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A PERSONAL VIEW

The racist "one drop rule" influencing science: it is time to stop teaching "race corrections" in medicine

Heidi L. Lujan and Stephen E. DiCarlo

Department of Physiology, College of Osteopathic Medicine, Michigan State University, East Lansing, Michigan

Abstract

Glomerular filtration rate (GFR) is a key index of renal function. The classic method for assessing GFR is the clearance of inulin. Several current methods using isotopic (^{125}I-iothalamate, ^{51}Cr-EDTA, or ^{99}Tc-DTPA) or nonisotopic (iohexol or iothalamate) markers are available. Clinically, GFR is estimated (eGFR) from serum creatinine or cystatin C levels. Estimated GFR based on creatinine and/or cystatin are less accurate than measured GFR. The creatinine-based equations calculate higher eGFR values (suggesting better kidney function) for black individuals. This upward adjustment for all black individuals is embedded in eGFR calculations on the belief of higher serum creatinine concentrations among black individuals than among white individuals. Thus "race-corrected" eGFR has become a widely accepted and scientifically valid procedure. However, race is not a genetic or biological category. Rather, race is a social construction defined by region-specific cultural and historical ideas. Furthermore, there is no accepted scientific method for classifying people as black or white individuals. Studies typically rely on self-identification of race. However, any person in the United States with any known black ancestry is considered to be a black individual. This is known as the "one-drop rule," meaning that a single drop of "black blood" makes anyone a black individual. It does not matter if an individual has 50%, 25%, 5%, or 0.5% African ancestry. The limited accuracy and reliability of this approach would not be allowed for any other scientific variable. Admixture and migration have produced such broad variations that race categories should not be used as experimental variables.

creatine; creatinine; estimated glomerular filtration rate; renal clearance

INTRODUCTION

> "The delusion that race is a biological inheritance rather than a political relationship leads plenty of intelligent people to make the most ludicrous statements about Black biological traits." Dorothy E. Roberts (1)

The assessment of glomerular filtration rate (GFR) is a critical first step in evaluating kidney function. The GFR is equal to the amount of blood filtered through all glomeruli in a given period of time (ml/min). GFR cannot be directly measured so cannot be known with certainty (2). However, a highly useful method for assessing GFR, renal plasma flow, and the how substances are handled by the kidney (i.e., filtered, reabsorbed or secreted) is the clearance technique. The clearance of a substance is the volume of blood that the kidneys completely clear of the substance in a given period of time (ml/min). It is equal to GFR if the substance being measured is freely filtered through glomeruli, not reabsorbed out of the urine, and not secreted into the urine. Measuring the clearance of a substance whose clearance is equal to GFR is the best way to evaluate kidney function. Thus, because of the quantitative importance of GFR for the proper functioning of the kidneys, and consequently the regulation of body fluids and electrolytes, it is critical to understand its measurement, the meaning, and the limitations to the determination of GFR.

Glomerular filtration rate is often expressed in milliliters per minute normalized to body surface area. The classic method for assessing GFR is measuring the clearance of the exogenous high molecular weight carbohydrate inulin (3). GFR can also be assessed using isotopic (^{125}I-iothalamate, ^{51}Cr-EDTA, or ^{99}Tc-DTPA) or nonisotopic (iohexol or iothalamate) "cold" markers (4–11). However, all of these procedures are costly and cumbersome and therefore not often used clinically. That is, none of these methods are used in routine clinical practice. Instead, creatinine clearance may be measured, or serum creatinine or cystatin C-based equations may be used clinically to assess GFR or estimate glomerular filtration rate (eGFR) (12, 13).

CALCULATING CREATININE CLEARANCE FOR ASSESSING GFR

Creatinine is an endogenous inert end product of creatine metabolism and is derived mainly from the large mass of muscle tissue. As long as muscle mass remains constant, creatinine is produced at a constant rate and its concentration in plasma is essentially constant. In 1948, Brod and Sirota

Correspondence: S. E. DiCarlo (dicarlos@msu.edu).
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(14) demonstrated that glomerular filtration rate could be evaluated using clearance of endogenous creatinine.

