- and race-adjusted normal values for serum creatinine and cystatin C (29,30). In children, eGFRcr requires specification of age, sex, and height but not race, likely reflecting differences between children and adults in the relationships among these variables with muscle mass (25).

Race Coefficients in GFR Estimating Equations

The 2009 CKD-EPI creatinine equation includes the variables age, sex, and race (specified as black versus nonblack) in addition to serum creatinine (Table 1) (28,31–37). The coefficient of 1.16 reflects that mGFR was 16% higher in blacks than nonblacks with similar age, sex, and creatinine in the dataset used to develop the equation.

Box 1. Recommendation for GFR evaluation by Kidney Disease Improving Global Outcomes 2012 clinical practice guideline for the evaluation and management of CKD

- Evaluate kidney function as GFR, not as serum concentration of endogenous filtration markers; express GFR in units of milliliters per minute per 1.73 m² rather than milliliters per minute
- Use two-stage testing, with initial testing followed by confirmatory testing as necessary; eGFRcr is the recommended initial test; confirmatory tests, including eGFRcys, eGFRcyscr, or a clearance measurement, are indicated in specific circumstances when eGFRcr is less accurate
- In adults, use the 2009 CKD-EPI equation to report eGFRcr and the 2012 CKD-EPI equations to report eGFRcys and eGFRcyscr in North America, Europe, and Australia; in other regions, use an alternative equation if it is more accurate than the CKD-EPI equations

Information is from the 2012 Kidney Disease Improving Global Outcomes CKD guideline (25). eGFRcr, eGFR from serum creatinine; eGFRcys, eGFR from serum cystatin C; eGFRcyscr, eGFR from the combination of serum creatinine and cystatin C; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
The CKD-EPI development dataset included 2601 blacks (31.5% of the total population), of whom the largest proportion was from the AASK, in which race was self-reported and all study participants were residents of the United States (Supplemental Table) (23,28). Of note, the black coefficient was 1.21 in the 1999 Modification of Diet in Renal Disease (MDRD) study equation; others have reported smaller differences (38). Reported differences in the magnitude of the black coefficients may relate to variation among blacks in the non-GFR determinants of serum creatinine (Table 1) (39). In one study, the black coefficient was too large for European blacks (40). Furthermore, the black coefficient did not predict well in Africa; several studies showed more accurate eGFRcre using the CKD-EPI or MDRD study equations without versus with the black coefficient, indicating heterogeneity among people of African descent in the non-GFR determinants of serum creatinine (41–45). In general, a black coefficient was smaller or was not required at all in eGFRcys or GFR estimating equations using serum β-2-microglobulin or β-trace protein (Table 1). The black coefficient for eGFRcre was intermediate between the coefficients in eGFRcre and eGFRcys as were the coefficients for age and sex (Table 1).

Coefficients for races other than black for eGFRcre are not agreed on. Using a four-level race variable in the 2009 CKD-EPI creatinine equation development dataset, coefficients for Asians (n=100; 1.2%) and a combined category for American Indians and Hispanics (n=353; 4.3%) were smaller (1.05 and 1.01, respectively) than for blacks (1.15) compared with whites and others, and use of the four-level variable compared with the two-level variable did not improve performance in the validation datasets (45). Other studies demonstrated that calibration factors improved the accuracy of the CKD-EPI creatinine or MDRD study equations in some Asian countries, which has often been interpreted as evidence in favor of use of a race coefficient for Asians (46). However, the calibration factors did not seem to be generalizable across countries, which may also reflect population differences in the non-GFR determinants. In general, the CKD-EPI cystatin C equation seemed more accurate than the CKD-EPI creatinine equation in Asian countries, and it did not require a calibration factor (46). It is important to point out that differences in the performance of an eGFRcre equation among studies may reflect differences among studies in methods for mGFR or serum creatinine determination as well as differences in the non-GFR determinants of serum creatinine (47).

An ideal study design to determine the explanation for the apparent need for race coefficients in a GFR estimating equation would be a large multicenter study with a diverse development population composed of multiple racial groups from around the world; with a wide range of biologic (including muscle mass), socioeconomic, and behavioral risk factors; with measurement procedures for GFR and endogenous filtration markers traceable to standardized methods; and with consistent ascertainment of race, ethnicity, and ancestry (including use of genetic ancestral markers) as well as access to and quality of health care.

