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Estimated Glomerular Filtration Rate and the Racial Multiplier: Clinical Implications and Current Attitudes

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Abstract

Chronic kidney disease (CKD) is associated with high morbidity and mortality and has high and increasing incidence worldwide. CKD is characterized by a reduction in glomerular filtration rate (GFR), but as GFR is difficult to measure directly, estimated glomerular filtration rate (eGFR) equations have been created to measure serum creatinine levels as a function of GFR. Some eGFR equations contain a racial multiplier that increases the eGFR of black patients, causing a spurious increase in reported kidney function. This study included a literature search that collected information on the rationale behind the multipliers usage and a survey that gathered information about healthcare professionals' reception of the racial multiplier's use. Use of the multiplier across the globe was found to be inconsistent. The survey found that there are many hospital systems across the US that report the racial multiplier and varying opinions among healthcare providers about its use. Applying the racial multiplier increases the eGFR of a patient by 16-21%, which may categorize a patient as being at a less severe stage of CKD than appropriate. The lack of consistency in the application of the racial multiplier, coupled with the understanding that race is not a biological characteristic, contraindicates its inclusion in a diagnostic algorithm. Inappropriate application of the racial multiplier causes delay to necessary treatments for affected patients. The inability to sort people into discrete racial categories on biological lines and lack of studies definitively supporting the racial multiplier calls for reevaluation of its use.

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Introduction

Chronic kidney disease (CKD) is a serious and concerning worldwide healthcare concern. More than 15% of adults in the US are estimated to have CKD and 90% of the population with CKD is unaware of their condition.[1] Worldwide incidence is climbing; in 2015, 1.2 million people died from kidney failure, a 35% increase from 2005. It is also estimated that 2.3-7.1 million people with end-stage kidney disease (ESKD) die without access to dialysis and that number is estimated to double by 2030.[2] CKD increases the risks associated with diabetes, hypertension, human immunodeficiency virus (HIV), and cardiovascular disease, increasing its impact on morbidity and mortality rates in all populations.[2]

Patients who reach ESKD have greatly reduced renal function that is insufficient for sustaining life, requiring kidney replacement therapy, either in the form of kidney transplantation or renal dialysis. Both treatments are associated with high morbidity and significant financial burden.[3] High-income countries spend greater than 2-3% of annual healthcare budgets on dialysis treatment although less than 0.03% of their population represents those who need treatment.[2] In the US, the black population is the most affected, comprising only 13% of the total US population, but 30% of the country's ESKD patients.[4] Other minority groups are disproportionally affected due to lack of early screenings and timely referral to treatment.[5] Because of high costs, people with ESKD in low-income populations may not have access to the treatment necessary to sustain kidney function, making the detection of early stages of utmost importance.

CKD is characterized by a sustained reduction in the kidneys' ability to filter plasma. It can occur as a secondary result of some diseases, most notably diabetes and hypertension, although glomerulonephritis, heart disease, exposure to toxic chemicals or drugs, and autoimmune conditions are also often implicated.[6] These diseases cause CKD by placing

additional strain on the kidneys which damages their structure and functionality, reducing their ability to filter blood normally. CKD symptoms are non-specific in early stages and may not be detected without routine screening tests. The symptoms that appear as the disease progresses are due to the loss of kidney function and accumulation of uremic retention solutes, which can affect nearly all body systems. As CKD progresses, symptoms such as edema, proteinuria, anemia, CKD mineral bone disease, and metabolic acidosis occur. If untreated, CKD most often leads to death. Effective treatment strategies are centered around kidney replacement therapy, utilizing either renal dialysis or transplantation.[3]

CKD is diagnosed using the glomerular filtration rate (GFR), which is defined as the volume of plasma filtrate that passes through the glomeruli per minute.[7] As GFR represents the filtration capabilities of the kidney, it is used to monitor kidney function in healthy patients as a screening test, as well as in patients who are taking certain medications or undergoing treatments that put them at risk for kidney damage. It is also used to stage the progression of CKD from its more moderate stages, where management of symptoms and preventing further renal damage is the focus, to ESKD, where the patient has minimal renal function and transplantation should be considered.[8] The implications of CKD diagnosis includes high rates of both morbidity and mortality with few treatment options. Therefore, being able to monitor at-risk patients for changes in GFR to detect early stages of CKD is essential. GFR can be measured directly by measuring the urinary clearance of an exogenous filtrate injected into a patient's bloodstream, generally inulin or iothalamate.[9] This procedure is both complex and expensive, requiring an inpatient stay, IV administration of the exogenous filtrate, and careful urine collection.[10] This method is considered the gold standard for assessing glomerular filtration rate, but it is relatively

difficult to perform on a large scale as a routine and screening test. Because of this, measured GFR is performed rarely and only as a confirmatory test or in research settings.

Alternatively, GFR is routinely reported using the estimated glomerular filtration rate (eGFR). eGFRs measure the serum levels of an endogenous filtrate, most commonly creatinine, and use a calculation to estimate the patient's GFR. Creatinine is used over other endogenous filtrates because it is produced by the body at a relatively constant rate as a product of muscle metabolism and is filtered at the glomerulus.[11] The serum levels of creatinine are used in the eGFR equations as a function of the kidneys' filtration rate. Creatinine is also cheaper to measure than other biomarkers that would have similar ability to estimate GFR, such as Cystatin C.[9] The eGFR is a widely reported metric, as calculations are easily built into laboratory systems and can be reported on any test that measures creatinine levels without adding additional labor or processing time. Its accessibility and low cost allow eGFR to be built into metabolic panels used in routine bloodwork, giving clinicians a metric to monitor kidney function without the involved and time-consuming procedure of the measured GFR. It is especially valuable for monitoring the kidney function of patients who may not fall into traditional at-risk categories such as those with diabetes, hypertension, obesity, and cardiovascular disease. Monitoring eGFR in the general population as well as those at risk is essential because early stages of CKD are often asymptomatic.[3]

eGFR values are calculated with a variety of different equations that have been developed in attempt to approximate the GFR as closely as possible. Using an endogenous filtrate is less precise, as any factor that affects the patient's blood concentration of the filtrate will affect the eGFR. These are considered non-GFR determinants and the goal of the eGFR equations is to reduce the non-GFR determinants that may cause variations in eGFR that are not directly due to

kidney function. Because creatinine is a product of muscle breakdown, increased muscle mass causes a serum creatinine increase that results in an underestimation of GFR. Diet, especially meat intake, also affects serum creatinine levels. Variables that are most often used to correct for these non-GFR determinants are age, sex, weight, height, and race.[8]

The first eGFR equation proposed by Cockcroft and Gault in 1976 did not propose a racial modifier, estimating creatinine clearance from serum creatinine with age, weight and sex.[12] The racial modifier appeared first in the 1999 Modification of Diet in Renal Disease (MDRD) equation and then was continued into the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, see **Table 1**. The inclusion of race as a non-GFR determinant originated from the idea that people who are black have increased muscle mass when compared to people of other races.[15,16] The MDRD study cites this rationale for the inclusion of a modifier that increases the eGFR of black persons by an additional 18.1%,[13] and was later increased to 21.1%.[17] The CKD-EPI study does not rationalize the use of a racial multiplier, but includes one that increases the eGFR of black persons by 15.9%.[14] These are the two most commonly used eGFR calculations currently. Both are widely used and taught in clinical laboratory textbooks without rationale for the use of a racial multiplier.[18–20]