Creatinine is excreted almost exclusively by the kidney and the primary mechanism by which it enters the tubule is glomerular filtration. It is not reabsorbed by the tubule but does undergo tubular secretion by a rate limited mechanism. Because it is secreted as well as filtered, the creatinine clearance overestimates the GFR. However, the creatinine secretory mechanism has a very low transport maximum and the degree of overestimation of GFR is small.

In clinical practice, it is convenient to use creatinine clearance to determine GFR since it does not require intravenous infusion of an exogenous substance like inulin. Often it is measured as a 24-h clearance. Under these conditions, bladder catheterization to ensure complete emptying of the bladder is not usually required as is the case for short term urine collections required in performing inulin clearances.

Blood samples are collected for measurement of plasma creatinine concentration, and the patient is provided with an appropriate container and preservative and instructed to collect all urine excreted over the next 24 h. The urine volume and creatinine concentration are measured, and the clearance is calculated.

As noted, the method required accurate measurement of urinary creatinine excretion through a 24-h timed collection of urine. This requirement often produced large errors especially among the elderly and young.

> "Race correction shows a failure to understand the meaning of race and its connection to racism." Dorothy E. Roberts (15)

FORMULA-BASED ESTIMATES OF GFR

The requirement of accurate measurement of urinary creatinine excretion through a 24-h timed collection period reduced the practicability of the creatinine clearance-based approach for assessing GFR. Thus, in 1976, Cockcroft and Gault (16) demonstrated that creatinine clearance could be estimated, relative to inulin clearance, based only on circulating creatinine concentrations, without measurement of urinary creatinine clearance. Their Cockcroft-Gault equation included modifiers for age, weight, and sex. It must be noted that the study population was nearly all male.

The limitations of the Cockcroft-Gault equation prompted the development of additional equations. In 1999, Levey and colleagues (17) developed the Modification of Diet in Renal Disease (MDRD) eGFR equation relative to iothalamate clearance. Specifically, the MDRD calculation estimates GFR in comparison to its measurement by the iothalamate method. The MDRD eGFR equation expressed glomerular filtration rate as milliliters of blood per minute per 1.73 m^2 of body surface area to adjust for differences in total creatinine clearance due to differences in body size. It also included an adjustment for race.

Subsequently, in 2009, Levey and colleagues (18) updated the MDRD equation for eGFR with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on a larger data set which adjusted for age, sex, gender, and ethnicity and also incorporated a factor for elevated creatinine values. The urinary clearance of iothalamate was used for the development and internal validation of the CKD-EPI equation but also included studies that used iothalamate and other filtration markers for external validation. The CKD-EPI creatinine equation was shown to be more accurate than the MDRD equation.

The MDRD and CKD-EPI equations incorporate a race correction factor based on data showing that black individuals have higher-than-average serum creatinine concentrations (19) suggesting (but not showing) that black individuals have a higher muscle mass and release higher amounts of creatinine into their plasma. In fact, the adjustments for race by the CKD-EPI formula adds 16% to the estimated GFR for black individuals compared with white individuals with the same serum creatinine values, age, and sex (18). The MDRD equation provides an eGFR 21% higher for black individuals (20). It is important to note that 19.4% of MDRD estimated values and 15.9% of CKD-EPI estimated values deviate from measured GFR by >30% (18, 21). This limited accuracy should be considered when using these formulas for clinical decisions. Furthermore, as noted by the editors of the *Annals of Internal Medicine*, "The sample used to develop the CKD-EPI equation included few elderly and nonwhite persons. Evaluation of the equation in these populations is needed" (18).