### Possible Causes for Race Differences in GFR Estimating Equations

In principle, race could affect the relationship of GFR to serum concentrations of endogenous filtration markers if race is associated with errors in measurement methods for mGFR or serum concentrations of endogenous filtration markers or with variation in the non-GFR determinants of the markers. To our knowledge, there are no reported associations of race with errors in clearance measurements or laboratory measurement procedures for the endogenous filtration markers, although one study showed a nonsignificant larger difference in within-person variability for creatinine but not cystatin C in blacks than nonblacks (48). For the remainder of the discussion, we will focus on associations of race with variation in the non-GFR determinants of the markers (Table 2).

It is well known that body size and composition may differ among racial groups. Creatinine generation is

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### Table 1. Age, sex, and race coefficients in Modification of Diet in Renal Disease study and CKD-EPI GFR estimating equations developed in CKD populations and diverse populations

<table>
<thead>
<tr>
<th>Filtration Marker (eGFR)</th>
<th>CKD Population</th>
<th>Diverse Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year (Reference)</td>
<td>Age (per 1 yr)</td>
</tr>
<tr>
<td>Creatinine (eGFRcre)</td>
<td>1999 (31,32,37)</td>
<td>Age-0.203</td>
</tr>
<tr>
<td>Cystatin C (eGFRcys)</td>
<td>2008 (33,34)</td>
<td>Age-0.13</td>
</tr>
<tr>
<td>Creatinine-cystatin C (eGFRcre-cys)</td>
<td>2008 (33,34)</td>
<td>Age-0.20</td>
</tr>
<tr>
<td>β-2 microglobulin (eGFRβ&lt;sub&gt;2M&lt;/sub&gt;)</td>
<td>2015 (36)</td>
<td>0.998&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>β-trace protein (eGFRTP)</td>
<td>2015 (36)</td>
<td>NA</td>
</tr>
<tr>
<td>β-2 microglobulin–β-trace protein (eGFRβ&lt;sub&gt;2M-TP&lt;/sub&gt;)</td>
<td>2015 (36)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable.

<sup>a</sup> All equations are CKD-EPI equations except the 1999 creatinine equation, which is the Modification of Diet in Renal Disease study equation. Equations developed in diverse populations (populations with and without CKD and with multiple geographic regions, races, and ethnicities) are preferred for clinical use. Equations are expressed on the raw scale. Coefficients for age, sex, and race are multiplicative factors.

<sup>b</sup> For serum creatinine >0.7 mg/dl in women and >0.9 mg/dl in men and for serum cystatin C >0.8 mg/L.
Table 2. Non-GFR determinants of serum concentrations of endogenous filtration markers and clinical conditions associated with their variation

<table>
<thead>
<tr>
<th>Endogenous Filtration Markers</th>
<th>Creatinine</th>
<th>Cystatin C</th>
<th>β-2 Microglobulin</th>
<th>β-Trace Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-GFR determinants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generation</strong></td>
<td>Muscle mass</td>
<td>All nucleated cells</td>
<td>All nucleated cells</td>
<td>CNS, testis, ovary</td>
</tr>
<tr>
<td><strong>Tubular handling</strong></td>
<td>Receptor-mediated tubular secretion (trimethoprim, cimetidine, fenofibrate, ritonavir, dolutegravir), level of GFR, cause of CKD (PKD versus others), antihypertensive agents (diuretics and CCB)</td>
<td>Receptor-mediated uptake and degradation in proximal tubular cells</td>
<td>Receptor-mediated uptake and degradation in proximal tubular cells</td>
<td>Receptor-mediated uptake and degradation in proximal tubular cells</td>
</tr>
<tr>
<td><strong>Extrarenal elimination</strong></td>
<td>GI (bacterial creatininase)</td>
<td>Multiple sites</td>
<td>Not known</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Variation in non-GFR determinants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Associated clinical conditions</strong></td>
<td>Muscle mass</td>
<td>Fat mass, inflammation (higher CRP, lower serum albumin), smoking, thyroid and corticosteroid hormone</td>
<td>Lymph-proliferative and plasma cell disorders, smoking, inflammation (higher CRP, lower serum albumin), proteinuria</td>
<td>Proteinuria, weight</td>
</tr>
</tbody>
</table>