Table 1: eGFR equations

Cockcroft-Gault (1976)[12]	$eGFR = \frac{(140 - age)(wt\ kg)}{72 \times S_{cr}\left(\frac{mg}{dl}\right)} \times 0.85\ if\ female$
MDRD (1999)[13]	$eGFR = 170 \times [S_{cr}]^{-0.999} \times [age]^{-0.176} \times [SUN]^{-0.170} \times [Alb]^{0.318} \times 0.762\ if\ female \times 1.180\ if\ patient\ is\ black$ Where SUN = serum urea nitrogen (mg/dL); Alb = serum albumin (g/dL)
CKD-EPI (2009)[14]	$eGFR = 141 \times \min\left(\frac{S_{cr}}{K}\right)^{\alpha} \times max\left(\frac{S_{cr}}{K}\right)^{-1.209} \times 0.993^{age} \times 1.108\ if\ female \times 1.159\ if\ patient\ is\ black$ Where K = 0.7 (if female) or 0.9 (if male); α = -0.329 (female) or -0.411 (male)

Because GFR is used to stage kidney disease and evaluate eligibility for participation in clinical trials and placement on a kidney transplant wait list, allowing race to modify this number requires significant justification as it can impact a patient's criteria to receive proper treatment.[22] A race multiplier means that two people with the same serum creatinine levels would have different eGFR values if one individual were black and the other was not, even if they were identical in every other way, including muscle mass. The multiplier increases eGFR, which indicates better kidney health than if the multiplier were not applied. If it were applied erroneously, it may classify a patient in a less-advanced stage; see **Table 2** for stages. This reclassification may delay access to proper treatment or approval for kidney transplant. This is complicated in populations of mixed racial heritage, raising questions about whether or not the modifier should be applied to them at all, or if a reduced modifier is more appropriate.[23]

Table 2: CKD Staging by eGFR[21]

Stage	eGFR
1	≥90 ml/min/1.73m^2
2	60-89 ml/min/1.73m^2
3	30-59 ml/min/1.73m^2
4	15-29 ml/min/1.73m^2
5	<15 ml/min/1.73m^2

The understanding that race is a social construct not a biological concept has been recognized in both social and medical disciplines.[4,24–26] This challenges the legitimacy of using a racial correction in a calculation to determine something biologic, such as organ function. The use of this multiplier must be strongly supported in past studies to justify its continued use. In a healthcare system trending towards individualized care models there is no space for broad categories such as race with little relationship to biological makeup to be used in diagnostic methods. Medical treatment of patients of African descent has a sordid history of ulterior eugenic

motives and any treatment of patients that differs on the basis of race must be supported strongly by the literature to ensure this trend is not perpetuated.[5,27]

The University of Washington School of Medicine made headlines in June 2020 when its laboratories chose to discontinue the use of the race multiplier in its eGFR calculations.[28] Since that time, a small number of other hospital systems have also publicly made this decision, but there is some hesitance among the medical community to abandon such a common practice. Some hospitals have made the decision to discontinue its use quietly, without releasing an official statement, making it difficult to quantify the percentage of hospitals that have moved away from this practice. The National Kidney Foundation and the American Society of Nephrology released a joint statement in July 2020 that they are committed to reevaluate the use of race in eGFR estimations in clinical practice across the United States.[29]

This study evaluates the current literature on the use of the racial multiplier in eGFR calculation, how it is being used and the arguments for and against its use. Current attitudes about the use of the racial multiplier among laboratorians, clinical laboratory educators, and physicians were also assessed.

The purpose of this project is to understand the implications of the use of the racial multiplier on the quality of care received by the affected populations, specifically how its continued use may or may not cause harm to those that the multiplier is applied to. For this, we explored the global use of the racial modifier and the current trends and rationale behind the discontinuation of its use. The fundamental aim of this study is to shed light on the use of race as a modifier of a biologic process and the negative repercussions, if any, towards the health of those it affects.

Methods

Objectives

The objective of the literature review portion of this study is to compile and summarize the summarize the available information about the use of the racial multiplier in eGFR, its scientific rationale and the clinical implications of its use. Does the literature support the use of a racial multiplier in creatinine-based eGFR calculations to provide the best approximation of renal function in black populations?

The objective of the survey portion of this study is to gather information about the reporting of an eGFR accompanied by a racial multiplier in laboratories in the United States. Are laboratorians aware of its use and laboratories trending away from reporting a racial multiplier with eGFR results?

Literature Search

Searches for sources were conducted in PubMed Central, MEDLINE, and the Cochrane Library from August to September 2020. Key search terms included: Glomerular filtration rate, race/ethnicity, estimated glomerular filtration rates and African Americans, MDRD, CKD-EPI. Of the studies retrieved, only those that provided information pertaining to the objectives were retained. This primarily included studies that measured GFR and correlated it to eGFR in different populations of differing races or studies that looked at eGFR normal ranges in black populations outside of the United States. Studies focused on the prevalence of end-stage renal disease and CKD in those affected by the racial multiplier were also included. The sources cited in the relevant studies were scanned for other relevant studies that may not have been captured in the database searches.

As this review is focused on the use of a racial/ethnic modifier used in conjunction with creatinine-based eGFR calculations, studies focusing on the validity of creatinine-based eGFR calculations as an approximation for measured GFR for reasons other than the racial/ethnic multiplier were not included. Additionally, studies proposing other eGFR methodologies to replace creatinine-based estimation for reasons not directly related to the racial multiplier were not included. Preference was given to studies published since 2017, but some older landmark studies and the primary studies proposing major eGFR calculations were included.

Information about the effectiveness of using the racial multiplier for black populations, the associated clinical consequences, and the rationale behind its usage historically was extracted from these publications. The information was then compiled to summarize the benefits and disadvantages a racial multiplier extends to the black population being evaluated for renal function and whether its continued use is supported.

Survey

This study also included a survey to assess current trends in clinical laboratories and opinions among clinical laboratory scientists across the States. The survey was created using Qualtrics and distributed via an anonymous link emailed to medical laboratory science program directors and affiliates. Emails of laboratory directors were also located

Table 3: eGFR opinion survey questions

Are you aware that estimated glomerular filtration rate (eGFR) us often reported as a different value based on the racial identity of the patient?
Does your laboratory currently report a race coefficient for eGFR calculations?
Has your laboratory reported a race coefficient with eGFR results in the past 5 years?
Over the last 5 years, do you recall hearing of or participating in discussions about the use of race in the calculation of eGFR?
Have you ever considered the scientific rationale or ethical implications concerning the use of race in the calculation of eGFR?
Would you say you have a positive, negative, or neutral opinion on the use of the racial multiplier in eGFR calculations?
Which of these categories best represents your role? Physician, Nurse, Medical technologist, Medical laboratory technician, supervisor, lab director, other

from online hospital directories. Approval of the retrieval of this de-identified information was granted from the Institutional Review Boards of the University of New Hampshire (IRB #8377). Of the 914 potential respondents contacted, 100 completed the survey from October 8th 2020 – November 13th 2020. The survey asked direct questions about whether participant's institutions currently or recently reported a racial multiplier for eGFR, whether the laboratorian is aware of this practice, and collected their general opinion towards its usage. Information about general laboratory trends was collected by the questions found in **Table 3**. Survey data was analyzed and stored in an Excel spreadsheet. Generation of figures was done primarily with formulas and charting tools in Excel, as well Visme, which was used to create map graphics from the data stored in Excel.