A more recent equation using cystatin C may be more accurate than the MDRD and CKD-EPI equations. Cystatin C is a small molecular weight protein constitutively synthesized by most nucleated cells. Equations that use both creatinine and cystatin C have been shown to be accurate, with only 8.5% of values deviating by >30% from measured GFR (7, 21). However, estimated GFR based on creatinine and/or cystatin are less accurate than measured GFR (22). Creatinine-based eGFR measurements are affected by body type, chronic illness, or meat-enriched or vegetarian diet (13, 21). Cystatin C-based eGFR measurements are affected by corticosteroid use, weight, height, smoking status, the concentration of C-reactive protein, and relatively common genetic variants of the cystatin C gene (13, 21, 23). Of note, the more accurate cystatin C-based eGFR calculation does not rely on a race-based assumption.

AMERICA'S DEFINITION OF WHO IS BLACK; ANY AFRICAN ANCESTRY MEANS ONLY AFRICAN ANCESTRY IN THE MINDS OF MANY AMERICANS

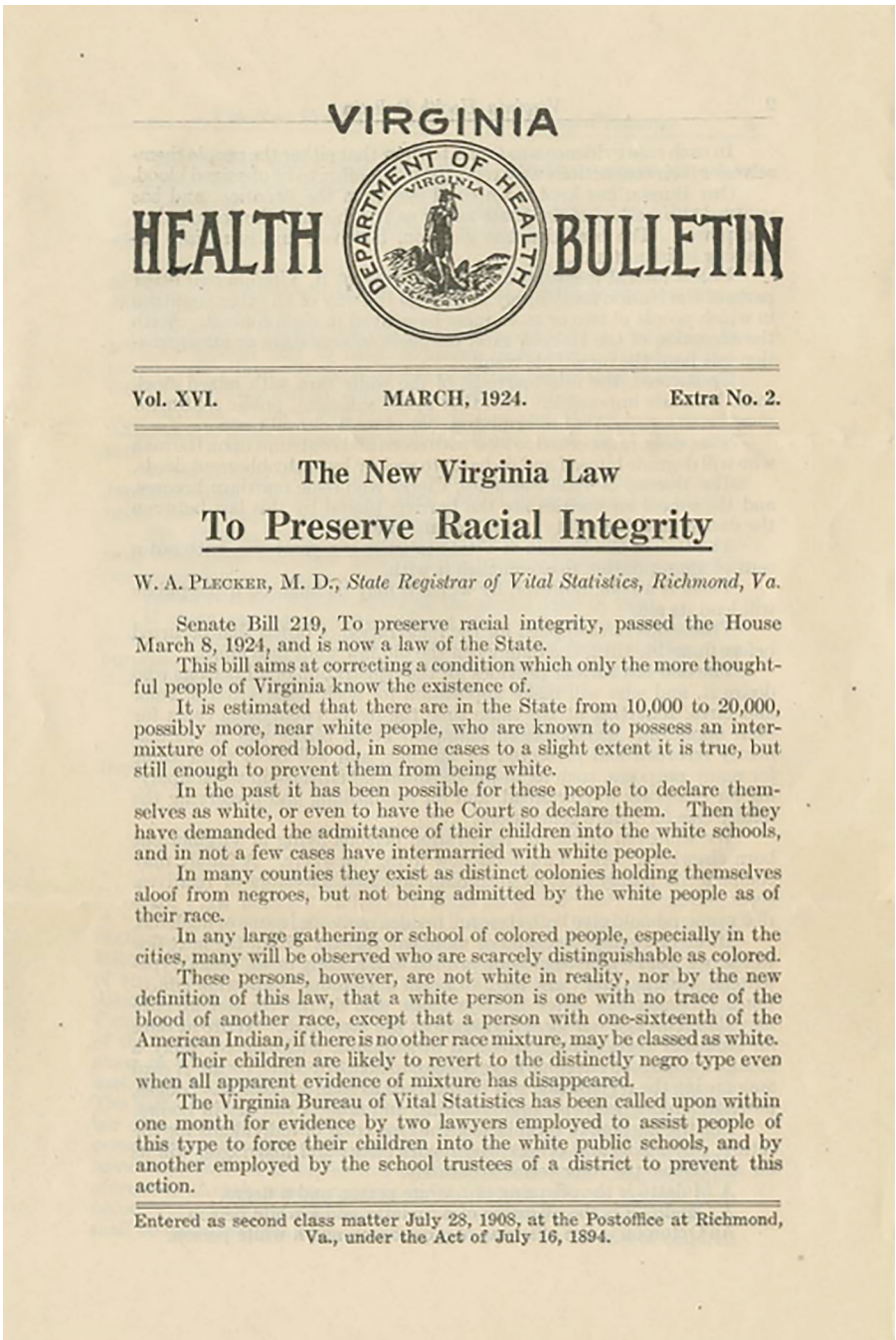
When evaluating formulas of renal clearance and GFR, it is essential to consider the methods used for classifying people as black or white individuals (24). Because there is no objective scientific method classifying people as black or white individuals, studies of renal clearance and GFR have typically relied on self-identification of race in the recruitment and racial classification of study participants. In addition, health care providers often make the determination of a person's race. For example, spirometers are used globally to diagnose respiratory diseases, and most commercially available spirometers "correct" for race (25). The National Institute for Occupational Safety and Health's Spirometry Training Guide states:

> "To evaluate pulmonary function and to make recordings, the operator must enter the subject's race. An attempt should be made to determine and record the

employee's race or ethnicity. Often this can be done with adequate accuracy merely by observation. If in doubt, ask the employee, explaining that race affects the reference values used for the test. If the employee considers the question objectionable, or if their race or ethnicity does not clearly fit the limited categories available, just record unknown and use Caucasian reference equations (no race correction or race-specific reference value)." (26)

These practices raise the critical question: how are Americans classified as black or white individuals (27, 28)?

The classification of Americans as black or white individuals has a long and disturbing history (29). In 1662 the Virginia legislature established a law whereby "children got by any Englishman upon a negro woman. . .shall be held bond or free only according to the condition of the mother" (30). Thus, children born of a black mother and white father (31) belonged to the owner of the mother of the offspring. That is, enslaved woman's children inherited the "condition" of their mother making slavery hereditable. All children born to slave women would be slaves for life. The law established strict racial barriers where skin color became the marker of division between white and black people (32). This



VIRGINIA

HEALTH BULLETIN

Vol. XVI. MARCH, 1924. Extra No. 2.

The New Virginia Law

To Preserve Racial Integrity

W. A. Plecker, M. D., *State Registrar of Vital Statistics, Richmond, Va.*

Senate Bill 219, To preserve racial integrity, passed the House March 8, 1924, and is now a law of the State.

This bill aims at correcting a condition which only the more thoughtful people of Virginia know the existence of.

It is estimated that there are in the State from 10,000 to 20,000, possibly more, near white people, who are known to possess an intermixture of colored blood, in some cases to a slight extent it is true, but still enough to prevent them from being white.

In the past it has been possible for these people to declare themselves as white, or even to have the Court so declare them. Then they have demanded the admittance of their children into the white schools, and in not a few cases have intermarried with white people.

In many counties they exist as distinct colonies holding themselves aloof from negroes, but not being admitted by the white people as of their race.

In any large gathering or school of colored people, especially in the cities, many will be observed who are scarcely distinguishable as colored.

These persons, however, are not white in reality, nor by the new definition of this law, that a white person is one with no trace of the blood of another race, except that a person with one-sixteenth of the American Indian, if there is no other race mixture, may be classed as white.

Their children are likely to revert to the distinctly negro type even when all apparent evidence of mixture has disappeared.

The Virginia Bureau of Vital Statistics has been called upon within one month for evidence by two lawyers employed to assist people of this type to force their children into the white public schools, and by another employed by the school trustees of a district to prevent this action.

Entered as second class matter July 28, 1908, at the Postoffice at Richmond, Va., under the Act of July 16, 1894.