There are two main methods for use in clinical studies to ascertain the association of race and other factors with the non-GFR determinants of endogenous filtration markers. For metabolites, such as creatinine, which are filtered and excreted in the urine, generation can be ascertained from urinary excretion in the steady state, tubular handling can be ascertained by comparison of urinary clearance with measured GFR, and extrarenal elimination can be ascertained by comparing plasma with urinary clearance. Then, variation in these processes can be assessed among racial groups (however determined) with and without adjustment for other explanatory factors. For low molecular weight proteins, such as cystatin C, which are filtered, reabsorbed, and metabolized with only small quantities excreted in the urine, inferences about variation in non-GFR determinants among racial groups are generally assessed by differences in the measured GFR filtration marker associations with and without adjustment for other factors. However, this latter method does not provide information about which physiologic process is affected. These methods could be supplemented by laboratory studies of the relevant mechanisms. CNS, central nervous system; PKD, polycystic kidney disease; CCB, calcium-channel blocker; GI, gastrointestinal; CRP, C-reactive protein.

*Adjusted for age, sex, and race.
affected by diet, particularly meat intake, and muscle mass, which varies by age, sex, and race; on average, creatinine excretion rates are higher in men than women, younger than older people, and people with self-reported black race than nonblack race (Table 2) (49–58). Self-reported race correlates strongly but imperfectly with genomically determined ancestry (59). Two studies reported positive and graded associations between the percentage of African ancestry (determined through genomic markers) and serum creatinine level (60). These differences are consistent with the magnitude and direction of the coefficients in the 2009 CKD-EPI creatinine equation. However, the aforementioned studies did not control for many possible confounding variables, and the causes of the observed racial differences in muscle mass and creatinine excretion are not well understood. One study showed that creatinine secretion in the AASK participants was lower than expected, but it did not include a comparison group of nonblacks (61). Enzymatic and transport processes involved in generation, tubular secretion, or extrarenal elimination of creatinine may reflect genetic variation. A meta-analysis of genetic determinants of eGFR did not find evidence for heterogeneity by ancestry at the vast majority of loci (62). Factors affecting the non-GFR determinants of novel metabolite filtration markers are less well known than for creatinine. As mentioned above, it is important to acknowledge that nonbiologic factors may be partly responsible for the higher serum and urine creatinine values observed in blacks.

After accounting for mGFR, cystatin C, β-2 microglobulin, and β-trace protein have weaker associations than creatinine with age, sex, and black race, findings that are generally interpreted, albeit without direct evidence, as reflecting smaller effects of muscle mass on generation of the markers (63–65). Associations with other clinical factors vary, including adiposity, smoking, inflammation, alterations in thyroid or corticosteroid hormones, proteinuria, and weight (Table 2) (63–68).

In principle, the use of multiple markers with non-GFR determinants that are not correlated with each other can reduce the contribution of non-GFR determinants of each marker and reduce error in GFR estimation. We have hypothesized that the use of a panel of filtration markers (panel eGFR) may avoid the need for these variables while providing more personalized estimates at the individual level and greater accuracy at the population level. Our results so far estimating GFR from a panel of novel metabolites provide proof of the concept that age, sex, and race are not necessary for GFR estimation and can be as accurate as provided by eGFRcr-cys (69,70). Studies evaluating combinations of metabolites and low molecular weight proteins in diverse populations are needed to

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**Figure 1.** Clinical decisions can be affected by accuracy of GFR assessment among blacks. Data from 2601 black participants from the Chronic Kidney Disease Epidemiology Collaboration development and internal validation sample were used in this plot (28). We computed eGFR from serum creatinine (eGFRₚ) values with (blue) and without (red) the application of the black coefficient and removed values below and above the 2.5 and 97.5 percentiles of these distributions, leaving 2463 participants for the analysis. The model plotted represents generalized additive models for eGFRₚ (milliliters per minute per 1.73 m²) on the difference between eGFRₚ and measured GFR (mGFR) (milliliters per minute per 1.73 m²). We truncated the horizontal axis to eGFRₚ values from 15 to 105 ml/min per 1.73 m², excluding 190 participants from the plot. The colored areas along the line represent 95% confidence intervals of the estimate. Upper boxes represent hypothetical situations of eGFRₚ values for the same mGFR, with numbers in blue representing the eGFRₚ with the black coefficient and the numbers in red representing the eGFRₚ without the black coefficient. AA, black; BSP, bisphosphonate; SGLT2, sodium-glucose transport protein 2. Modified from ref. 72, with permission.
imprecision in eGFRcr is the main limitation in its individual versus population level. For individuals, the performance of eGFRcr is worse in blacks (root mean square error of 0.258 versus 0.243) more in blacks (0.244 versus 0.238) (Table 3) (72). Other consequences might be overdiagnosis of CKD, underestimation of the relationship of risk of adverse outcomes to reduced GFR, inadequate use or dosing of drugs excreted by glomerular filtration (including metformin), and limited access to tests (including imaging procedures) and treatments that require a higher level of GFR assessment, then ignoring the black coefficient may be of little consequence. However, if the level of GFR is moderate to high, where elimination of the black coefficient may lead to a large change in eGFR, or if the clinical decision requires accurate GFR assessment and race is uncertain, then confirmatory, guideline-recommended testing would be appropriate.