Results

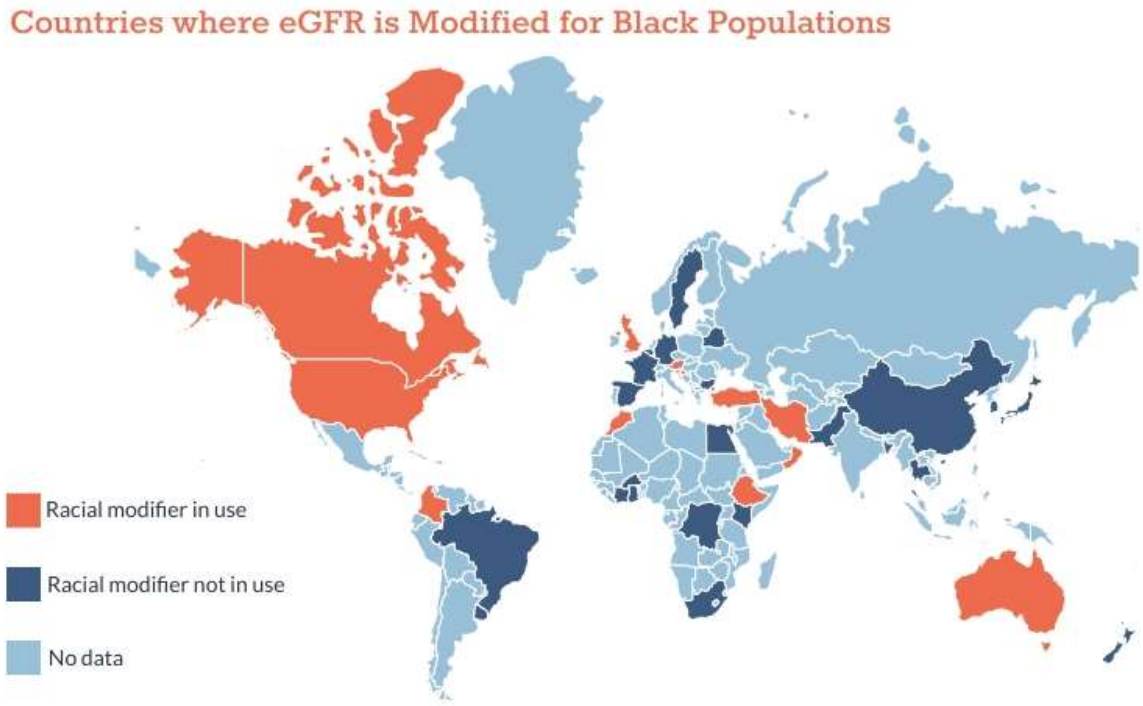

Figure 1. Countries where the racial modifier is applied when calculating eGFR for black populations. *Countries that use the modifier highlighted in orange and countries that do not in dark blue. Countries with no data are indicated in light blue.*

Global usage of the racial multiplier

In order to understand how the eGFR racial multiplier is used across the globe, literature search was used to identify countries where the racial modifier is applied when calculating eGFR (Figure 1). The most commonly used eGFR equations were developed and are used in the United States.[13,14] Medical laboratories in Canada use the same multiplier for black populations as was developed from the studies conducted in the United States.[30] Data on the usage of a racial multiplier in eGFR calculations in the Caribbean and Central American countries is scarce despite a higher percentage of people of African descent.[31] Studies done in Saint Kitts and Nevis and Jamaica utilized the racial multiplier in the eGFR determination in black participants.[32,33]

Comparative studies done between measured eGFR methods and iohexol clearance found that applying the racial multiplier to eGFR calculations overestimates kidney function compared to measured methods and should not be used with the Brazilian or Brazilian-African population.[34,35] The multiplier has also been shown to be unnecessary for application to Uruguayan populations that identify as black.[36] A study conducted in Colombia showed that eGFR measured with the MDRD equation and the corresponding racial modifier approximated other eGFR values determined from calculations that do not utilize a modifier for race, such as the Cockcroft-Gault and Cockcroft-Gault equation adjusted for body surface. However, it was determined that the CKD-EPI equation overestimates eGFR in the black population. Therefore, the racial modifier is suggested for the MDRD equation but not the CKD-EPI equation in this country.[37]

Usage of the racial multiplier in Europe varies from country to country. The United Kingdom uses the racial modifier, although the population to which it applies varies. Some studies correct by black racial identity and others by more specific ethnic groups, such as African-Caribbean ethnicity.[38,39] The racial modifier is routinely applied to eGFR calculations in Croatia.[40] Studies in Austria also include the racial multiplier as a variable, but a largely unutilized one due to a relatively small black population.[41] Studies conducted in Germany do not routinely have a large enough black population to justify the routine use of the racial multiplier.[42] Similarly, studies conducted in Spain omitted the racial multiplier from eGFR calculations, even when using the MDRD or CKD-EPI equations.[43,44] The racial multiplier is also omitted from the CKD-EPI equation in Belgium.[45] Bulgarian studies do not include a racial multiplier.[46] In Belarus, a modified version of the MDRD, known as the MDRD-MDPvD is used and no racial multiplier is necessary.[47] In Sweden, the Lund-Malmo equation is favored for eGFR calculation

and relies on age, sex, and serum creatinine as its only variables; it does not contain a racial multiplier.[48–50] Use of the racial multiplier is illegal in France due to unique laws surrounding the situations in which racial and ethnic categories can be collected and utilized.[51,52]

Many Asian populations use modified versions of the CKD-EPI or MDRD because the equations created and validated in the United States do not represent GFR in their respective populations. In Japan, a correction coefficient of 0.813 is applied to the CKD-EPI equation because when uncorrected, it overestimates the eGFR in their population.[53] Thailand utilizes a similar multiplier with the MDRD equation, except that it increases the eGFR by a multiplicative factor of 1.129 in Thai populations but does not include a racial modifier for black populations.[54] A modified equation for the CKD-EPI equation in Pakistani populations is best represented as $0.686(\text{CKD-EPI}^{1.059})$, where CKD-EPI does not include a modifier for black populations.[55] In China, the racial modifier not broadly used. It is applied to African-Americans, as that is the population for which the modifiers were validated when the equations were created, but the multiplier is not used with African, African-Asian or other black populations.[54,56] A multiplier of 1.23 applied to the MDRD has been validated for the native Chinese population[57,58] The MDRD and CKD-EPI equations were validated in South Korean populations without the racial multiplier for black individuals.[59,60] The racial multiplier is used exclusively for African-Americans in Turkey, as the multiplier was created and validated in the US, applying it to other black populations is contraindicated.[61] The racial multiplier is applied to African-American populations only in Iran as well.[62] The racial multiplier is applied to black populations in Oman.[63]

The racial multiplier for black populations is used in Australia, but it is not acceptable to apply to native Australian populations.[64] The CKD-EPI equation has been validated in New

Zealand without the addition of the racial multiplier. [65]

Studies conducted in Côte d'Ivoire and the Democratic Republic of the Congo demonstrated that adjustment for race did not improve performance of the eGFR equations in their populations.[66,67] A study in South Africa found that removing the racial multiplier decreased the bias between measured and estimated GFR.[68] A similar study in Kenya determined that biases were eliminated when the race coefficient was removed from the eGFR equations.[69] An Egyptian study found that MDRD and the accompanying racial multiplier were not as effective as the Cockcroft-Gault equation, which does not correct for race.[70] The racial multiplier was demonstrated to overestimate GFR in Burkina Faso.[71] The racial modifier is used in Morocco and Ethiopia, as a part of the eGFR calculations based off of the US studies and validations.[72,73]