Figure 1. In 1924, a Virginia Act for "Preservation of Racial Integrity" defined a white person as someone with "no trace whatsoever of any blood other than Caucasian" (32). The Virginia legislature in 1930 defined as colored "any one in whom there is ascertainable any negro blood."

established a long history of customs, norms, and juridical understandings.

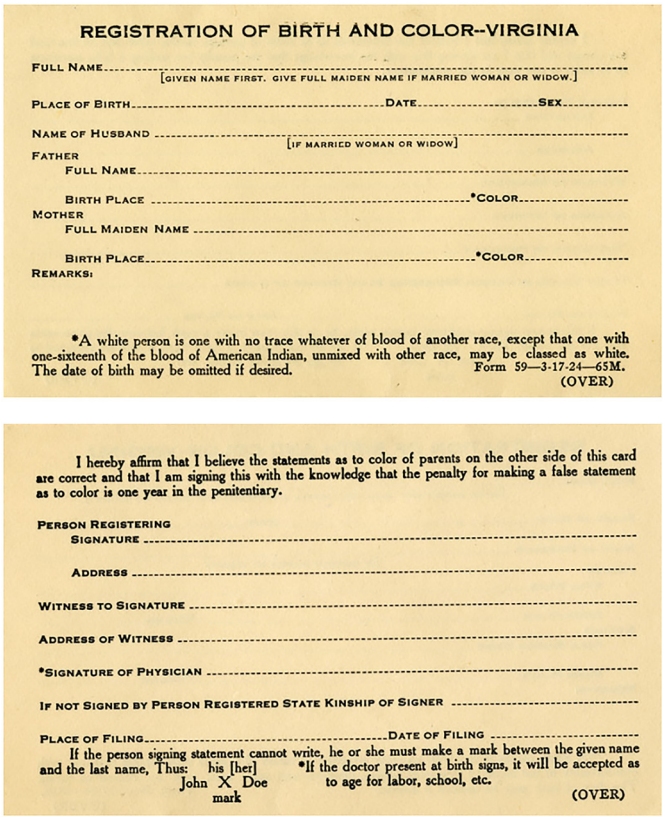
THE ONE-DROP RULE

To eliminate the potential for light-skinned black individuals passing as white individuals, many state officials categorized any person with one drop of black ancestry as a black person. Specifically, Jim Crow Laws defined a black individual as anyone with any African ancestry. This one-drop rule became the social and legal principle of racial classification in the United States. Anyone with even a single ancestor of African descent was considered a black individual (negro in historical terms). This certainly seems scientifically unsound since every human alive today can trace their ancestry back to individuals who migrated from Africa (33).

The one-drop concept evolved during the 19th century and became the law of many states. Tennessee was the first state in 1910 to place the one-drop rule into law. Louisiana, Texas, Arkansas, Mississippi, North Carolina, Virginia, Alabama, Georgia, and Oklahoma followed. Florida, Kentucky, Maryland, Missouri, Indiana, Nebraska, North Dakota, and Utah amended their old "blood fractions" to one-sixteenth or one-thirty-second which is nearly the equivalent of the one-drop rule. Thus, in 1911, for example, Arkansas passed Act 320 (House Bill 79), which defined as "Negro" anyone "who has. . .any negro blood whatever."

Virginia and other states began to classify people only as black or white. For example, in 1912 Virginia lawmakers established the Bureau of Vital Statistics and enacted strict segregation laws and a prohibition on interracial marriage. Walter Plecker, a physician, and staunch promoter of eugenics became the first Registrar of Statistics and held the position to 1946. Plecker successfully advocated for the Virginia General Assembly to pass the Racial Integrity Act of 1924 (Ref. 32; Fig. 1), a law that criminalized interracial marriage and required that every birth in the state be recorded by race with the only options being "White" and "Colored" (Ref. 34; Fig. 2). Plecker wrote: "Two races as materially divergent as the White and Negro, in morals, mental powers, and cultural fitness, cannot live in close contact without injury to the higher" (35). Accordingly, the Act to Preserve Racial Integrity, effectively separated citizens into only two racial categories based solely on color: "White" and "Colored" (Fig. 2). "The term "white person" shall apply only to such person as has no trace whatever of any blood other than Caucasian." All others were "colored" (35). However, in 1967, the United States Supreme Court struck down Virginia's law prohibiting interracial marriage in the case of Loving v. Virginia and ruled the Virginia Racial Integrity Act, and similar one drop rules, unconstitutional (36).

