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Review

Limited Evidence for Use of a Black Race Modifier in eGFR Calculations: A Systematic Review

Mark A. Marzinke [a,†] Dina N. Greene [b,†] Patrick M. Bossuyt [c] Allison B. Chambliss [d] Lauren R. Cirrincione [e] Christopher R. McCudden,[f] Stacy E.F. Melanson,[g] Jaime H. Noguez,[h] Khushbu Patel,[j] Asa E. Radix [k,l] Yemisi Takwoingi [m] Gabrielle Winston-McPherson,[n] Bessie A. Young [o] and Melanie P. Hoenig [p,*]

BACKGROUND: Commonly used estimated glomerular filtration rate (eGFR) equations include a Black race modifier (BRM) that was incorporated during equation derivation. Race is a social construct, and a poorly characterized variable that is applied inconsistently in clinical settings. The BRM results in higher eGFR for any creatinine concentration, implying fundamental differences in creatinine production or excretion in Black individuals compared to other populations. Equations without inclusion of the BRM have the potential to detect kidney disease earlier in patients at the greatest risk of chronic kidney disease (CKD), but also has the potential to over-diagnose CKD or impact downstream clinical interventions. The purpose of this study was to use an evidence-based approach to systematically evaluate the literature relevant to the performance of the eGFR equations with and without the BRM and to examine the clinical impact of the use or removal.

CONTENT: PubMed and Embase databases were searched for studies comparing measured GFR to eGFR in racially diverse adult populations using the Modification of Diet in Renal Disease or the 2009-Chronic Kidney Disease Epidemiology Collaboration-creatinine equations based on standardized creatinine measurements. Additionally, we searched for studies comparing clinical use of eGFR calculated with and without the BRM. Here, 8632 unique publications were identified; an additional 3 studies were added post hoc. In total, 96 studies were subjected to further analysis and 44 studies were used to make a final assessment.

SUMMARY: There is limited published evidence to support the use of a BRM in eGFR equations.

Introduction

Estimated glomerular filtration rate (eGFR) equations provide important clinical information on renal function; these equations are commonly used in the diagnosis and stratification of chronic kidney disease (CKD), drug and dose selection, and safety assessments for radiologic and oncologic interventions (1). Estimation equations utilize the combination of an endogenous filtration marker with additional surrogates for non-GFR determinants that may impact marker concentrations (2).

Worldwide, creatinine is the most frequently used filtration marker in eGFR calculations, and although its use is widely accepted, its concentration is affected by nonglomerular factors such as variability in tubular secretion and extra-renal variables such as diet, muscle mass, and use of certain drugs. Within the USA, the 2 most commonly used estimation equations for adults are the 4-variable Modification of Diet in Renal Disease (4v-MDRD) and the 2009-Chronic Kidney Disease Epidemiology Collaboration-creatinine (CKD-EPI$_{Cr}$) calculations (3, 4). In practice, eGFR is commonly reported in conjunction with blood creatinine, and implementation of these equations has been fairly straightforward, as neither equation requires an individual's

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height or weight. Rather, both equations estimate glomerular filtration using an individual's serum creatinine concentration, age, sex, and a Black race modifier (BRM). In the original reports describing the development of these equations, incorporation of the BRM appeared to improve accuracy in the populations evaluated, but specific criteria for when to apply the BRM was not defined (3, 4). Inclusion of the BRM results in a 21% and 15.9% higher eGFR at any given creatinine for the 4v-MDRD and CKD-EPI$_{Cr}$ equations, respectively. A higher eGFR in a Black person with the same creatinine concentration as a non-Black person has the potential to impact multiple facets of healthcare, including transplant donor candidacy, transplant recipient prioritization, CKD diagnosis, and drug administration (5).

In laboratory medicine, extensive quality control and quality assurance measures are taken to ensure accuracy and precision, particularly for analytes in which clinical decision points are based. The advent of estimating equations to assess filtration rates prompted such standardization for creatinine measurements. For example, there have been important efforts in establishing standardized creatinine measurements to ensure that the bias between laboratories is minimized (6, 7). By analogy, there is no method to standardize the application of race. Race is a social construct and not a binary term that can be defined by specific demographic or genetic markers (8). Race is inconsistently inferred based on skin color or assessed by self-identification, and is often poorly described in literature, including in studies that use race as a covariate. The potential heterogeneity in the assignment and interpretation of race compromises the applicability of the BRM in eGFR calculations. There are few instances in medicine where visual assessments are appropriate standards. Thus, allowing for bias in estimates based on race influences laboratory result interpretation and downstream clinical care.

The use of the BRM in eGFR calculations has been heavily debated (9). Many clinicians support the removal of the BRM from the MDRD and CKD-EPI$_{Cr}$ calculations, but there has been limited concrete evidence to support a broad scale movement to change this practice. Recently, newly derived equations, which use age, sex, and serum creatinine only, have been published in hopes of reducing racial bias in eGFR assessment (10). Our purpose here was to further examine the use of the BRM as classically applied by an evidence-based approach to systematically assess the medical literature. The application of the BRM in the MDRD and CKD-EPI$_{Cr}$ eGFR equations was questioned and the downstream clinical impact of the use or removal of the BRM was assessed. Our ultimate goal was to assimilate the available literature to evaluate the applicability of the BRM in eGFR calculations, as well as the influence of the modifier on clinical outcomes, particularly in North American settings, which frequently use the BRM.

Methods

This study was conducted by the American Association for Clinical Chemistry (AACC) eGFR and Race Equity Task Force. The Task Force was composed of individuals with expertise in clinical laboratory medicine, nephrology, primary care, pharmacy, and/or evidence-based medicine. Using an evidence-based approach, we performed a systematic review to determine whether there were data supporting the use of the BRM in creatinine-based eGFR calculations.

POPULATION/INTERVENTION/COMPARATOR/OUTCOME PRINCIPLE

The group used the Population/Intervention/Comparator/Outcome (PICO) principle to frame the question used for our literature search to capture relevant studies (11). A schematic of the PICO principle applied to our research question is shown in Fig. 1. The population evaluated included adults in any setting (inpatient, outpatient, community). The intervention and associated comparator were defined as creatinine-based eGFR equations ± BRM compared to a direct measurement of GFR (mGFR) or creatinine clearance. Comparator equations used to calculate eGFR included the 4v-MDRD and CKD-EPI$_{Cr}$ equations, unless otherwise stated. In some cases, the eGFR calculation without the BRM was inferred but was not directly provided in the publication. Outcomes evaluated included: early identification of kidney disease; potential delay in progression of renal disease; more rapid decline in kidney function; morbidity related to kidney disease; drug dose changes; morbidity not related to underlying kidney disease and cardiovascular events; delay in need for dialysis or transplant; referral as transplant recipient or donor; and/or survival.