For populations, bias is the main limitation in the accuracy of eGFRcr. In the absence of routinely performed confirmatory tests, a systematic underestimation of mGFR in blacks throughout the GFR range is likely to have wide-ranging implications (Figure 1) (72). Eneanya et al. (27) call attention to the possibility that blacks may be disadvantaged from late referral for kidney transplantation because of systematically higher eGFRcr than nonblacks with the same serum creatinine, age, and sex. However, systematic underestimation of mGFR by eliminating the black coefficient could lead to unintended consequences. Although earlier referral for transplantation might be helpful in overcoming the disparity in kidney transplantation, inappropriate early transplantation or dialysis initiation could be harmful. Other consequences might be overdiagnosis of CKD, underestimation of the relationship of risk of adverse outcomes to reduced GFR, inadequate use or dosing of drugs excreted by glomerular filtration (including metformin), and limited access to tests (including imaging procedures) and treatments that require a higher level of GFR (Figure 1), including living donor kidney donation, another important disparity affecting blacks (72,73).

Clinical research and public health might also be compromised by failure to recognize this systematic bias and failure to focus attention and resources where they are most needed. For example, recognition of the causes and consequences of increased incidence of kidney failure and faster rate of disease progression in blacks in population studies requires accurate assessment of and adjustment for baseline eGFRcr (74,75). Appropriately, identification of the mechanisms underlying these associations and developing therapies to target these differences are the focus of much current research.

Table 3. Can use of height and weight eliminate the need for race in GFR estimation in the CKD-EPI creatinine equation?

<table>
<thead>
<tr>
<th>Variables Used in Equations for eGFR</th>
<th>All, n=8254</th>
<th>Black, n=2603, Root Mean Square Errorb</th>
<th>Nonblack, n=5653, Root Mean Square Errorb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine, age, sex, race</td>
<td>1.16 (1.14 to 1.17)</td>
<td>0.236 (0.229 to 0.242)</td>
<td>0.232 (0.225 to 0.241)</td>
</tr>
<tr>
<td>Serum creatinine, age, sex</td>
<td>NA</td>
<td>0.244 (0.238 to 0.251)</td>
<td>0.238 (0.230 to 0.247)</td>
</tr>
<tr>
<td>Serum creatinine, age, sex, race, height, weight</td>
<td>1.15 (1.14 to 1.17)</td>
<td>0.235 (0.229 to 0.242)</td>
<td>0.232 (0.225 to 0.241)</td>
</tr>
<tr>
<td>Serum creatinine, age, sex, height, weight</td>
<td>NA</td>
<td>0.243 (0.237 to 0.250)</td>
<td>0.238 (0.230 to 0.246)</td>
</tr>
</tbody>
</table>

Data are from the pooled CKD-EPI development and internal validation datasets. Mean (SD) measured GFR = 68 (40) ml/min per 1.73 m² (28). Other GFR estimating equations using serum creatinine were not considered because they are not more accurate than the CKD-EPI creatinine equations in external validation datasets. 95% CI, 95% confidence interval; NA, not applicable. Modified from ref. 72, with permission.

Triangular coefficient for equation expressed on the multiplicative scale of GFR.

Root mean square error for the regression of measured GFR on eGFR computed on the logarithmic scale. A lower root mean square error indicates higher accuracy of the eGFR.