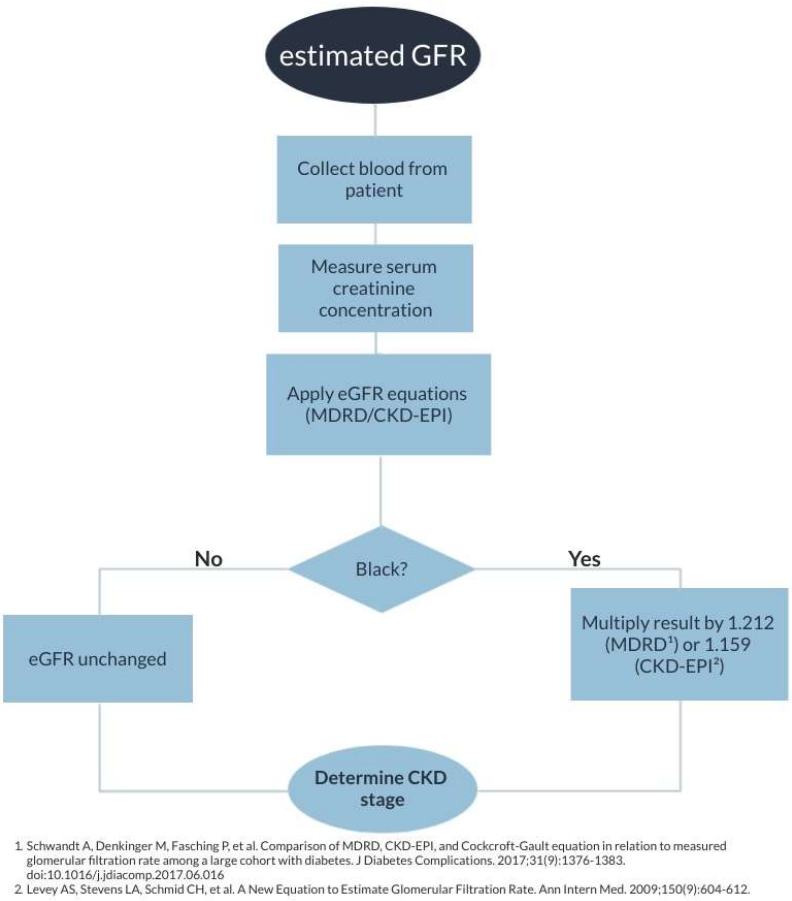

Figure 2. Flowchart depicting how eGFR is determined and how the racial multiplier, when used, is applied. Institutions that do not use the race multiplier proceed directly from eGFR equation output to CKD staging.

When the eGFR is calculated and modified by race in the countries that utilize the racial modifier, **Figure 2** represents the general process. Serum creatinine (Scr) is measured from a

blood sample. One of many eGFR equations is then applied to the Scr value and an eGFR is determined. The most common eGFR equations worldwide are MDRD and CKD-EPI, both of which contain racial modifiers. If a different equation is used, the eGFR can be directly used to stage CKD. In the CKD-EPI and MDRD equations, the eGFR is increased by a multiplicative factor of 1.21 in the MDRD and 1.18 in the CKD-EPI equations for patients that are black before CKD stage determination.[13,14] eGFR values are then used to categorize CKD by stages 1-5 (**Figure 3)**. Stage 1 is the least severe and is considered kidney damage with a normal GFR (>90 mL/min/1.73m^2). Stage 2 is characterized by kidney damage with mildly decreased GFR (60-89mL/min/1.73m^2). Stage 3 is defined as a GFR of 30-59mL/min/1.73m^2 with moderate reduction in kidney function. Stage 3 is often broken up into sub-stages, with 3a corresponding to a GFR of 45-59mL/min/1.73m^2 and 3b with a GFR of 30-44mL/min/1.73m^2.[74] Severe reduction in GFR (15-29mL/min/1.73m^2) is considered stage 4, and a GFR below 15mL/min/1.73m^2 is stage 5, also considered kidney failure or end-stage renal disease.

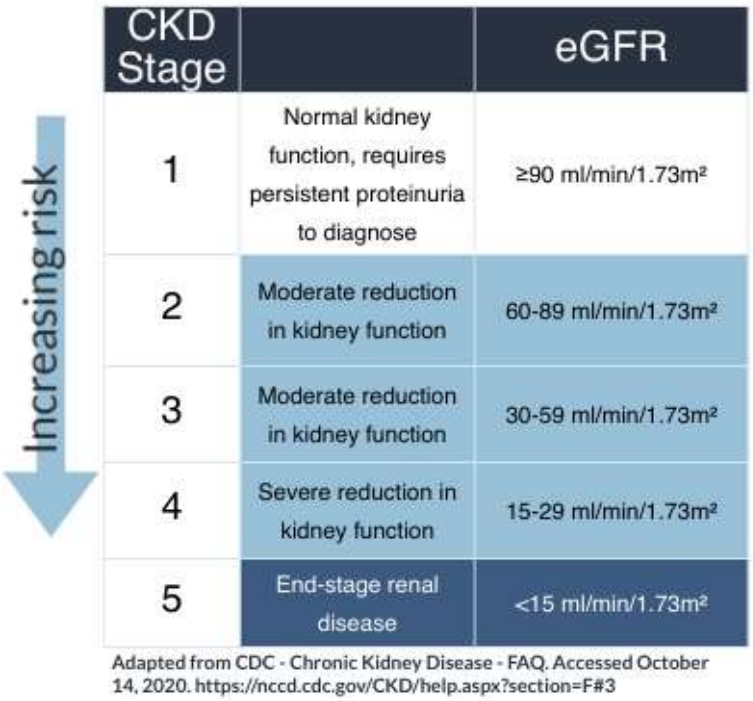

Figure 3. Classification of CKD by eGFR. Persistent proteinuria or other markers of renal damage may be used in conjunction with eGFR to stage CKD in some institutions.