LITERATURE SEARCH

Our strategy aimed to retrieve a wide range of publications that would provide indirect assessment or linkage to outcomes because randomized controlled trials or robust comparative studies were unlikely to be available. Databases were queried in consultation with librarians at the University of Washington Health Sciences Library (Seattle, WA). PubMed and Embase Elsevier databases were searched using medical subject headings (MeSH) terms and keywords in the title or abstract fields from inception through May 6, 2021, for concepts of kidney function and race. Supplemental File 1 in the online Data Supplement summarizes the search

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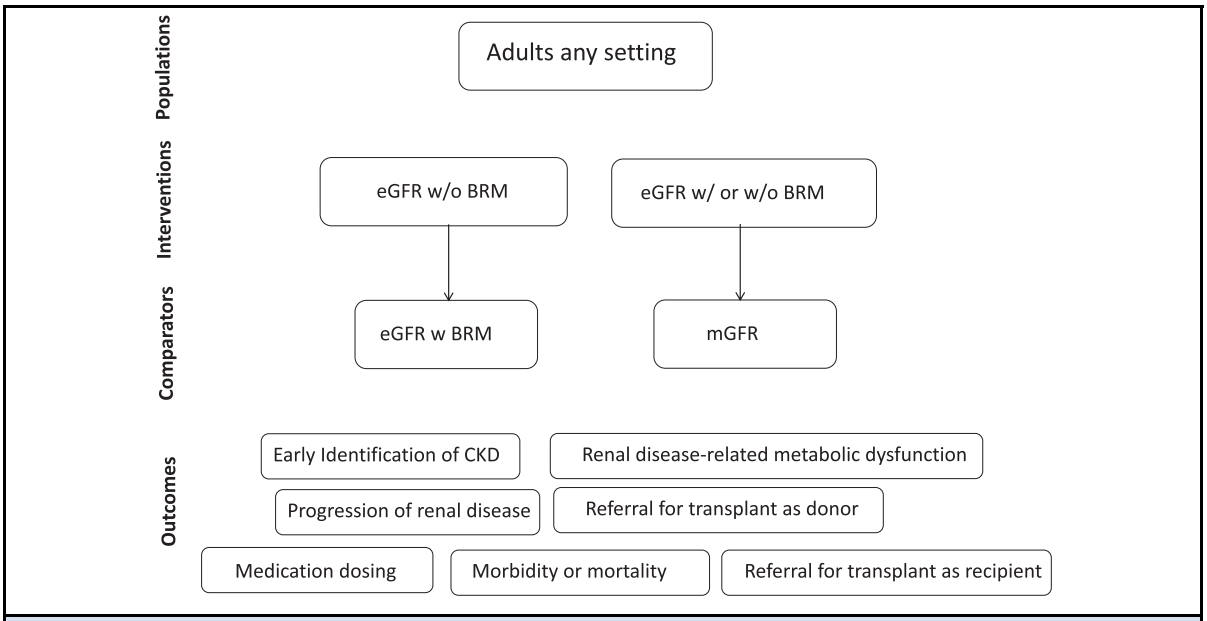

Fig. 1. Schematic of the population/intervention/comparator/outcome principle used to assess the utility of using the BRM in eGFR equations.

terms used. Identified studies were collated as an .xml file and uploaded into the Covidence™ systematic review management software program (Melbourne, Australia). Studies were screened for duplications, and nonduplicated publications were extracted as an .xml file and uploaded into Covidence. Literature screening and review steps were conducted in Covidence.

ELIGIBILITY SCREENING

Publications were eligible if they reported on studies that had assessed the following in a racially diverse adult cohort: compared eGFR with the inclusion and/or exclusion of the BRM to gold-standard mGFR methods (^{51}Cr-EDTA, ^{99m}TC-DTPA, or iohexol clearance); eGFR comparisons with and without the BRM; or linkage of eGFR with or without the BRM to clinical outcomes. Studies were ineligible if race was used exclusively as a risk factor; if CKD reclassification was evaluated without assessing exclusion of the BRM (e.g., MDRD with BRM to CKD-EPI$_{Cr}$ with BRM); if there was insufficient data to perform an informed comparison.

Studies were excluded based on one of the following criteria: publication in a non-English language; use of an Asian-specific eGFR equation; opinion piece/review; case report; incorrect analyte (e.g., focus on urine albumin, cystatin C); non-4v-MDRD or non-CKD-EPI$_{Cr}$ equation/comparator; population <18 years of age; or selective population (e.g., race was not specified; individuals with acute kidney injury).

Each publication's title and abstract were screened by 2 individuals to determine if the published content contained information that evaluated the use of the BRM in commonly used eGFR equations, and scored as "yes," "no," or "maybe." Publications screened "yes" by both reviewers were selected for a full-text review; publications screened "no" by both reviewers were excluded from further analysis; abstracts assigned as "maybe" by either reviewer and abstracts with discordant reviews were adjudicated by a third member or subjected to a group discussion.

Full-text reviews were performed independently by 2 individuals to further evaluate whether the publication was relevant to the research question; included studies were then subjected to qualitative data extraction. If a study was excluded for more than one reason, the highest ranked exclusionary criterion was selected in Covidence. Discordant assessments were adjudicated by a subset of Task Force members with specific expertise in kidney care and/or laboratory medicine.

DATA EXTRACTION

Data from included studies were extracted using word-based extraction templates (Supplemental File 2). Key parameters captured included: demographic information (including the reported race of participants), study design and setting, analytical methods and eGFR equations, interventions conducted, and outcomes assessed. During data extraction, reviewers were allowed to

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further exclude studies if they did not meet the group's PICO principle; exclusion of studies at this step was based on a subgroup discussion and consensus agreement. Further, additional studies were evaluated for inclusion during this step if they were identified from references within the primary search literature or were found in the public domain but had not been retrieved from the initial query.

DATA CATEGORIZATION

Included studies were divided into 2 main categories, those that assessed whether the BRM improved the accuracy of the eGFR and those that explored outcomes related to the use of the BRM. The majority of studies in the former group were performed in African settings; however, we also identified several reports from Brazil. Studies in the outcomes category were stratified as follows: metabolic derangements and renal outcomes; kidney transplant donors; medication dosing; and changes in CKD categorization.

METHODOLOGICAL QUALITY ASSESSMENT

To identify potential deficiencies in included studies, the team assessed overall methodological quality. Given the variety of study designs that were anticipated, we chose to evaluate quality as pertaining to the review questions rather than to use a single instrument or assessment tool. Our evaluation of methodologic quality was informed by, but not limited to, the following features: quality of study population; quality of the study design; analytical methods used, including assessment of creatinine methodology and isotope dilution mass spectrometry traceability; and author interpretation. We prospectively identified areas of particular concern as the following: repeated use of the same population; small number of Black participants; repeated conclusions by same authorship; use of nonstandardized creatinine measurements; and/or deficiencies in data analysis.

REGISTRATION

This study was registered with the Open Source Framework (Number 10.17605/OSF.IO/59X86).

Results

IDENTIFICATION OF PUBLICATIONS FOR DATA EXTRACTION

Using defined MeSH terms, 8632 unique publications were identified (Fig. 2). Of these, 413 full-text publications were assessed for eligibility and 320 were excluded. Studies were most commonly classified as ineligible due to insufficient data for comparing eGFR results (27%) and using an incorrect study design, such as the use of Black race as a risk factor for kidney disease (20%). Studies were most commonly excluded due to use of Asian-specific eGFR equations (10%). After exclusion and initial eligibility assessments, 93 studies (1.08% of all studies screened) remained for analysis and data extraction. After evaluation of study references and augmented review of literature databases, an additional 3 studies were identified, resulting in a total of 96 studies for further analysis.

Of the 96 studies, 12 focused on Indigenous populations from Australia or the USA and did not use the BRM; 30 studies considered the performance of the BRM in African and Brazilian populations and 54 explored the accuracy of the equations and the impact of the equations on outcome. These 84 included studies were subjected to data extraction using a standardized template (Supplemental File 2). Overall, we noted that race was inadequately defined or described in many of the studies included in our analysis.

COMPARISON OF eGFR CALCULATIONS TO mGFR IN AFRICAN/BRAZILIAN POPULATIONS

There were 30 studies conducted in African and Brazilian settings, including 27 cross-sectional studies, 2 longitudinal studies, and 1 commentary (Fig. 3). One study was excluded post hoc because it was a commentary, and 1 cross-sectional study was excluded because it was an abstract. Methodologic shortcomings were noted in 8 of 28 (29%) of eligible African/Brazilian studies; these deficiencies may compromise the validity of the findings. The most common shortcomings included over-interpretation of study findings; deficiencies in study design; and inadequate description of the criteria for assigning race in the study group evaluated. However, none of these were identified in studies in which there was a direct comparison between eGFR calculations and mGFR.

