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Removing Race from eGFR calculations: Implications for Urologic Care

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Abstract

Equations estimating the glomerular filtration rate are important clinical tools in detecting and managing kidney disease. Urologists extensively use these equations in clinical decision making. For example, the estimated glomerular function rate is used when considering the type of urinary diversion following cystectomy, selecting systemic chemotherapy in managing urologic cancers, and deciding the type of cross-sectional imaging in diagnosing or staging urologic conditions. However, these equations, while widely accepted, are imprecise and adjust for race which is a social, not a biologic construct. The recent killings of unarmed Black Americans in the US have amplified the discussion of racism in healthcare and has prompted institutions to reconsider the role of race in estimation of glomerular filtration rate equations and raced-based medicine. Urologist should be aware of the consequences of removing race from these equations, potential alternatives, and how these changes may affect Black patients receiving urologic care.

INTRODUCTION

The recent killings of unarmed Black Americans have amplified the discussion of racism in the United States (U.S.) and sparked a series of social movements advocating for racial justice and encouraging everyone to consider attitudes toward race. Racism and discrimination are deeply ingrained in the health care system, and Black Americans experience a disproportionate burden of disease, injury, and mortality when compared with

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white Americans.[1] While race is a social construct − and not necessarily reflective of biology − many commonly used clinical algorithms and equations account for "race."[2] In many cases, race functions as a surrogate measure of structural barriers experienced by minorities, such as access to care. The renewed discussion of race in clinical medicine has brought focus to the use of race in clinical diagnostic tools, such as estimation of kidney function. African American race is considered in the estimation of glomerular filtration rate (GFR) from age, sex, and serum creatinine. The CKD-EPI equation, introduced in 2009, is the most widely used regression equation that assigns a higher eGFR to Black patients. The difference has been attributed to greater muscle mass in Black compared with non-Black patients, without sufficient evidence to support that contention (which itself could represent inappropriate racial stereotyping).[3,4] Herein we review the use of race in estimating kidney function, and discuss potential impact on Black urology patients if race is omitted.

Omitting race from eGFR calculations will assign Black patients a lower eGFR. Conversely, failure to eliminate this factor will assign Black patients a higher eGFR. The choice to include − or remove − race as a covariate, highlights the inherent imprecision in our efforts as urologists to estimate the GFR. Our goal as a specialty must be to pursue equitable care. In considering removing race as a covariate, we must consider the possible effect that this decision makes on the care of patients with urologic disease, both when made at the institutional level and by individual urologists.

HISTORY OF EQUATIONS TO ESTIMATE THE GLOMERULAR FILTRATION RATE

Measuring kidney function is highly relevant to Black Americans, who are four times more likely to develop end stage kidney disease than white counterparts, particularly at younger ages.[5] Estimating GFR from age, sex, and serum creatinine obviates the need for direct clearance measurements with injected pharmaceuticals like iothalamate, which are impractical to perform. In 1973, the Cockcroft-Gault equation was developed in a cohort of 249 white Canadian men and did not include race as a variable in its estimation of GFR.[6] The Modification of Diet in Renal Disease (MDRD) equation was introduced in 1999 and was simplified to include serum creatinine, age, sex and race as variables.[7] Race was included as a coefficient because it improved model fit. Without this term the equation underestimated the measured GFR in Black Americans and remains unclear why there was increased accuracy with the inclusion of race. The most widely used of the MDRD equations, the 4-variable equation including age, sex, race (Black versus non-Black), estimated a race coefficient of 1.21, yielding an estimate of GFR that is 21% higher for Black patients than for white patients for the same serum creatinine concentration. The CKD-EPI equation, which included additional cohorts, was published in 2009 and estimated a modified race coefficient of 1.16, which yields an estimate of GFR that is 16% higher for Black Americans.[8] The CKD-EPI equation computed coefficients for sex, age, and race from direct measurements of GFR using iothalamate. In clinical practice, these equations may provide a false sense of precision Table 1.

We now appreciate that race is a social construct and a poor surrogate for ancestry and genetic background.[9] For example, the high-risk alleles in the APOL1 gene that offer protection from African Sleeping Sickness (trypanosomiasis resulting from infection with *Trypanosoma brucei*, transmitted by the tsetse fly) have been associated with progressive loss of kidney function in patients of West African descent with focal segmental glomerulosclerosis and other kidney diseases, including diabetic kidney disease.[10] However, APOL1 is not an example of a "Black gene," but is commonly found among populations in endemic areas. Extrapolating genetic or biologic differences from race categories in the post-genomic era is imprecise and fails to meet the lofty goals of truly personalized medicine.