The social and legal concept of the one-drop rule does not exist outside the United States. Furthermore, the legal aspect of the one-drop rule no longer exists within the United States; however, assigning minority status to mixed-race individuals is accepted today in the categorization of individuals. For example, consider why we claim President Barack H. Obama as America's first black president or Halle Berry as the first African American to win the best actress Oscar. President Obama is the son of a black Kenyan father, Barack Hussein Obama Sr, and a white American mother, Ann Dunham. Halle



REGISTRATION OF BIRTH AND COLOR--VIRGINIA

FULL NAME ____ [GIVEN NAME FIRST. GIVE FULL MAIDEN NAME IF MARRIED WOMAN OR WIDOW.]

PLACE OF BIRTH ____ DATE ____ SEX ____

NAME OF HUSBAND ____ [IF MARRIED WOMAN OR WIDOW]

FATHER
FULL NAME ____
BIRTH PLACE ____ *COLOR ____

MOTHER
FULL MAIDEN NAME ____
BIRTH PLACE ____ *COLOR ____

REMARKS:

*A white person is one with no trace whatever of blood of another race, except that one with one-sixteenth of the blood of American Indian, unmixed with other race, may be classed as white. The date of birth may be omitted if desired. Form 59—3-17-24—65M.

(OVER)

I hereby affirm that I believe the statements as to color of parents on the other side of this card are correct and that I am signing this with the knowledge that the penalty for making a false statement as to color is one year in the penitentiary.

PERSON REGISTERING
SIGNATURE ____
ADDRESS ____
WITNESS TO SIGNATURE ____
ADDRESS OF WITNESS ____
*SIGNATURE OF PHYSICIAN ____
IF NOT SIGNED BY PERSON REGISTERED STATE KINSHIP OF SIGNER ____
PLACE OF FILING ____ DATE OF FILING ____

If the person signing statement cannot write, he or she must make a mark between the given name and the last name, Thus: his [her] John X Doe mark

*If the doctor present at birth signs, it will be accepted as to age for labor, school, etc.

(OVER)

Figure 2. A registration of birth and color form in Virginia used during Plecker's term as the first registrar of Virginia's Bureau of Vital Statistics (34). It required a strict definition of race. This was part of the Racial Integrity Act of 1924 (Library of Virginia): "A white person is one with no trace whatever of blood of another race, except that one with one-sixteenth of the blood of American Indian, unmixed with other race, may be classed as white."

Barry is the daughter of a white mother, Judith Ann Hawkins, who was a psychiatric nurse, and a black father, Jerome Jesse Berry, who was a hospital attendant in the same ward. Both President Obama and Ms. Barry have, at most, 50% African ancestry. This is an important concept because during colonial days' racial status defined who could be enslaved. During the period of government-enforced segregation, racial status defined a person's right to eat in a restaurant, sit on a bus, or attend school. Today, racial status can affect access to high-quality medical care, exposure to environmental toxins, rates of incarceration, and exposure to racial discrimination.

In summary, any person with any known black ancestry is considered to be a black individual in the United States. This is known as the "one-drop rule,'" meaning that a single drop of "black blood" makes a person a black. It does not matter if an individual has 50%, 25%, 5%, or 0.5% African ancestry. Anthropologists call this uniquely American practice the "hypodescent rule" (27). The one-drop rule is taken for granted throughout the United States by people of all races. The definition of a black person as anyone with any trace of African ancestry is deeply engrained in American society as courts have called it the "traceable amount rule." The limited accuracy, reliability and precision of this approach is beyond question.