Ten cross-sectional studies compared mGFR via ^{51}Cr-EDTA, ^{99m}TC-DTPA, or iohexol clearance with the 4v-MDRD or CKD-EPI$_{Cr}$ eGFR equations in the presence or absence of the BRM (Table 1) (12–21). Across these studies, data from 1749 individuals were evaluated; settings were enriched for Black African, Brazilian, or admixed populations. Healthy persons, persons living with human immunodeficiency virus (HIV) and naïve to antiretroviral therapy, and individuals with CKD were all represented in these studies. We extracted comparison data from the 10 studies to identify the estimation calculation that provided the closest overall agreement with mGFR. In all studies, calculations without the BRM showed closer agreement with mGFR results in Black participants. Three of these studies evaluated eGFR using the kidney biomarker cystatin C; in all of these studies, cystatin C-based equations showed improved agreement with mGFR when compared to creatinine-only estimations (13, 17, 20). In Black African populations, generalized conclusions from these studies recommend exclusion of the BRM in

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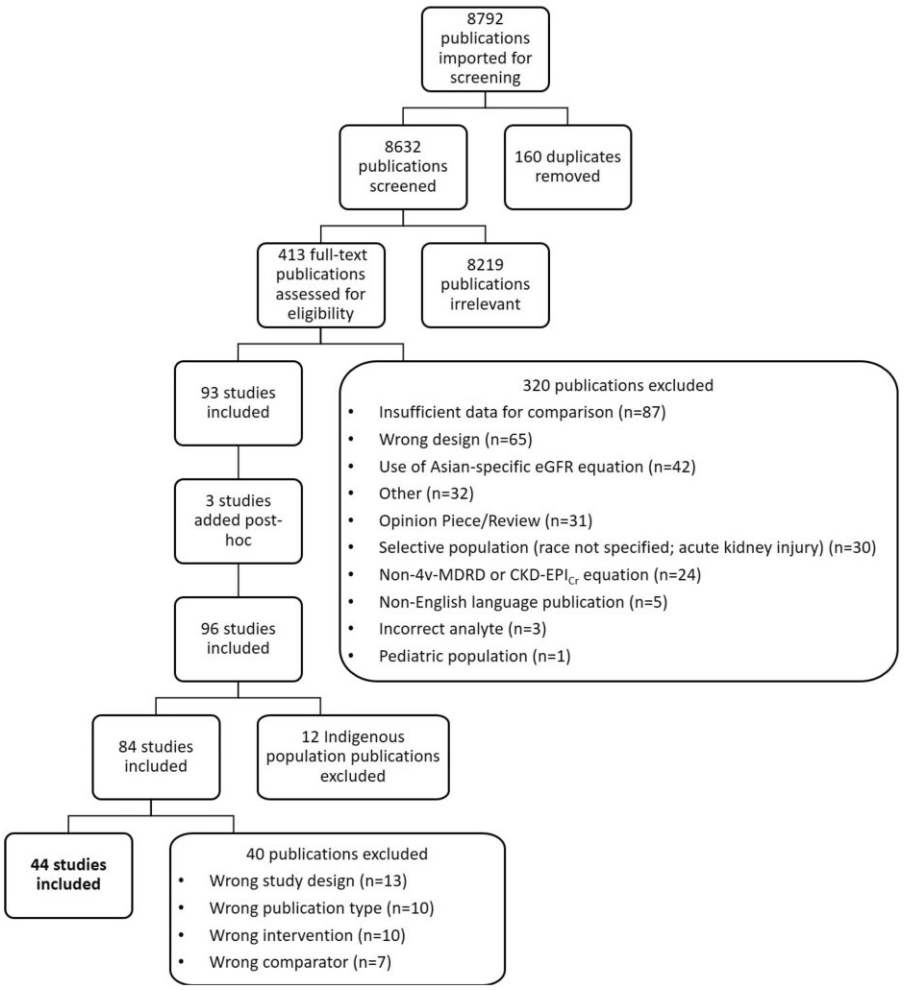

Fig. 2. **Preferred reporting items for systematic reviews and meta-analyses diagram. Workflow for the identification of relevant studies to address the utility of the BRM in eGFR equations.**

eGFR equations due to poorer agreement with mGFR results.

Nine of the 28 (32%) studies compared equation performance to other measures of kidney function, including 24-hour CrCl, estimated clearance by the Cockcroft–Gault equation, and urinary albumin to creatinine ratio (Supplemental Table 1). Although 24 h CrCl and the Cockcroft–Gault clearance overestimate filtration and are associated with increased scatter, 24 h CrCl was still viewed as a reference method at the time many of these studies were conducted (22). Within 7 (78%) of these studies, eGFR equations without the BRM demonstrated improved agreement with CrCl or the presence of albuminuria. Two studies presented mixed results; however, neither study compared eGFR results to mGFR (8, 9). Omuse and colleagues supported the use of the CKD-EPI$_{Cr}$ equation with the BRM in a non-CKD African population, but acknowledged that additional work was required to determine if inclusion of the BRM was appropriate as a screening tool in African community settings (23). Nobrega and colleagues demonstrated comparable performance of the 4v-MDRD ± BRM and Cockcroft–Gault equations with CrCl in an admixed Brazilian population; however, the authors conceded that, in this population, inclusion of the BRM may not improve accuracy of filtration equations and may not be applicable in a Brazilian population (24).

In the remaining 9 of 28 studies conducted in African and Brazilian settings, a direct comparison of eGFR ± BRM was not assessed. However, in 5 of these studies, eGFR calculations without the BRM were used to evaluate

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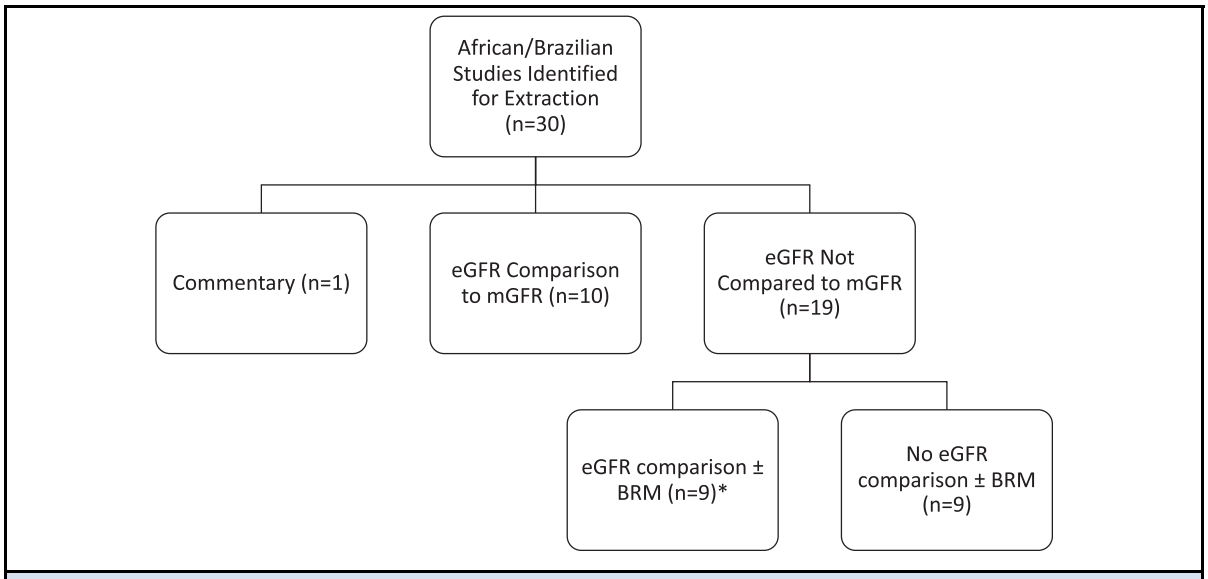

Fig. 3. Categorization of African/Brazilian studies identified for data extraction and evaluation. *One study was excluded because it was an abstract.

kidney function in diverse populations throughout the Democratic Republic of Congo, South Africa, Uganda, and Zimbabwe (Supplemental Table 2). Within these studies, removal of the BRM to estimate GFR was based on the findings from previous reports, which showed that BRM inclusion overestimates kidney function in these populations.