Consequences of Eliminating Race from GFR Estimates Using Creatinine

The benefits of nonrace-based inferences for care should be judged alongside the risk and harms of doing this. Eneanya et al. (27) suggest elimination of the black coefficient by substituting objective data on body size and composition, such as height or weight. Elimination of the black coefficient in the CKD-EPI creatinine equation would introduce a systematic error in eGFRcr in blacks, an underestimation of mGFR (Figure 1). Development of a new equation without a race variable would worsen the performance in estimating mGFR (root mean square error of 0.244 versus 0.236) more in blacks (0.258 versus 0.243) than in nonblacks (0.238 versus 0.232) (Table 3) (72). Inclusion of height and weight in addition to race does not meaningfully reduce the effect of race on eGFRcr (coefficient 1.15 versus 1.16) or improve performance (root mean square error of 0.235). Even when height and weight are included, omission of race worsens equation performance (root mean square error of 0.243) more in blacks than in nonblacks (0.255 and 0.238, respectively). To date, our experiences with the CKD-EPI equation and those of others collecting and analyzing data have not yielded other routinely available clinical data that could improve the accuracy of eGFRcr.

It is important to differentiate the consequences of the loss of accuracy of eGFRcr from eliminating the black coefficient from the CKD-EPI creatinine equation at the individual versus population level. For individuals, imprecision in eGFRcr is the main limitation in its accuracy; the clinical implications of further loss of accuracy would depend on the level of GFR, the clinical decisions that need to be made, and the availability of confirmatory tests (Figure 1) (72). For example, if the level of GFR is low, where elimination of the black coefficient does not lead to a large change in eGFR, or if the clinical decision does not require highly accurate GFR assessment, then ignoring the black coefficient may be of little consequence. However, if the level of GFR is moderate to high, where elimination of the black coefficient may lead to a large change in eGFR, or if the clinical decision requires accurate GFR assessment and race is uncertain, then confirmatory, guideline-recommended testing would be appropriate.

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Clinical research and public health might also be compromised by failure to recognize this systematic bias and failure to focus attention and resources where they are most needed. For example, recognition of the causes and consequences of increased incidence of kidney failure and faster rate of disease progression in blacks in population studies requires accurate assessment of and adjustment for baseline eGFRcr (74,75). Appropriately, identification of the mechanisms underlying these associations and developing therapies to target these differences are the focus of much current research.
Box 2. Suggestions for GFR estimation in adults and clinical decision making now and in the future

Goals: Maintain and improve accuracy of GFR estimates and avoid disadvantaging any racial group

General Suggestions
- Full disclosure of the use of race in GFR estimation, accommodation of those who decline, and shared decision making between patient and health care provider
- Mindful use of endogenous filtration markers in addition to creatinine, such as cystatin C
- Ongoing research on the causes of racial differences in the relationship of measured GFR to serum concentrations of endogenous filtration markers and clinical outcomes

Specific Suggestions: Now
- Use CKD-EPI eGFRcr with the black coefficient for blacks and without the coefficient for nonblacks (including mixed race combinations) or if race is not specified
- In some Asian countries, use other equations that have been proven to be more accurate
- Use confirmatory tests if greater accuracy is needed for clinical decision making: CKD-EPI eGFRcys and eGFRcr-cys, measured urinary creatinine clearance, or measured GFR using exogenous markers

Specific Suggestions: Future
- Develop a panel of endogenous filtration markers (panel eGFR either without or with creatinine) and simplified measured GFR determination as a confirmatory or initial more accurate tests for GFR evaluation without needing to specify race or other demographic factors

Moving Forward
We agree with Eneanya et al. (27) that specification of race for GFR estimation in adults is sometimes difficult and inaccurate and that it ideally should be replaced by physiologic measures that reflect variation in non-GFR determinants of serum creatinine. However, in the absence of suitable surrogates for these physiologic variables, we are concerned that the loss of accuracy from eliminating specification of race in eGFRcr could disadvantage blacks both at the individual and population levels. Therefore, we propose a more cautious approach. In our view, the goals should be to maintain and improve accuracy of GFR estimates and to avoid disadvantaging any racial group (Box 2). In general, we suggest full disclosure of the use of race in GFR estimation, accommodation of those who decline, and shared decision making between health care providers and patients regarding GFR estimation. We also suggest mindful use of endogenous filtration markers in addition to creatinine, such as cystatin C, when important clinical decisions must be made. Furthermore, we encourage more research to understand the underlying causes of race differences, including muscle mass, diet, and tubular secretion, in the relationship of mGFR to serum creatinine and other filtration markers. In the future, confirmatory tests in addition to eGFRcys and eGFRcr-cys could include a panel of filtration markers (panel eGFR), either without or with creatinine, that is not affected by race. In principle, use of panel eGFR as an initial test might avoid the need for specification of race altogether. Much more work is required for development and implementation of panel eGFRs for routine clinical care (71). Measuring filtration markers in addition to creatinine would increase the cost of GFR estimation, but the benefit may be worth the cost if it improves accuracy, improves generalizability across populations, and avoids specification of race.