Although the "one-drop" rule was the decisive determination of black ancestry for over a century, data from the 2010 census reported a large increase in the number of persons self-identifying as African American in combination with another race. This increase in the multiple-race identification of people of African American heritage documents a shift in thinking about the meaning of race. This shift in thinking should be extended to race corrections in medicine. However, most government and private agencies, educational institutions, and advocacy organizations continue to perpetuate the hypodescent, one-drop racialization when classifying individuals.

CONCLUSIONS

> "I am happy that today, the only race we're talking about is the human race." Francis Collins (25, 37)

"Race-corrected" eGFR has become a widely accepted and scientifically valid procedure. However, GFR estimates based on race reinforce the perception that black bodies are biologically different from white ones (20, 38) and assumes that black people are a homogeneous group of people. However, there is no accepted scientific method for classifying people based on race. Studies typically rely on self-identification of race. Any person in the United States with any known black ancestry is considered to be a black individual. This is known as the "one-drop rule," meaning that a single drop of "black blood" makes anyone a black individual. The limited accuracy and reliability of this approach would not be allowed for any other scientific variable, and thus it is time to stop teaching race corrections in medicine.

The human genome project taught us that race is not a reliable representation for genetic variations. For humankind, there is no such thing as biological race, because "most human genetic variation is found within populations, not between them" and "individuals are frequently more similar to members of other populations than to members of their own population" (25, 39). Thus caution must be used when considering ancestry to make inferences about individual phenotypes (25, 39). Admixture and migration have produced such broad variation that race categories cannot be used as experimental variables for risk assessment or guide clinical decisions. Doing so will direct valuable resources to white individuals rather than to members of racial minorities.

Specifically, chronic kidney disease is a major public health problem that disproportionally affects minority and low-income persons (40–42). In fact, black individuals have significantly higher rates of end-stage kidney disease and death due to kidney failure than the overall population (19). Despite these major health disparities, black individuals with chronic kidney disease have worse outcomes, lower dialysis access placement, and lower rates of transplantation (43). Race adjustments that estimate higher GFR in black individuals may be a mechanism for inequitable outcomes by delaying referral and leading to worse outcome. For example, Ahmed and colleagues (43) reported that removing race corrections would reclassify additional black individuals as having more severe stage of chronic kidney disease and potentially prevent delays in referrals.

Similar race corrections affect kidney transplantation practices (44). For example, donor characteristics, including race, are used to predict the risk of kidney graft failure (45). The assumption is that a kidney from a black donor has a higher risk of failure than a kidney from other donors (46). Thus, if a donor is identified as black, the kidney is assigned a higher risk score for graft failure, marking the candidate a less suitable donor (19). Since black individuals are more likely to receive kidneys from black donors, this practice could contribute to the wait-time race disparity (19, 46).

RECOMMENDATIONS

Our main recommendation is to stop teaching "race corrections" in medicine because some African ancestry does not mean only African ancestry (25, 47, 48). In addition, our students should be taught to focus on biological factors, including muscle mass, diabetes, and high blood pressure, rather than superficial classifications around skin color and hair texture in determining appropriate GFR estimate. The focus on innate racial differences in renal function diverts attention and resources from many social determinants, including the lack of access to high-quality medical care; food deserts in poor neighborhoods; exposure to environmental toxins; high rates of incarceration; and experiencing the stress of racial discrimination (25, 48). We should also consider using the race-free cystatin C-based equation to estimate GFR (20, 38).

> "I believe one of the great truths to emerge from this triumphant expedition inside the human genome is that in genetic terms, human beings, regardless of race, are more than 99.9 percent the same." June 2000, President Bill Clinton (49) .

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

H.L.L. and S.E.D. conceived and designed research; H.L.L. and S.E.D. prepared figures; H.L.L. and S.E.D. drafted manuscript; H.L.L. and S.E.D. edited and revised manuscript; H.L.L. and S.E.D. approved final version of manuscript.

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