EQUATION COMPARISONS IN NON-AFRICAN/BRAZILIAN POPULATIONS AND STUDIES LINKED TO OUTCOME

Fifty-four unique studies were identified that compared eGFR to mGFR outside of African and Brazilian settings or linked the equation to outcome (Fig. 4). Of these, 51 were identified from the forward search; 3 were identified using a reverse approach whereby the committee extracted the text of select references within the included studies. On further review, 38 studies were excluded due to: using Black race exclusively as a risk factor (wrong comparator; $n = 7$), wrong publication type (commentary, abstract only, review $n = 8$), wrong study design (no BRM assessment; $n = 13$), or wrong intervention (comparison of only BRM-inclusive equations; $n = 10$) (Supplemental Table 3). Most of the included studies were cross-sectional ($n = 12$) (25–36), 3 were longitudinal (37–39), and 1 was both cross-sectional and longitudinal (40). Fifteen of the 16 included studies featured North American populations; 1 report (28) was conducted in the UK.

The 16 included studies fell into 4 broad categories: those that examined metabolic or kidney endpoints in the context of the eGFR ($n = 4$), those evaluating kidney donors ($n = 4$), and those which recalculated eGFR with and without the BRM to identify the number of individuals who would be affected at clinically meaningful thresholds of care due to medication dosing ($n = 2$) or changes in CKD categorization ($n = 6$) (Table 2). Overall, the most consistent quality deficiency of the included studies was that most were unable to document actual outcomes related to the potential CKD reclassification (4 of 6 studies) or clinical impact of medication changes (2 of 2 studies). This is a general limitation of cross-sectional and/or retrospective studies and prohibited definitive conclusions regarding kidney function and appropriate management with or without the BRM. An additional bias was seen in sampling from the same population. Levey et al. demonstrated that mGFR most closely correlated to eGFR calculated with the BRM, but this cohort was identical to that used to derive the equation, limiting its broader applicability (34).

METABOLIC DERANGEMENTS AND KIDNEY OUTCOMES

Metabolic parameters or kidney endpoints were assessed in 4 studies. de Boer et al. examined patients at different levels of kidney function, categorized by eGFR, and found that compared to White participants, Black participants had more secondary hyperparathyroidism at higher eGFRs using the BRM (25). Similarly, Ibrahim found that Black participants with eGFR <60 mL min^{-1} (1.73 m^2)$^{-1}$ using the BRM more frequently presented with anemia, hyperuricemia, and hyperparathyroidism

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Table 1. Comparison of eGFR calculations to mGFR in African/Brazilian populations.

Author	Year	Country	*N*	% Black	Population enriched	Equations	mGFR method	eGFR equation with closest agreement with mGFR
Van Deventer et al (12)	2008	South Africa	100	100	Hypertension; T2DM; HIV+	C-G; 4v-MDRD	^{51}Cr-EDTA clearance	4v-MDRD without BRM
Van Deventer et al. (13)	2011	South Africa	100	100	Hypertension; T2DM; HIV+	CKD-EPIcr[a]; 4v-MDRD[a]; novel Cr and Cys equations	^{51}Cr-EDTA clearance	Novel equations with cys; CKD-EPI$_{Cr}$ without BRM
Madala et al. (14)	2012	South Africa	148	62	CKD	C-G; 4v-MDRD	^{99m}Tc-DTPA clearance	4v-MDRD without BRM
Zanocco et al. (15)	2012	Brazil	244	8	CKD	C-G; CKD-EPI$_{Cr}$; 4v-MDRD; Mayo Clinic; Brazil eGFR	iohexol clearance	CKD-EPI$_{Cr}$ without BRM
Wyatt et al. (16)	2013	Kenya	99	NS	HIV+/ART-naïve	C-G; CKD-EPI$_{Cr}$; 4v-MDRD	iohexol clearance	CKD-EPI$_{Cr}$ without BRM
Seape et al. (17)	2015	South Africa	97	100	HIV+/ART-naïve	C-G; CKD-EPI$_{Cr}$; CKD-EPI$_{cys}$; CKD-EPI$_{Cr-cys}$; 4v-MDRD; novel S-Cys-C equation	^{51}Cr-EDTA clearance	CKD-EPI$_{Cr-cys}$ without BRM
Moodley et al. (18)	2018	South Africa	287	66	Malignancy; Hypertension; T2DM; HIV+	CKD-EPI$_{Cr}$; 4v-MDRD	^{99m}Tc-DTPA clearance	CKD-EPI$_{Cr}$ without BRM
Bukabau et al. (19)	2019	Democratic Republic of CongoCôte d'Ivoire	494	NS	None; community	CKD-EPI$_{Cr}$; 4v-MDRD; FAS	iohexol clearance	CKD-EPI$_{Cr}$ without BRM
Rocha et al. (20)	2020	Brazil	100	61[b]	CKD	CKD-EPI$_{Cr}$; CKD-EPI$_{Cr-cys}$	^{51}Cr-EDTA clearance	CKD-EPI$_{Cr-cys}$ without BRM
Holness et al. (21)	2020	South Africa	80	NS[c]	CKD	CKD-EPIcr; 4v-MDRD	^{99m}Tc-DTPA clearance	CKD-EPIcr without BRM

Abbreviations: 4v-MDRD: 4 variable Modification of Diet in Renal Disease; ART: antiretroviral therapy; BRM: Black race modifier; C-G: Cockroft-Gault; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; Cr: creatinine; cys: cystatin C; DTPA: Diethylenetriamine pentaacetate; EDTA: Ethylenediaminetetraacetic acid; HIV: human immunodeficiency virus; mGFR: measured glomerular filtration rate; T2DM: type 2 diabetes mellitus.
[a]BRM not used for eGFR calculations.
[b]African-Brazilian; admixed population.
[c]All participants self-identified as mixed ancestry.

(26). Peralta et al. documented that Black men with an eGFR of 60–80 mL min^{-1} (1.73 m^2)$^{-1}$ had a 2.5-fold higher prevalence of albuminuria and hyperuricemia when compared to White participants with similar kidney function (27). Last, Mahmud et al. evaluated baseline eGFR in cirrhotic patients with and without the use of the BRM, finding that removal of the BRM increased the association between lower eGFR and higher rates of acute kidney injury (AKI) (37). In these 4 studies, use of the eGFR with the BRM resulted in discordance with other markers of kidney disease in Black patients.

KIDNEY TRANSPLANT DONORS

Evaluation of potential kidney donors using the eGFR with BRM was assessed in 3 studies (28–30). By comparing mGFR to eGFR, all 3 concluded that the eGFR overestimated the mGFR in Black donor candidates and that use of the BRM had the potential to allow kidney donation by candidates who should be rejected for reduced kidney function. One of these studies was conducted in the UK and the authors postulated that the BRM might not be applicable outside North America. Decline in kidney function based on the eGFR in living kidney donors was assessed in a single study where the investigators compared eGFR in White and Black patients before and after kidney donation and found that Black donors had a more significant decline in eGFR after donation, suggesting that inclusion of the BRM in eGFR calculations may overestimate kidney function in Black kidney donors (38).