Until better methods are developed, continuing to assess eGFRcr using the CKD-EPI creatinine equation with the black coefficient in blacks and without the coefficient in nonblacks (including mixed race combinations) or if race is not specified seems reasonable. In some Asian countries, other equations that have been proved to be more accurate than the CKD-EPI creatinine equation can be used. If greater accuracy is needed, eGFRcys in which specification of race is not required and eGFRcr-cys in which the bias from ignoring the black race coefficient is smaller (8%) also seem reasonable. Other confirmatory tests for critical clinical decision making (e.g., medication use and performance of diagnostic tests) include measured creatinine clearance and mGFR, which do not require specification of race. We believe that these strategies are consistent with the current KDIGO guidelines and the criteria proposed by Eneanya et al. (27) for using race to guide clinical care. In addition, we remind clinicians that the appropriate detection, evaluation, and management of kidney disease in all races require evaluation of cause of disease in addition to both GFR and albuminuria (25).

In conclusion, kidney disease is a worldwide public health problem, with racial disparities in incidence, prevalence, and outcomes. Criteria for the definitions of AKI and CKD are independent of race, but eGFRcr, the initial test in GFR assessment, requires specification of race for optimal accuracy, which has limitations. Specification of race improves the accuracy of eGFRcr, in part because of purported race associations with muscle mass and creatinine generation, an important non-GFR determinant of serum creatinine. Serum cystatin C is less affected by muscle mass than serum creatinine; thus, eGFRcys and eGFRcr-cys, confirmatory tests in GFR assessment, are less dependent on specification of race. In the future, using a panel of multiple filtration markers with or without creatinine may enable more accurate GFR estimation without specification of race. We believe that the limitations of use of race in GFR evaluation can be lessened by greater transparency in the use of race in eGFRcr, by mindful use of filtration markers in addition to creatinine, and by future research to address the gaps in mechanistic understanding that we have described.
Acknowledgments
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Supplemental Material
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Supplemental Box. Race, ethnicity, and ancestry.
Supplemental Table. Descriptive characteristics of Chronic Kidney Disease Epidemiology Collaboration participants by race.

References


Supplemental Box. Race, Ethnicity and Ancestry*

**Descriptions and Methods for Ascertainment**

- **Race.** There is no consensus on how to define race; initially proposed as a phenotypic classification based on physical features as a proxy for the identification of a pool of distinct genetic traits; currently understood as a social construct, a “culturally structured, systematic way of looking at, perceiving and interpreting” reality.(1-9)
- **Ethnicity.** Group of individuals tied by the assumption of a common cultural background, derived from beliefs or identities related to nationality, language, culture, diet, “race”, socio-economic status, political and/or religion.(3)
- **Ancestry.** Defined as ancestral descent/lineage. No consensus on exact definition, neither in how to deal with multisource ancestry. May be defined geographically, geopolitically, culturally or genetically. Genetic ancestry can be measure by testing a large number of genetic variants (SNPs) and comparing results to a reference library (for example, Hap Map); alternative genetic ancestry measures are chromosome Y or mitochondrial haplogroups.(10)

**2001 Revised Standards for the Classification of Federal Data on Race and Ethnicity by the US Office and Management and Budget(11)**

**Categories for Race**
- American Indian or Alaska Native. A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.
- Asian. A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
- Black or African American. A person having origins in any of the black racial groups or Africa.
- Native Hawaiian or Other Pacific Islander. A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- White. A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

**Categories for Ethnicity**
- Hispanic or Latino. A person of Cuban, Mexican, Puerto Rican, South or Central American, of other Spanish culture or origin, regardless of race.
- Not Hispanic or Latino.