Survey Results

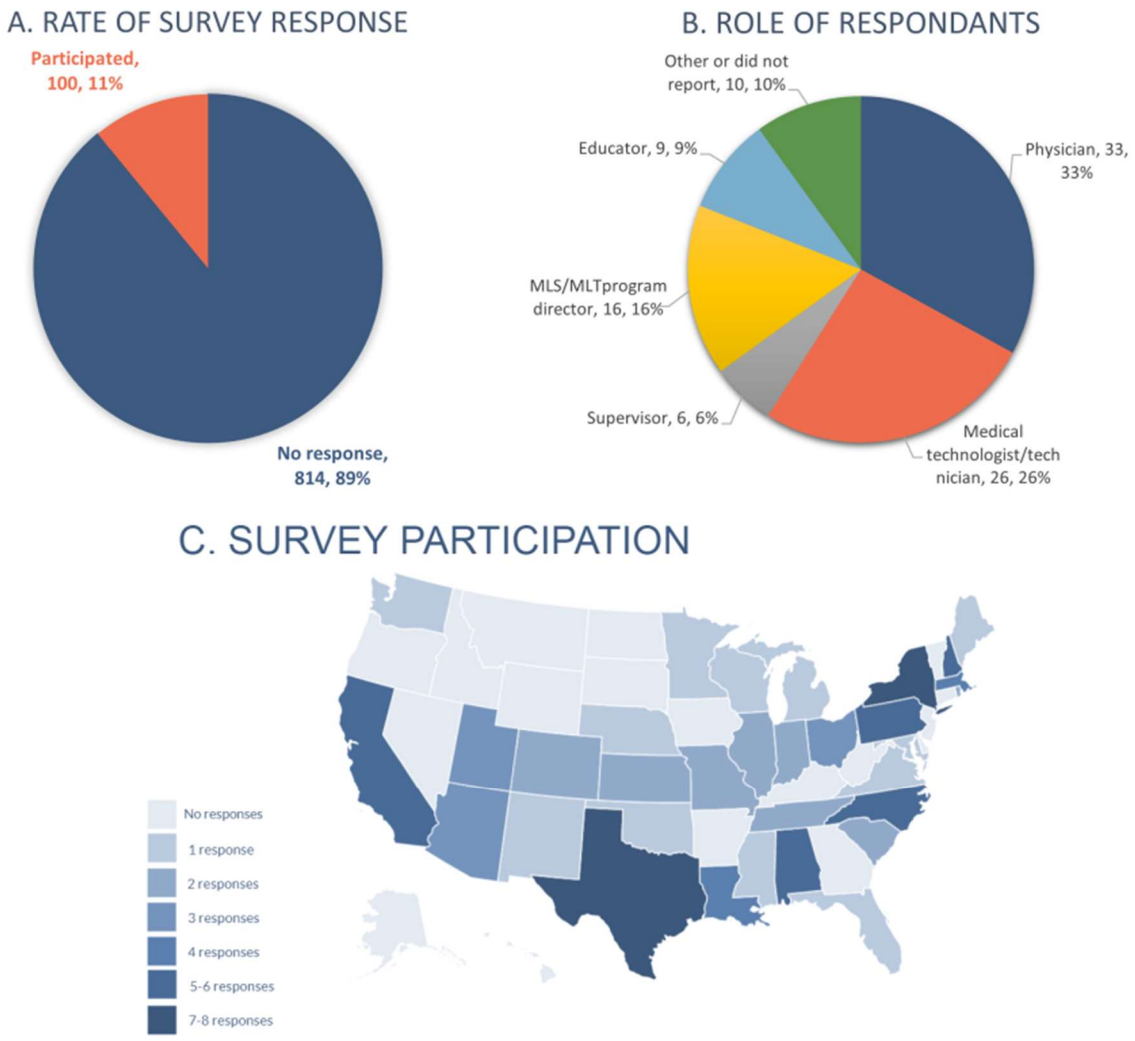

Figure 4. A) Comparison of survey respondents to number of people contacted by recruitment email. B)Role of respondents. Physicians in navy, medical technologists/technicians in orange, MLS/MLT program directors in yellow, educators in light blue, laboratory supervisors in grey, did not report in green. C) Location of participants in United States. Darker blue states indicate more participants, lightest blue indicates no participants.

Of the 914 individuals contacted by email recruitment, 100 (10.9%) individuals agreed to participate (**Figure 4a**). The roles of participants is as follows: 33% physicians, 26% medical laboratory technologists/medical technician, 6% laboratory supervisors, 16% Medical laboratory science/Medical laboratory technician educational program director, 9% medical educators, and 10% other or did not report a role (**Figure 4b)**. Distribution of survey respondents across the United States is seen in **Figure 4C**. Eight participants were from New York, Seven from Texas, Six from New Hampshire, North Carolina, and Pennsylvania. Five responses were recorded from

Alaska and California. Four responses were recorded from Louisiana and Massachusetts. Arizona, Utah, and Ohio had three respondents each. Two responses were recorded from Colorado, Illinois, Indiana, Kansas, Missouri, Rhode Island. South Carolina, and Tennessee. One response was collected from the following States/territories: Washington DC, Florida, Iowa, Maine, Maryland, Michigan, Minnesota, Mississippi, Nebraska, New Mexico, Oklahoma, Puerto Rico, Virginia, and Washington. Eight participants declined to report location.

Of those participants, 86 (91%) indicated that they were aware of the use of the racial multiplier in eGFR calculation (**Figure 5a**). When asked if the participant recalled hearing of or participating in discussions about the use of race in the calculation of eGFR, 35 (37.2%) responded "yes, many times", 25 (26.6%) responded "once or few times", 33 (35.1%) responded "No" (**Figure 5b)**. 48 (64%) of recipients indicated that their lab currently reports a racial multiplier with eGFR calculations. 13 (17%) of recipients indicated that their lab does not currently report a racial coefficient with eGFR calculations, while 14 (19%) were unsure (**Figure 5c**). Of the participants that responded that their lab does not currently report a race multiplier, 8(62%) reported that they have reported a race multiplier within the last five years, 2(15%) reported that the race multiplier has not been in use for five years or longer (**Figure 5d**). When participants were asked if they had ever considered the scientific rationale or ethical implications concerning the use of race in the calculation of eGFR, 65 (69.9%) responded "yes", 21 (22.6%) responded "no, never considered it", 6 (6.5%) responded "No, unaware of its use" (**Figure 5e**). 25 (26.9%) of participants said they had a positive opinion on the use of the racial multiplier, 35

(37.6%) said their opinion was neutral, 25 (26.9%) said their opinion was neutral, and 8 (8.6%) said they had no opinion (**Figure 5f**).

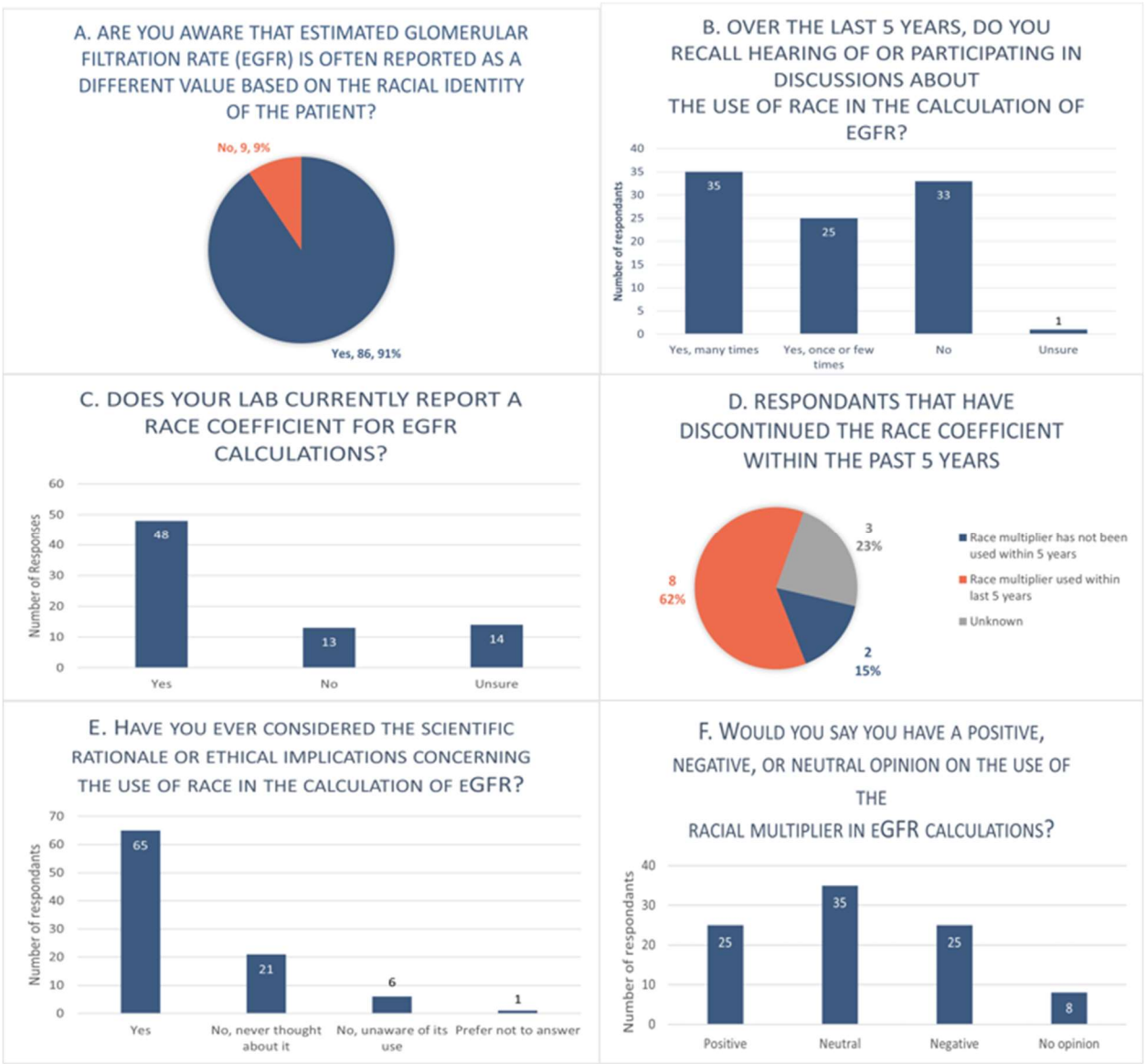

Figure 5. A)Awareness of the usage of race in the determination of the eGFR among survey participants. B) Breakdown of participants by engagement in or recognition of conversations surrounding the use of the racial multiplier C) Current use of the racial multiplier in eGFR reporting in the laboratories of the participants of this study D) Use of racial multiplier within the past five years among participants that do not currently use the racial multiplier E) Participants' responses concerning previous considerations of the ethical or scientific implications of the use of the racial multiplier. F) Participants' opinion of the use of the racial multiplier, categorized by "positive", "neutral", "negative" or "no opinion.