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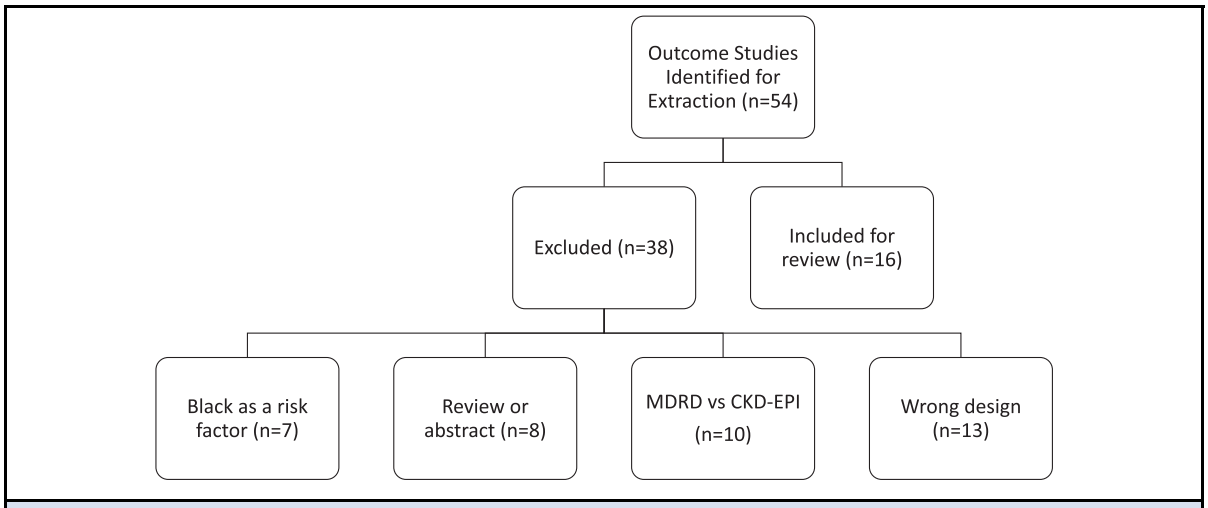

Fig. 4. Categorization of outcome studies identified for data extraction and evaluation.

MEDICATION DOSING

The influence of the BRM in medication dosing was evaluated in 2 studies. Miller and Knorr compared CKD-EPI$_{Cr}$ with and without the BRM deindexed for body surface area and concluded that the exclusion of the BRM correlated more closely with estimated CrCl from the Cockcroft–Gault equation, which was used to establish most dosing guidelines (31). The second study recalculated eGFR in patients from the NHANES database with type 2 diabetes mellitus to determine how many patients would no longer be eligible for metformin or sodium-glucose transporter type 2 (SGLT2) inhibitors after removal of the BRM. These studies were not designed to confirm which medication dosing was most clinically appropriate, only that use of the BRM would change prescribing patterns in a subset of Black individuals (32).

CHANGE IN CKD CATEGORIZATION

Four studies retrospectively re-examined datasets to evaluate the effects of excluding the BRM from eGFR calculations. In these mathematical exercises, removal of the BRM for Black patients reclassified many individuals to a more severe stage of CKD. Ahmed et al. found that 33.4% of patients with established CKD at a large metropolitan hospital system would be reclassified to a later stage of CKD and 3.1% would achieve a qualifying eGFR to be eligible for kidney transplantation listing (40). Diao et al. found that 29.1% of NHANES participants with established CKD based on eGFR with the BRM would be reclassified as having a more severe stage of CKD in the absence of the BRM. In addition, they reported that the number of Black persons with CKD stage 4 would increase from 1.0% to 1.3% with removal of the BRM (35). Ku et al. examined transplant eligibility for Chronic Renal Insufficiency Cohort participants and found that removal of the BRM reduced the disparity between Black and White participants (36). The results also documented an attenuated difference in proteinuria between Black and White participants when the BRM was removed. In a cohort of HIV positive persons, Anker et al. calculated that removal of the BRM improved the association between eGFR and all-cause mortality (39).

Two studies looked at the performance of eGFR calculations as a function of the bias between mGFR and eGFR. One of these compared mGFR to eGFR ± BRM using data from the Black patients included in the CKD-EPI development cohorts. The authors concluded that eGFR with the BRM improved the association with mGFR (34). The second study observed that, relative to mGFR, eGFR calculated with the BRM for Black women had the most bias compared to Black men and White men or women, although minimal bias between demographic categories was observed for eGFR values <60 mL min^{-1} (1.73 m^2)$^{-1}$ (33).

Discussion

Using a PICO-guided, evidence-based approach, we observed that there is little published evidence to support the inclusion of the BRM in commonly utilized eGFR equations. Only 1 of the identified studies demonstrated that the modifier improved estimation accuracy on a population level and suggested clinical benefits in Black populations. However, this report used the study group from which the CKD-EPI$_{Cr}$ equation was derived (34). Overall, the use of the BRM in the 4v-MDRD and

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Table 2. Comparison of eGFR calculations to mGFR in non-African/Brazilian populations; Linkage of eGFR to clinical outcomes.

Author	Year	Population assessed	*N*	% Black	Outcome evaluated	eGFR equations used	mGFR	eGFR assessed ±BRM
A. Metabolic derangements and kidney outcomes								
De Boer et al. (25)	2002	CKD clinic	218	22	Metabolic derangements	4v-MDRD	no	no
Ibrahim et al. (26)	2008	NHANES participants	8918	11	Metabolic derangements	4v-MDRD	no	no
Peralta et al. (27)	2010	CARDIA participants	3504	47	CKD, metabolic derangements, albuminuria	4v-MDRD; CKD-EPI$_{Cr}$; CARDIA	no	no
Mahmud et al. (37)	2021	cirrhotic patients	72 267	19.7	AKI risk	4v-MDRD; CKD-EPI$_{Cr}$	no	yes
B. Kidney transplant donors								
Parasuraman et al. (38)	2008	Kidney donors	103	52	Decline in eGFR after donation	4v-MDRD	no	no
Bhuvanakrishna et al. (28, *)	2015	potential kidney donors	508	11.8	Donor candidacy vs ^{51}Cr-EDTA clearance	CG; 4v-MDRD; CKD-EPI$_{Cr}$	yes	no
Akhimiona et al. (29)	2018	potential kidney donors	210	11.4	Donor candidacy vs I^{125}-labeled iothalamate clearance	CKD-EPI$_{Cr}$	yes	yes
Garg et al. (30)	2019	potential kidney donors	769	10.4	Donor candidacy vs I^{125}-labeled iothalamate clearance	CKD-EPI$_{Cr}$; CrCl; CER2, CER4	yes	no
C. Medication dosing								
Miller et al. (31)	2021	hospitalized patients	210	84	Antibiotic dosing discordance	CG; CKD-EPI$_{Cr}$–deindexed for BSA	no	yes
Walther et al. (32)	2021	NHANES participants	923	100	Change CKD category; eligibility for T2DM medications	CKD-EPI$_{Cr}$	no	yes
D. Change in CKD categorization								
Anker et al. (39)	2016	HIV veterans	21 905	55	Change in CKD category; mortality	4v-MDRD; CKD-EPI$_{Cr}$	no	yes
Inker et al. (33)	2018	MESA participants	294	47	Equations vs iohexol clearance	CKD-EPI$_{Cr}$; CKD-EPI$_{cys}$; CKD-EPI$_{Cr\text{-}cys}$	yes	no
Ahmed et al. (40)	2020	outpatients at 2 tertiary care centers	56 845	3.9	Change in CKD category; transplant eligibility	CKD-EPI$_{Cr}$	no	yes
Levey et al. (34)	2020	CKD-EPI population	2601	100	Equation performance	CKD-EPI$_{Cr}$	no	yes
Diao et al. (35)	2021	NHANES participants	9522	100	Change in CKD category; transplant eligibility	CKD-EPI$_{Cr}$	no	yes
Ku et al. (36)	2021	CRIC participants	444	65	Transplant eligibility	CKD-EPI$_{Cr}$; CKD-EPI$_{cys}$; CKD-EPI$_{Cr\text{-}cys}$	no	yes

Abbreviations: 4v-MDRD: 4 variable Modification of Diet in Renal Disease; BRM: Black race modifier; BSA: body surface area; AKI: acute kidney injury; CER: creatinine excretion rate; CARDIA: Coronary Artery Risk Development in Young Adults; C-G: Cockroft-Gault; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; Cr: creatinine; cys: cystatin C; CrCl: creatinine clearance; CRIC: Chronic Renal Insufficiency Cohort; EDTA: Ethylenediaminetetraacetic acid, HIV: human immunodeficiency virus; MESA: Multiethnic Study of Atherosclerosis; mGFR: measured glomerular filtration rate; NHANES: National Health and Nutrition Examination Survey; T2DM: type 2 diabetes mellitus.
*Conducted in the UK.