*Definitions of race, ethnicity, and ancestry are not uniform. The 2003 report by the Institute of Medicine(12) adopted the 2001 revised classification of race and ethnicity recommended by the US Office of Management and Budget(11), because it is “… commonly accepted among researchers, and most federally funded research utilizes these terms” and “… access to and the allocation of healthcare resources differ with striking consistency across these population groups, making them useful in tracking disparities in care.” However, the report noted “these definitions have been subject to considerable criticism, including: reinforcement of the concept of ‘race’ as reflecting genetic or biologic differences between population groups; failure to reflect the fluid and dynamic nature of sociopolitical identity; and failure to reflect the way many Americans choose to define themselves.”*
Supplemental Table. Descriptive characteristics of CKD-EPI participants by race.

<table>
<thead>
<tr>
<th></th>
<th>CKD-EPI Development</th>
<th>CKD-EPI External Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>African American</td>
<td>Non-African American</td>
</tr>
<tr>
<td></td>
<td>(n=2601)</td>
<td>(n=5653)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53 (12.0)</td>
<td>44 (15.2)</td>
<td>49 (14.0)</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>397 (15.2)</td>
<td>2524 (44.6)</td>
</tr>
<tr>
<td>≥40 - &lt;65 years</td>
<td>1729 (66.5)</td>
<td>2425 (42.9)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>475 (18.3)</td>
<td>704 (12.5)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1575 (60.6)</td>
<td>3073 (54.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>297 (11.4)</td>
<td>2109 (37.3)</td>
</tr>
<tr>
<td>Transplant</td>
<td>24 (0.9)</td>
<td>336 (5.9)</td>
</tr>
<tr>
<td>mGFR (mL/min/1.73m²)</td>
<td>55 (27.2)</td>
<td>73 (43.0)</td>
</tr>
<tr>
<td>GFR category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 (mL/min/1.73m²)</td>
<td>502 (19.3)</td>
<td>1193 (21.1)</td>
</tr>
<tr>
<td>≥30 - &lt;60 (mL/min/1.73m²)</td>
<td>1020 (39.2)</td>
<td>1314 (23.2)</td>
</tr>
<tr>
<td>≥60 - &lt;90 (mL/min/1.73m²)</td>
<td>803 (30.9)</td>
<td>884 (15.6)</td>
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<tr>
<td>≥90 (mL/min/1.73m²)</td>
<td>276 (10.6)</td>
<td>2262 (40.0)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.9 (1.1)</td>
<td>1.6 (1.2)</td>
</tr>
<tr>
<td>eGFR&lt;sub&gt;cr&lt;/sub&gt; (mL/min/1.73m²)</td>
<td>55.6 (27.1)</td>
<td>71.3 (38.5)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.00 (0.25)</td>
<td>1.90 (0.23)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.6 (6.7)</td>
<td>27.2 (5.5)</td>
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<tr>
<td>BMI category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 (kg/m²)</td>
<td>46 (1.8)</td>
<td>138 (2.4)</td>
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<td>≥20 - &lt;25 (kg/m²)</td>
<td>400 (15.4)</td>
<td>1828 (32.4)</td>
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<tr>
<td>≥25 - &lt;30 (kg/m²)</td>
<td>854 (32.8)</td>
<td>2132 (37.7)</td>
</tr>
<tr>
<td>≥30 (kg/m²)</td>
<td>1301 (50.0)</td>
<td>1555 (27.5)</td>
</tr>
</tbody>
</table>

Variables are expressed as mean (standard deviation) or n (%). BSA, body-surface area; BMI, body-mass index; mGFR, measured GFR; eGFR<sub>cr</sub>, estimated GFR based on the CKD-EPI creatinine equation. In the external validation population, for BMI and BSA, there were 18 missing values among non-African Americans and 3 missing values among African Americans.

From CKD-EPI study.(13, 14) Note, in the original publication, the development dataset included two subgroups: a development population (2/3) and internal validation population (1/3). African Americans were referred to as Blacks and non-African Americans included Hispanic, Asians, and white or other.
**Kidney Disease, Race and GFR Estimation**
Andrew S Levey, MD; Silvia M Titan, MD, PhD; Neil R Powe, MD, MS, MBA; Josef Coresh, MD, PhD; Lesley A Inker, MD, MS

**References**