Discussion

The usage of the racial multiplier across the globe varies widely. Many countries that use it do so based on the results of the eGFR equation studies, which were calculated in an American population. Therefore, the racial multiplier may only be reflective of African Americans, as that was the only population included in the studies.[14] Both the MDRD and the CKD-EPI equations propose the use of the multiplier for all black patients, although the multipliers were determined from African American populations, neither study included a large population of black patients.[14,75] The original MDRD study had only 197 black participants out of the total 1628 participants.[75] The CKD-EPI study was comprised of a 32% black population, but its external validation was conducted with only 10% black participants.[14] These studies also lack defined parameters for determining what classifies a person as black or how to apply the multiplier to a person of mixed race. The complicated nature of determining who the multiplier should be applied to leads to varied interpretation of the racial multiplier's application and inconsistent reporting practices across medical institutions, states, and countries. Some institutions apply the multiplier to all people who identify as black or are of African origin. Other institutions apply the modifier to ethnic groups. In the UK, the multiplier is used for patients of Afro-Caribbean descent.[39] Racial modifier reporting in both Iran and Turkey is limited to African-American populations, which likely indicates it is rarely reported.[61,62] The lack of consistency among racial modifier reporting is a point of concern for quality of healthcare for the affected patients.

Many of the studies presented in this study were observed to lack consistency in the definitions of race and ethnicity. Race is broadly defined as a heritage-based association with a general geographic region accompanied by the physical phenotypes commonly attributed to the people from that region, most commonly skin color.[76] Race was previously considered a

biological characteristic, and some of the earliest race theories suggested that races were either separate species or sub-species of humans. It was assumed members of individual races were genetically distinct from other races and genetic analysis could sort humans into discrete racial groups. Following the Human Genome Project, it is now understood that race is not a biological characteristic, as there are more differences in genetic makeup within a race than between races.[77–81] If race were a concrete biological category, differences between other races would be expected to be greater than genetic variation within a racial group. Genetic commonalities within racial groups are more likely attributed to a likelihood to partner and mate with other members of the same race, producing offspring that may be more likely to have similar traits, but race itself is not an inherited, biological, genetic characteristic.[82–85]

Ethnicity refers to a cultural group with some unifying characteristic, generally nationality, location, or tradition and a claimed kinship.[76] Relevant examples include such as African Americans, afro-Caribbean, or Haitian which all may be considered individuals of black race but may not be genetically very similar. Neither ethnicity nor race are genetic characteristics, yet they may have an impact on glomerular filtration rate because there may be associated differences in diet or general body structure, but those are less attributed to the social constructs we consider as race or ethnicity. Other determinants my include access to early care, especially in the United States where access to healthcare is notably reduced in African-American population and often regarded with a sense of distrust[86,87]. Rates of morbidity and mortality due to common diseases are higher in African Americans than nearly all other ethnic groups in the United States, but there is evidence that the health disparities are due to socially-mediated factors such as poverty, poor access to care, discrimination, and differences in

treatment, and that differences in genetics due to racial heritage have minimal effect on these outcomes.[85]

As race is not determined by discrete genetic differences, it begs the question of what the threshold of percent black race is necessary to qualify a patient for the racial multiplier. The first inclusions of race in medical care were strongly influenced by eugenic practices, so the inclusion of such a racial multiplier must be supported strongly by clinical studies and clearly defined as to who the multiplier should be applied to.[88] This is complicated by the inability to sort all people into discrete racial groups and the increasingly large global population of individuals of mixed racial heritage. Historical classifications have utilized the principle of hypodescent which classifies a person as black if they have "one drop of African blood"[89,90]. It is unlikely that the most nominal African ancestry would affect the skeletal muscle significantly enough for the eGFR to require modification, but there must be criteria for determining who, if anyone, is benefitted most by the application of the modifier.

The MDRD and CKD-EPI being created in the United States means that they are best utilized in other countries where validation studies comparing measured GFR and eGFR of a representative population have been done. Because both equations are based off of endogenous creatinine levels, they are indirectly affected by muscle mass, diet, and sex. Meat consumption may result in higher levels of serum creatinine, producing a falsely decreased eGFR.[91,92] Diets vary by country and region by culture and availability of food and diet is likely more tied to changes in endogenous creatinine levels than the racial identity of the patient. Dietary differences may be one explanation for why there are modifiers used in some east Asian countries that lower the eGFR when using the MDRD or CKD-EPI. Comparative mGFR and eGFR studies are necessary in all populations to ensure that the equations are valid for the population and the

racial modifier should be assessed to determine whether it improves the accuracy of the eGFR in the population it is applied to.

Usage of the racial modifier varies in the United States, but as recently as 2019 it was almost universally used. Many hospital systems, including Mass General/Brigham and Women's Health System, University of Washington, and Vanderbilt University, all discontinued the use of the racial multiplier in summer 2020.[28,93,94] The concurrence of the racial unrest happening in the United States and the removal of the racial multiplier also raised questions about whether the move to remove the racial multiplier was in haste. If the basis for this move was in an attempt to show support for the political movement or appear politically correct, it may actually have been harmful instead of a step towards achieving the desired equality.[95] If the modifier makes the eGFR estimation more accurate, removing it without sufficient rationale is as problematic as using a multiplier when it is not needed. Removal of the racial multiplier lowers the eGFR, which may cause earlier referral for dialysis or transplantation which are risky procedures that are costly to the patient and should not be utilized unless there is no alternative. Alternatively, use of the racial multiplier on those that do not qualify, or if racial multiplier does not accurately represent a difference in glomerular function, it would increase the eGFR and delay the patients access to dialysis or renal transplantation. Because of the potential for harmful outcomes is substantial, it is essential that the racial modifier is only used if it truly provides a closer approximation of the patient's GFR.

This study found that most of North America uses the racial multiplier. Canada has a similar racial profile compared to the United States, as well as similar dietary practices, expectably producing a population in which the American eGFR calculations would correlate well. No data was recovered for racial multiplier usage in Mexico, an unexpected finding, as

Mexico has the sixth highest CKD mortality rate in the world.[96] In such a high risk country it would be expected there would be more studies on the potential effect that race or ethnicity may have on eGFR determination and therefore CKD diagnosis. Little data was found about the race multiplier in Caribbean countries, but would be a valuable population to study due to large percentages of mixed race populations.[97] The two countries where data was found, St. Kitts and Nevis and Jaimaica, both used the racial multiplier with little explanation for why it was included. The geographical proximity to the other North American countries, or perhaps the influence of the American healthcare system in general may have prompted the use of the multiplier without comparative or validation studies. It is difficult to find data about the use of eGFR equations in the Caribbean countries and in South America, likely due to reduced access to laboratory services for routine creatinine testing even though CKD rates are high in both regions. Research on the validity of the racial multiplier would be beneficial to these populations, as mortality and morbidity rates are high to ESKD/HIV comorbidities and better management of renal health could lessen both economic and health burden in this region.[98]

A direct comparison study between the measured GFR and the eGFR done in Brazil demonstrated that the racial multiplier overestimates glomerular filtration rate, both with the general Brazilian population and with African-Brazilians. It is an important finding because Brazil is considered to be one of the most ethnically diverse countries on earth. In Brazil, race is also primarily determined by appearance, not by ancestry.[99] This would complicate utilizing a racial multiplier because a patient's identified race is not directly associated with the patients' genetic makeup. In such a mixed population it would be difficult to determine to whom the multiplier should be applied, so determining that the racial multiplier is not a useful metric in this population eliminates such complications. Other populations compromised of mixed ethnic

backgrounds should consider similar comparative studies if they are routinely utilizing the racial multiplier.