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$CKD\text{-}EPI_{Cr}$ equations showed lower concordance with gold-standard measures of GFR; this was highly evident across Black African cohorts. Further, our findings demonstrate that there is insufficient data to illustrate a benefit of using the BRM in supporting clinical outcomes.

We identified several critically relevant studies conducted in Black African populations that directly assessed the applicability of the BRM in eGFR equations. When compared to iohexol, ^{99m}Tc-DTPA, or ^{51}Cr EDTA clearance assessments, it was consistently observed that the use of the BRM resulted in increased bias and decreased precision and accuracy of filtration rate estimates (12, 16, 18, 21). For example, in an admixed African population enriched for CKD, the percentage of patients whose eGFR was within ±30% of ^{99m}Tc-DTPA clearance (P_{30}) decreased from 80% to 51% when the BRM was applied to the 4v-MDRD equation; similar observations were made when the $CKD\text{-}EPI_{Cr}$ equation was used (21). Bukabau and colleagues concluded that the BRM was not accurate in healthy or diseased African populations, and that BRM-inclusive eGFR bias and imprecision were exacerbated in healthy populations (19). The authors further suggested that the lack of transferability of the BRM to African populations may be attributable to differences in muscle mass or diet between sub-Saharan African participants and African-Americans. However, the use of muscle mass or body weight as stratifying features has also been called into question (41). The finding that the BRM does not improve eGFR accuracy in African populations is not a new observation; however, this is the first time that these studies have been combined in a systematic review that includes data on 1749 Black individuals, nearly 10 times the number of Black individuals in the MDRD study and comparable to the number of Black individuals in the development set of the $CKD\text{-}EPI_{Cr}$ equation (3, 4).

Although the use of BRM-inclusive eGFR equations is commonplace in the USA and Canada, the BRM is frequently not used when estimating GFR in African settings. During our review of studies, we also noted similar approaches in Asian-enriched populations; many eGFR equations have been developed in Asian populations, which include population-specific modifiers or employ alternative equations to estimate GFR (42). Importantly, none of the race modifiers for eGFR equations consider how to define race or whether to equate it with ancestry; none account for individuals of mixed race, what proportion of ancestry is required for use of a race modifier, and how to apply the coefficient if ancestry differs from how an individual self-identifies (43). Use of binary coding to reflect ethnic and ancestral backgrounds oversimplifies the genetic diversity of the population and is error prone (44). Indeed, in a study comparing self-reported ancestry to genetic background, those who self-reported as African American were on average 82% African but the range was 0.6%–100% and those who self-reported as Hispanic/Latino Americans were 28.6% African with a range of 0%–100% (45). These discrepancies underscore the challenges of using an imprecise and often subjective term in estimation equations in the categorization of kidney function.

Our systematic review identified a limited number of studies that linked the use of the BRM in estimated GFR calculations to outcomes. Several studies identified more metabolic consequences of CKD in Black individuals with higher eGFRs. Instead of questioning whether BRM inclusion may overestimate kidney function, the authors postulated that there may be additional innate differences in metabolism of urate or race-specific differences in parathyroid hormone dynamics to explain these findings (25, 26). These studies did not assess if removal of the BRM would minimize the observed disparities, but, taken together, these outcomes suggest that the use of the BRM in the eGFR may overestimate kidney function.

Removal of the BRM will predictably result in a lower eGFR for Black participants compared to the estimate when the BRM is applied. In the cohort of Black patients used to develop the $CKD\text{-}EPI_{Cr}$ equation with the BRM, this leads to an apparent underestimate of kidney function, which was the foundation for including the modifier in clinical practice recommendations (34). Proponents of the equations with the BRM suggest simply removing the BRM will result in a range of adverse consequences, including exclusion of potential kidney donors. We identified 3 studies that addressed donor evaluation, and all found that BRM inclusion overestimated potential donor kidney function in Black participants. Thus, removal of the BRM may protect potential donors from harm rather than limit donation by a healthy donor. Further, we identified one report that found a greater decline in eGFR after donation for Black donors. The authors postulated that calculated eGFR overestimated kidney function in Black donors or that Black donors might have less functional reserve than White donors (38).

The BRM also has important implications for the potential kidney transplant recipient. Since the eGFR equations result in higher estimates of kidney function at any given creatinine for Black patients, Black patients must have a higher creatinine than White patients to achieve a qualifying eGFR for kidney transplant eligibility. Removal of the BRM has the potential to allow Black patients to be listed for kidney transplant with the same criteria as non-Black patients; several studies calculated the number of individuals who would benefit from such a change (35, 36, 40). Recently, this benefit was demonstrated at one institution in a small number of patients who achieved a qualifying eGFR without the BRM and were listed for preemptive transplant, on average, 1 year earlier than if the eGFR was calculated with the BRM (46).

Removal of the BRM would assign a more severe CKD stage for a percentage of patients whose kidney

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function is close to clinically significant thresholds for care. This may result in a new diagnosis of CKD that should prompt simple measures such as an increased attention to blood pressure and measurement of urinary albumin or additional assessment of kidney function to confirm the diagnosis in the spirit of shared decision-making between patients and providers (47).

Reclassification of CKD staging can also impact pharmacologic dosing. This is of particular concern for patients with reduced kidney function who have type 2 diabetes mellitus, as both metformin and SGLT2 inhibitors are not recommended below eGFR of 30 mL min^{-1} $(1.73\ m^2)^{-1}$ (32). We found only 1 report that examined this issue but it was based on hypothetical changes in renal function rather than clinical practice (32). Recently, this topic was examined in a sample of cancer patients for dosing chemotherapeutic agents that are renally cleared. In this simulation, 1%–18% of patients would have required a reduction in therapeutic dosing. Since eGFR is a calculated estimate, and chemotherapeutic agents are associated with significant potential toxicity, careful assessment of kidney function is required (48).

Adoption of eGFR equations prompted a movement to streamline the terminology used to describe kidney function and standardization of creatinine measurement. These efforts also led to the adoption of a more comprehensive and collaborative federal response to CKD (49). Yet the use of BRM-inclusive calculations, which result in better kidney function for Black patients at every creatinine concentration, can lead to harm. Since race is a social construct and cannot be precisely defined or implemented, the use of race-specific modifiers in healthcare can contribute to significant disparities in clinical diagnoses, access to care, and clinical interventions (50–53). The inclusion of race in eGFR equations inherently engenders bias and promotes mistrust between marginalized patient populations and the healthcare system. Social justice reforms in the medical community are needed to achieve healthcare equity (54).

The findings from this work align with current position statements and commentaries calling for the removal of the BRM in eGFR equations (5, 55–57). Several institutions have already initiated changes to eGFR reporting practices (50). Deployed modifications include removal of the BRM from the 4v-MDRD or CKD-EPI_{Cr} equations and reporting a single eGFR result per creatinine measurement; the re-expression of race as low or high muscle mass; reporting eGFR as a range; or the inclusion of an interpretive comment to provide clinical decision support on the appropriate interpretation of eGFR values. While there is merit to each of these approaches, caution is also needed, as increased variability can lead to further destandardization of eGFR reporting, leading to unintended consequences on clinical care. In 2020, the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) established a joint task force to examine the social and clinical implications of including the BRM in eGFR equations, as well as identifying approaches to GFR estimating equations that are unbiased and promote healthcare equity. An interim report published in June 2021 outlined the steps taken to reach consensus (9). The NKF/ASN Task Force subsequently published a unifying report and a new equation (10, 58). The equation is designed to reduce bias in eGFR and offer a standardized approach for implementation. Further, the new equation removes the necessity to identify people by race, which aligns with the data collated in this systematic review. Our Task Force endorses this unifying approach to eGFR reporting, which reinforces the steps that laboratories take for precision in creatinine measurements and their postanalytical interpretation.

As evidenced by this work, there is an absence of substantial data demonstrating analytical or clinical benefit to the use of the BRM in eGFR equations. Further, these results illustrate that an estimated filtration rate is still an estimate, and when values are close to a clinically significant cut off, it should not be used independent of other factors. Other biomarkers of kidney dysfunction, including serum/plasma cystatin C and the urine albumin/creatinine ratio, can also provide useful information on filtration rate and future risk of kidney failure, respectively (59, 60). Although studies focused solely on cystatin C as a renal biomarker were not part of our eligibility criteria, several eligible studies compared creatinine-based eGFR equations with estimation equations containing cystatin C. Notably, estimation equations that only use cystatin C as the kidney biomarker do not require a race modifier, suggesting potential expansion and adoption of cystatin C as a preferred kidney biomarker, particularly in highly admixed or diverse populations (61). The NKF/ASN Task Force has also incorporated cystatin C into their recommendations, deriving a new equation that uses cystatin C and creatinine. This equation is free of racial modifiers and more accurately classifies patients relative to the creatinine-only equations in estimating GFR (10, 58).

Although our findings are consistent with previous evaluations, there are limitations in our methodologic approach. In this systematic review, we noted heterogeneity in the types of studies available in publicly available databases; there was an overall paucity in the number of studies that performed direct equation comparisons in the presence of absence of the BRM or used a randomized design. Consequently, we did not expect to observe substantial direct evidence demonstrating the health effects of the BRM for Black populations; rather, we relied on indirect evidence, including the linkage of eGFR in the presence and/or absence of the BRM to clinical outcomes. Further, given the variety of study designs encountered in our investigation, we were

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unable to use a single instrument to evaluate methodological or reporting quality; we therefore relied on subjective assessments of study population appropriateness, study design quality, and author interpretation. In some studies, including many ineligible or excluded studies, we commonly noted concerns as related to author interpretation of study findings. This was predominantly observed in studies that tried to link evidence between eGFR and clinical outcomes. Another limitation of our study, at the core of the issue with the BRM, is that race is a social construct and whether defined by self or other, it is inconsistently applied. As such, the included studies were inherently flawed by the inconsistent manner in which race was defined or reported. Last, we did not account for data missingness in this assessment; the studies included during the eligibility screening and data extraction were based on only 2 databases. A cutoff date of May 6, 2021, was implemented. Given the timely nature of this topic, it is expected that additional studies will become available and may be included in future assessments.

In conclusion, our systematic review of the literature suggests there is little evidence supporting the inclusion of a race modifier in eGFR calculations. The use of the BRM does not demonstrate any analytical or clinical benefit in clinical diagnoses and treatment, but rather may contribute to healthcare inequities and social harms. Pursuit of alternatives to BRM-inclusive eGFR calculations is therefore recommended to mitigate health disparities among marginalized populations and provide a more accurate assessment of renal function in adult populations, agnostic of social constructs of race and ethnicity.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: eGFR, estimated glomerular filtration rate; BRM, Black race modifier; CKD, chronic kidney disease; mGFR, measured GFR; MDRD, Modification of Diet in Renal Disease; CKD-EPI$_{Cr}$, 2009-Chronic Kidney Disease Epidemiology Collaboration-creatinine; 4v-MDRD, 4-variable Modification of Diet in Renal Disease; PICO Principle, population/intervention/comparator/outcome; CrCl, creatinine clearance; MeSH, medical subject headings; SGLT2, sodium-glucose transporter type 2; HIV, human immunodeficiency virus; NKF, National Kidney Foundation; ASN, American Society of Nephrology.

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References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Supplements 2013;3:1–150.
2. Miller WG. Estimating glomerular filtration rate. Clin Chem Lab Med 2009;47:1017–9.
3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.
4. Levey AS, Stevens LA, Schmid CH, Zhang Y(L), Castro AF, Feldman HI, et al.; for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
5. Eneanya ND, Yang W, Reese PP. Reconsidering the consequences of using race to estimate kidney function. JAMA 2019;322:113–4.
6. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006; 52:5–18.
7. Miller WG. Uncertainty in estimated glomerular filtration rate is much larger than the race adjustment term. Clin Chem 2021;67:693–5.
8. Cooper RS, Kaufman JS. Race and hypertension: science and nescience. Hypertension 1998;32:813–6.
9. Delgado C, Baweja M, Burrows NR, Crews DC, Eneanya ND, Gadegbeku CA, et al. Reassessing the inclusion of race in diagnosing kidney diseases: an interim report from the NKF-ASN Task Force. J Am Soc Nephrol 2021; 32:1305–17.
10. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021; 385:1737–49.
11. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.
12. van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South

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Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. Clin Chem 2008; 54:1197–202.