The European countries looked at in this study largely did not utilize the racial multiplier, specifically because the percentage of patients that identify as black is smaller than other regions where the multiplier is widely used. The process of validating the equations for use with the racial multiplier may be prohibitive to its routine use. Due to laws preventing the use of race or religion as a modifier of health care, the racial multiplier cannot be applied to black patients in France, even if it more accurately reflects their renal function.[51] Countries surrounding France also notably do not use the racial multiplier, perhaps due to similar social pressures against using race as a modifier in the assessment of a physiologic process. A validation study done in Spain did not include any individuals of African descent.[100] It would be unethical to use the racial multiplier in a population where it have not been validated.

The low rate of the usage in other east Asian countries is likely due to a small percentage of black patients. Many Asian countries use modified eGFR equations because unmodified versions of the equations overestimate eGFR.[53,55] It is interesting to note that these populations require a modifier to accurately represent GFR but it has not been widely considered to apply a reductive multiplier to the eGFR estimation of Asian populations in the United States. If the rationale for this modifier were based in race, it would make sense to apply it to all Asian populations, but the modifiers used in Asian eGFR calculations differ by country and are not universally applicable to all Asian countries.

Comparative studies done in Africa largely found that the racial multiplier overestimates the glomerular filtration rate, especially in Sub-Saharan Africa. Kenya and Morocco were the only two African countries using the racial multiplier identified in this study. Notably, no

measured GFR and eGFR comparison studies were found for these countries either. Most of the countries in Africa that do not use the multiplier have performed and published comparative studies validating the eGFR equations without the racial multiplier against measured GFR. It is important to note that all studies directly comparing measured and estimated GFR in African populations found the racial multiplier to overestimate the glomerular filtration rate. If there is a biological difference in the GFR as a function of black race, it would be expected to be seen in African populations. The fact that the racial multiplier is not effective in this population indicates that the discrepancy between black patients' eGFRs and other patients' GFRs seen in the MDRD and CKD-EPI studies is unlikely to be directly attributed to race. There is a strong possibility that the difference in populations is associated with race, but a not a biological attribute due to race itself. It is also important to note that the difference in eGFR by race is most commonly attributed to an increased in muscle mass in African Americans compared to other populations. In Sub-Saharan Africa, mean BMI and nourishment levels are expectedly lower, which may also attribute to a difference in the reported eGFR levels.

This aligns with the idea that race is not a biological characteristic, but a social construct. The differences seen in eGFR in two populations in the United States, black and non-black, could be attributed to race, but could also be attributed to differences in social and life experiences between these two groups that leads to differences in renal function. If the multiplier does not hold with other members of the same race in other countries, then it cannot be a function of race. It therefore has to be either the function of a biological characteristic present in a smaller ethnic groups, such as African Americans, or can be due to external stressors on that group of people that results in significant renal function. The racial multiplier does not make sense with the understanding that race is not a biological characteristic. However, even though

the basis of race is not biological, the social effects of being a minority in the United States extends into access to healthcare, and its social ramifications affect how people experience life, health, and healthcare.

The original MDRD and CKD-EPI cite differences in muscle mass as the rationale for a racial multiplier for the black population.[14,75] Muscle mass is also affected by age and sex, the other most common variables in eGFR equations. The inclusion of race is supported by other studies that have found an increased muscle mass in African American populations.[101–103] It has also been found that skeletal muscle mass decreases faster in aging African-Americans than people of other races.[104] It would be expected that the racial modifier loses its accuracy as a patient ages and the difference in skeletal muscle mass between black patients and other patients decreases. In both the MDRD and CKD-EPI equations the racial multiplier is applied to the final product of the other variables and is a fixed variable, not affected by the age of the patient. This complicates the utilization of the racial multiplier, but the primary concerns against using it is that it does not accurately reflect a difference in renal function, has relatively unknown applications for mixed race populations, and has not been extensively studied in large black populations.

The survey portion of this study was primarily sent to laboratory scientists, medical laboratory science program directors, and nephrologists associated with medical schools. Because emails for laboratory and medical professionals are most accessible to the public when associated with an academic program, most of the participants were from academic settings and may not be reflective of the general population. Professionals in academic fields may be more likely to be aware of and engaged in the current trends in medicine. Only 6% of the participants in this survey were unaware of the use of the racial multiplier for eGFR reporting, but it is likely

laboratory professionals not actively engaged in academic pursuits would be less aware of its use. The increased percentage of academic professionals likely also affected the response rate to the question about hearing or participating in discussions about the use of race in the calculation of eGFR. The use and discontinuation of the racial multiplier is a current topic of interest and is likely a point of discussion in many academic circles but may not be as commonly encountered in routine laboratory settings. This question was designed to assess whether participants simply know that the racial multiplier is used or if it is something that they are cognizant of its usage enough to be aware or engaged in conversations about the associated controversy.

Most of the respondents reported that their laboratory reported the race multiplier with eGFR. This demonstrates that the use of the racial multiplier is still widely in use in the United States, despite many reports of hospitals discontinuing its use. Of the participants that reported they were not using the racial multiplier, most of them reported that they had reported a race multiplier within the last five years, indicating that the decision to discontinue the multiplier's use is primarily a movement of the past five years. Most regions of the United States were represented well in the survey, excepting the Northwestern states, although it is not expected that the usage varies greatly from the rest of the country.

One question on the survey asked participants to classify their opinion of the use of the racial multiplier as a positive opinion, neutral opinion, or negative opinion. The intended purpose of this question was to gather information about general opinions among participants about the use of the racial multiplier. However, these terms were poorly defined with no guidelines for what constitutes a positive or negative opinion. The responses were distributed following a normal curve and likely hold little significance to this study due to the poor question wording.

When asked if they had considered the scientific rationale or ethical implications for the use of the racial multiplier, most of the participants responded that they have. However, 22.6% of participants that had responded that they were aware of the racial multiplier and had not ever considered the scientific or ethical implications of its use. It is possible that these individuals were introduced to the reasoning for the race multiplier's inclusion at the same time as the eGFR equations themselves. However, most clinical chemistry textbooks do not include rationale for the inclusion of the racial multiplier in eGFR calculations.[18,19,105] Having a significant portion of respondents not have considered how the multiplier came to be and how it affects care is concerning, as modifiers such as these must be carefully considered and scientifically supported to rationalize their use. The history of healthcare in the US is full of inequalities based in race, from studies that unfairly exploited racial minorities to eugenic medical practices. Preventing such disparities in healthcare and treatment practices between races is an active process requiring careful consideration and evaluation of all those involved.

Beyond the racial multiplier used in eGFR determination, there are other racial modifiers used in healthcare that have been called into question in recent years. Most similar is the Kidney Donor Risk Index (KDRI), where a potential donor is assessed for history of health complication, height and weight, race, and other factors to determine the likelihood that the transplant will fail. Potential donors that identify as black are assigned a higher risk of failure, although the initial study does not include rationale for this inclusion.[106] This exacerbates the increased wait times for black kidney transplant recipients, as they are more likely to receive a kidney from a black donor and the use of the KDRI reduces the likelihood of finding a viable match.[5]

The Vaginal Birth after C Section (VBAC) algorithm is another predictive model that is modified by race or ethnicity. This equation predicts a lower likelihood of successful vaginal

delivery after C section from previous pregnancy in black and Latina women.[107] Other determinants that indirectly attributed higher likelihood of success was insurance and marital status, although these determinants have not been integrated into the equation, as seen with race.[108] Vaginal birth is less likely to have serious complications than a cesarean delivery, so the VBAC's increased risk score for black and Latina patients must be weighed carefully.[109] The inclusion of a race, a characteristic not firmly rooted in genetics, in the VBAC algorithm may exacerbate increased risk for childbirth complications in minority populations.[110,111]

The American Heart Association (AHA) has a heart failure risk score used to predict the risk of death in admitted patients, intended to direct cardiac referral and allocation of resources. Higher scores indicate higher risk for death by heart failure and lower scores indicate lower risk. Without known rationale, non-black patients are assigned additional points, effectively increasing their perceived risk over a black patient.[112] This channels resources to non-black patients and away from black patients who are already known to be at the highest risk for death by cardiovascular disease in the United States.[113]

The American Academy of Pediatrics uses a calculator for estimating the probability of an urinary tract infection (UTI) in febrile, preverbal children (UTICalc) that uses race as a variable to determine whether a patient should be tested for a UTI. Race is used in conjunction with age, fever temperature and duration, and lack of identifiable fever source to determine the likelihood that the child should be tested for a UTI.[114] Black patients are considered to be lower risk for UTI, so a black child who presents with UTI risk factors would require more risk factors to indicate testing for UTI. This can be harmful for black patients who do have UTIs and are delayed treatment because the calculator does not indicate that testing is necessary until a later stage than other non-black patients.

Isoniazid, one of the drugs of choice for tuberculosis treatment, has shown hepatoxicity that varies by racial background of the patient. It is metabolized by liver N-acetyltransferases (NAT). "Slow acetylaters" have a quantitative defect of the NAT enzyme that results in a higher concentration of the drug circulating in their bloodstream.[115] Approximately 50 percent of Caucasians and African Americans are "slow acetylators" and therefore are more likely to experience hepatotoxicity, therefore requiring careful monitoring of the liver for development of hepatocellular liver damage. The remaining 50 percent of Caucasians and African Americans, as well as the majority of Asians, are "fast acetylators," and can metabolize isoniazid three times faster than "slow acetylators."[116] While there is an association with increased risk in some ethnic groups, it still only comprises 50 percent of the population in these groups, therefore decreasing the amount of the of isoniazid prescribed for entire racial groups would not be appropriate. Therefore, it must be determined if the patient is truly a "slow acetylator" before modifying their treatment.

Racial modifiers have found their way into clinical and predictive algorithms across medical disciplines. These modifiers have the potential to overestimate or underestimate organ functionality or potential risk for a patient, which may cause harm to the patient due to delays in receiving necessary care or complications from unnecessary procedures or treatments. Therefore, assessing whether these multipliers are truly indicative of a physiological difference between racial groups is necessary. It is also necessary to have distinct guidelines for how to determine if a patient falls within a racial group. It is unlikely that hospital systems assigning race to a patient based upon a set of developed criteria would be well received, but allowing the patient to self-assign race without full understanding of how their response could affect their care has ethical complications as well.

Furthermore, the lack of consistency between interpretation of which patient populations to apply the multiplier to further complicates the use of the multiplier. The discontinuation of eGFR racial multiplier usage in some but not all hospitals in the US means that a patient could switch hospital systems and suddenly their eGFR value might appear 15-21% different than their results from their previous healthcare provider. The difference in eGFR due to discontinuation of the racial multiplier is enough to change the patient's CKD stage and may cause questions about how to proceed with treatment. If the patient was on the transplant list while at a hospital that does not use the racial multiplier and switched to a hospital that does, they would no longer be a candidate for transplantation. A study done at Brigham and Women's hospital found that removing the racial multiplier from eGFR reporting reclassified 1 in 3 black patients to a more severe stage of CKD.[93] The lack of consistent guidelines for use and application of the multiplier coupled with lack of evidence for a biological basis for race does not support the continued use of this multiplier. Modifying the process of estimating renal health by eGFR to eliminate the use of race would provide a better standard of care. Incorporation of skeletal mass directly in the eGFR equations would improve the efficacy of the multiplier for all racial groups and remove the need for a racial correction. Exploring alternative endogenous markers to calculate eGFR that are not affected by muscle mass or any traits that have been associate with racial characteristics would also eliminate need for the racial multiplier. Comparing an individual patient's measured GFR and eGFR with and without the racial multiplier may also be beneficial to see if the modifier increases accuracy in that patient. This study demonstrates that current use of the racial multiplier is problematic due to the inability to create and assign racial categories based solely in genetic inheritance, current practices being based in racial self-identification from the patient,

lack of consistency among medical institutions, and the scarcity of studies directly comparing measured GFR and eGFR in black patients to evaluate the racial multiplier.

Diagnostic medicine is most effective when the variables used give you information about an individual patient, but a patient's race has no causative relationship to genetic makeup and thereby is not a reliable component of a diagnostic algorithm. In light of this, diagnostic medicine should always be trending towards more accurate markers of disease, eliminating extraneous and unrelated variables wherever possible. This study showed that race as a variable is problematic because populations cannot be discretely divided by race and therefore there is no basis for universal definition. This study also demonstrated that the use of the racial multiplier is not universal nor is it consistently applied even within the US. Such a lack of definitive categorization makes it an unreliable metric with the potential for great risk of adverse patient outcomes and therefore should not be used for diagnostic medicine.

Future Directions

This study could have been improved with the addition of more specific questions based on participant's role. Gathering information about teaching trends among educators, as well as information about if and how they educate medical and laboratory students about the racial multiplier would provide important information about how health professionals are taught to think about the use of race in diagnostic procedures. Data from nephrologists on the clinical significance of the eGFR compared to other measurements of renal function as well as the direct influence of the eGFR on treatment would have supported the discussion on the direct effects of the racial multiplier on patient care. Assessing the usage of measured GFR versus eGFR among nephrologists would have been helpful to understand how often the eGFR is relied on without confirmatory testing. Data from healthcare institutions or providers about how the racial modifier is applied and how racial identity of the patient is assessed or defined would be valuable to understand how such classifications are made and whether the process is highly variable between institutions. If an institute allows a patient to self-report race, data from patients being treated for kidney disease could be collected to determine their awareness that their identified race affects their care.

Assessing the usage of the racial multiplier by state with respect to the percentage of black populations could be used to determine if the population of patients affected by the multiplier makes an institution more or less likely to utilize it. This study was limited by the number of participants and could not have effectively assessed the multiplier's usage, as many states yielded only one participant. Increased participation and dispersion of participants would have made the sample more representative, as would increasing the number of non-academic participants. Likewise, collecting information about eGFR vs measured GFR, methodology for

classifying patients by race, and overall usage data for the racial multiplier in other countries would support the discussion about worldwide practices concerning the racial multiplier.

Assessing how the discontinuation of the racial multiplier at some institutions impacted patients experience and treatment options would be valuable for other institutions that are considering discarding the multiplier. Studying if and how patients' treatment plans changed, how providers explained any changes to the patients, and how it was received by the patients are all data points of use. Promoting and encouraging hospitals to assess and study their use of race as a variable in diagnostic equations is an important step towards better quality of care as well as eradication of racism in healthcare. Assessing the use of race in the eGFR calculation could be done by measuring GFR alongside the eGFR in some patients to determine if the racial multiplier approximates the patients GFR more accurately. Researchers should prioritize creating equations for diagnoses based on objective variables, including assessing muscle mass or other determinants of endogenous creatine concentrations in place of race in eGFR calculation.

As this study found that education about the use of the racial multiplier in eGFR calculation is overlooked, better teaching about race and how it is used in medicine is essential. Reducing racial disparities in healthcare relies on educating healthcare workers to think critically about race's place in healthcare. Textbook writers and educators should be encouraged to include the scientific rationale when presenting diagnostic algorithms that are modified by race.

There is much room for growth in diagnostic medicine where the use of race in medicine is concerned. More study of differences in access to healthcare or other factors that may lead to the discrepancies in health outcomes for patients in minority racial groups is necessary. Removing a nonspecific variable, like race, from a diagnostic equation can only serve to increase the quality of care. Race should not be a variable in a patient's health, not in access to care, treatment plan,

or diagnostic algorithms. Removing race from the eGFR equation is a small but necessary step towards achieving equity in healthcare.

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