13. van Deventer HE, Paiker JE, Katz IJ, George JA. A comparison of cystatin C- and creatinine-based prediction equations for the estimation of glomerular filtration rate in black South Africans. Nephrol Dial Transplant 2011; 26:1553–8.
14. Madala ND, Nkwanyana N, Dubula T, Naiker IP. Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with ^{99}mTc-DTPA imaging. Int Urol Nephrol 2012;44:847–55.
15. Zanocco JA, Nishida SK, Tiveron Passos M, Rodrigues Pereira A, Silva MS, Pereira AB, et al. Race adjustment for estimating glomerular filtration rate is not always necessary. Nephron Extra 2012;2:293–302.
16. Wyatt CM, Schwartz GJ, Owino Ong'or W, Abuya J, Abraham AG, Mboku C, et al. Estimating kidney function in HIV-infected adults in Kenya: comparison to a direct measure of glomerular filtration rate by iohexol clearance. PLoS One 2013;8:e69601.
17. Seape T, Gounden V, van Deventer HE, Candy GP, George JA. Cystatin C- and creatinine-based equations in the assessment of renal function in HIV-positive patients prior to commencing Highly Active Antiretroviral Therapy. Ann Clin Biochem 2016;53:58–66.
18. Moodley N, Hariparshad S, Peer F, Gounden V. Evaluation of the CKD-EPI creatinine based glomerular filtration rate estimating equation in Black African and Indian adults in KwaZulu-Natal, South Africa. Clin Biochem 2018;59:43–9.
19. Bukabau JB, Yayo E, Gnionsahé A, Monnet D, Pottel H, Cavalier E, et al. Performance of creatinine- or cystatin C-based equations to estimate glomerular filtration rate in sub-Saharan African populations. Kidney Int 2019;95: 1181–9.
20. Rocha AD, Garcia S, Santos AB, Eduardo JCC, Mesquita CT, Lugon JR, et al. No race-ethnicity adjustment in CKD-EPI equations is required for estimating glomerular filtration rate in the Brazilian population. Int J Nephrol 2020;2020:1–9.
21. Holness JL, Bezuidenhout K, Davids MR, Warwick JM. Validation of equations to estimate glomerular filtration rate in South Africans of mixed ancestry. S Afr Med J 2020;110:229–34.
22. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266.
23. Omuse G, Maina D, Mwangi J, Wambua C, Kanyua A, Kagotho E, et al. Comparison of equations for estimating glomerular filtration rate in screening for chronic kidney disease in asymptomatic black Africans: a cross sectional study. BMC Nephrol 2017;18:369.
24. Nóbrega AM, Gomes CP, Lemos CC, Bregman R. Is it possible to use modification of diet in renal disease (MDRD) equation in a Brazilian population? J Nephrol 2006;19: 196–9.
25. De Boer IH, Gorodetskaya I, Young B, Hsu CY, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol 2002;13:2762–9.
26. Ibrahim HN, Wang C, Ishani A, Collins AJ, Foley RN. Screening for chronic kidney disease complications in US adults: racial implications of a single GFR threshold. Clin J Am Soc Nephrol 2008;3:1792–9.
27. Peralta CA, Lin F, Shlipak MG, Siscovick D, Lewis C, Jacobs DR, et al. Race differences in prevalence of chronic kidney disease among young adults using creatinine-based glomerular filtration rate-estimating equations. Nephrol Dial Transplant 2010;25:3934–9.
28. Bhuvanakrishna T, Blake GM, Hilton R, Burnapp L, Sibley-Allen C, Goldsmith D. Comparison of estimated GFR and measured GFR in prospective living kidney donors. Int Urol Nephrol 2015;47:201–8.
29. Akhimiona CO, Nguyen DT, Graviss EA, Gaber AO, Suki WN. Suitability of estimated glomerular filtration rate for liver kidney donor selection. Transplant Proc 2018;50: 3071–5.
30. Garg N, Snyder G, Li J, Mandelbrot D, Poggio ED. Performance of creatinine clearance and estimated GFR in assessing kidney function in living donor candidates. Transplantation 2020;104:575–82.
31. Miller J, Knorr JP. Impact of removing the race coefficient in renal function estimate equations on drug dosage recommendations. Ann Pharmacother 2021;56: 44–51.
32. Walther CP, Winkelmayer WC, Navaneethan SD. Black race coefficient in GFR estimation and diabetes medications in CKD: national estimates. J Am Soc Nephrol 2021;32:1319–21.
33. Inker LA, Levey AS, Tighiouart H, Shafi T, Eckfeldt JH, Johnson C, et al. Performance of glomerular filtration rate estimating equations in a community-based sample of Blacks and Whites: the multiethnic study of atherosclerosis. Nephrol Dial Transplant 2018;33:417–25.
34. Levey AS, Tighiouart H, Titan SM, Inker LA. Estimation of glomerular filtration rate with vs without including patient race. JAMA Intern Med 2020;180:793–5.
35. Diao JA, Wu GJ, Taylor HA, Tucker JK, Powe NR, Kohane IS, et al. Clinical implications of removing race from estimates of kidney function. JAMA 2021;325:184–6.
36. Ku E, McCulloch CE, Adey DB, Li L, Johansen KL. Racial disparities in eligibility for preemptive waitlisting for kidney transplantation and modification of eGFR thresholds to equalize waitlist time. J Am Soc Nephrol 2021;32: 677–85.
37. Mahmud N, Asrani SK, Reese PP, Kaplan DE, Taddei TH, Nadim MK, et al. Race adjustment in eGFR equations does not improve estimation of acute kidney injury events in patients with cirrhosis. Dig Dis Sci 2021; doi: 10.1007/s10620-021-06943-1
38. Parasuraman R, Venkat KK. Utility of estimated glomerular filtration rate in live kidney donation. Clin J Am Soc Nephrol 2008;3:1608–9.
39. Anker N, Scherzer R, Peralta C, Powe N, Banjeree T, Shlipak M. Racial disparities in creatinine-based kidney function estimates among HIV-infected adults. Ethn Dis 2016;26:213–20.
40. Ahmed S, Nutt CT, Eneanya ND, Reese PP, Sivashanker K, Morse M, et al. Examining the potential impact of race multiplier utilization in estimated glomerular filtration rate calculation on African-American care outcomes. J Gen Intern Med 2021;36:464–71.
41. Braun L, Wentz A, Baker R, Richardson E, Tsai J. Racialized algorithms for kidney function: Erasing social experience. Soc Sci Med 2021;268:113548.
42. Teo BW, Zhang L, Guh J-Y, Tang SCW, Jha V, Kang D-H, et al. Glomerular filtration rates in Asians. Adv Chronic Kidney Dis 2018;25:41–8.
43. Batai K, Hooker S, Kittles RA. Leveraging genetic ancestry to study health disparities. Am J Phys Anthropol 2021; 175:363–75.
44. Caulfield T, Fullerton SM, Ali-Khan SE, Arbour L, Burchard EG, Cooper RS, et al. Race and ancestry in biomedical research: exploring the challenges. Genome Med 2009;1:8.
45. Udler MS, Nadkarni GN, Belbin G, Lotay V, Wyatt C, Gottesman O, et al. Effect of genetic African ancestry on eGFR and kidney disease. J Am Soc Nephrol 2015;26: 1682–92.
46. Hoenig MP, Mann A, Pavlakis M. Removal of the Black race coefficient from the estimated glomerular filtration equation improves transplant eligibility for Black patients at a single center. Clin Transplant 2021; e14467; https://doi.org/10.1111/ctr.14467.
47. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney disease, race, and GFR estimation. Clin J Am Soc Nephrol 2020;15:1203–12. doi:10.2215/CJN.12791019.
48. Casal MA, Ivy SP, Beumer JH, Nolin TD. Effect of removing race from glomerular filtration rate-estimating equations on anticancer drug dosing and eligibility: a retrospective analysis of National Cancer Institute phase 1 clinical trial participants. Lancet Oncol 2021;22:1333–40. doi: 10.1016/S1470-2045(21)00377-6.
49. Narva AS, Briggs M, Jordan R, Pavkov ME, Burrows NR, Williams DE. Toward a more collaborative federal response to chronic kidney disease. Adv Chronic Kidney Dis 2010;17:282–8.
50. Roberts DE. Abolish race correction. Lancet 2021;397: 17–8.
51. Ioannidis JPA, Powe NR, Yancy C. Recalibrating the use of race in medical research. JAMA 2021;325:623–4.
52. Roberts DE. Is race-based medicine good for us? African American approaches to race, biomedicine, and equality. J Law Med Ethics 2008;36:537–45.
53. Witzig R. The medicalization of race: scientific legitimization of a flawed social construct. Ann Intern Med 1996; 125:675–9.
54. Norris KC, Eneanya ND, Boulware LE. Removal of race from estimates of kidney function: first, do no harm. JAMA 2021;325:135–7.
55. Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight–Reconsidering the use of race correction in clinical algorithms. N Engl J Med 2020;383:874–82.
56. Grubbs V. Precision in GFR reporting: let's stop playing the race card. Clin J Am Soc Nephrol 2020;15:1201–2. doi:10.2215/CJN.00690120.
57. Zelnick LR, Leca N, Young B, Bansal N. Association of the estimated glomerular filtration rate with vs without a coefficient for race with time to eligibility for kidney transplant. JAMA Netw Open 2021;4:e2034004.
58. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. Am J Kidney Dis 2021; doi:10.1053/j.ajkd.2021.08.003
59. Levey AS, de Jong PE, Coresh J, Nahas MEl, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17–28.
60. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. Am J Kidney Dis 2013;62:595–603.
61. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, et al.; CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369: 932–43.

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