Recently, equations to estimate the glomerular filtration rate have received increased scrutiny for incorporating a race coefficient. First, the use of a race coefficient implies that race is physiologically related to kidney function. Second, these equations simplify the race coefficient as Black or non-Black. This dichotomy incorrectly assumes all Black patients share a similar genetic heritage, ignores the complexities of racial identity within the growing interracial population in our country, and potentially misclassifies all patients without race information either through incorrect inference from physical attributes (most notably skin color) or the assumption that the absence of a racial designation in the electronic medical record implies non-Black. These innate shortcomings of a race variable highlight the need to understand the clinical implications of keeping or removing the race-correction term currently used to estimate GFR.

RECENT EFFORTS TO REMOVE RACE FROM EGFR EQUATIONS

Medical professionals and institutions have already acted or are now considering removing race from the eGFR equations used in clinical practice. In a recent JAMA article[5], Professor Neil R. Powe discussed the use of race in eGFR and summarized efforts of a number of institutions in attempting to address the issue. Beth Israel Deaconess Medical Center discarded race from eGFR reporting in 2017 due to concerns brought up by medical students. Two years later, Zuckerberg San Francisco General Hospital moved to replace race with muscle mass after growing concerns from faculty and trainees. There are concerns that this replaces an imprecise term (race) with another measure that can be difficult to estimate—muscle mass. More recently, four additional academic medical centers, University of Washington, Brigham and Women's Hospital, Massachusetts General Hospital, and Vanderbilt University Medical Center, have removed race from their eGFR reporting.[5] As the push to abolish race-based medicine in kidney disease grows many more institutions are likely to follow suit. Or will they?

CONSEQUENCES OF REMOVING RACE OF EGFR EQUATION: RENALISM

Eliminating race from the MDRD and CKD-EPI equations lowers eGFR estimates for Black patients by 21% and 16% respectively, thus assigning all patients the non-race adjusted result. This change would 'reclassify' thousands of Black patients to higher stages of chronic kidney disease (CKD).[2,11] Diao et al[11] modeled the effect of the race coefficient on the diagnosis and staging of CKD for Black patients in the United States using data

from the National Health and Nutrition Examination Survey. They estimated that removal of the race coefficient would increase the percentage of Black patients diagnosed with CKD (eGFR <60 mL/min/1.73m^2) from 14.9% to 18.4%. Moreover, among Black patients with CKD, the removal of the race coefficient would reclassify 29.1% into a more advanced stage of CKD. This change could stand to benefit Black patients by potentially providing earlier access to CKD education and specialists. For Black patients with CKD, it may accelerate a Black patient receiving a clinical diagnosis of end-stage kidney disease, providing eligibility for Medicare services.[5,11] These efforts may thereby reduce the racial and socioeconomic disparities in receipt of specialty kidney care.[12]

However, this reclassification could also subject some Black patients to overtreatment, while significantly increasing health care costs and economic burden[13] experienced by Black patients who now carry a kidney disease diagnosis. Further, Black patients (already at risk for receiving different care based on race) may be subject to further discrimination based on their kidney function. There are well-documented examples of “renalism” − whereby patients with impaired kidney function receive different care than individuals with normal kidney function. For example, older patients with chronic kidney disease experiencing acute myocardial infarction have been shown to be less likely to receive coronary angiography.[14] Examples of renalism may extend to Black patients with CKD reclassified to a lower eGFR, as they may be less likely to receive beneficial therapies such as RAAS and SGLT2 inhibitors. The act of simply removing race from equations estimating kidney function will not end structural racism in clinical medicine. If not thoughtfully considered, it may have the unintended consequence of further disadvantaging Black patients.

ROLE OF ESTIMATING KIDNEY FUNCTION IN UROLOGIC CARE

Accurately estimating kidney function is paramount for the care of patients with urologic disease. The eGFR is used to ensure the safety of radiocontrast agents during diagnostic imaging studies, to select and appropriately dose medications, and to plan surgical intervention. Black patients with normal or near-normal kidney function are less likely to be affected by removing race from equations that estimate kidney function. However, there is significant concern that removing this coefficient may initially harm Black patients with kidney function near clinical cutoffs used in heuristic-based medical decisions. Here, we consider several examples of how removing race from eGFR equations may affect Black patients receiving urologic care.

KIDNEY TRANSPLANTATION

Perhaps the strongest example of how including race in eGFR equations can harm Black patients relates to eligibility for deceased donor kidney transplantation, which requires a metric of kidney function (either estimated creatinine clearance from the Cockcroft-Gault equation or estimated GFR from either the MDRD or CKD-EPI equations below 20 mL/min or 20 mL/min/1.73m^2). Assuming two patients of similar age, sex, and serum creatinine only differed by race, a Black patient’s higher eGFR would delay listing for deceased donor kidney transplantation. An example of this was emphasized in a recent prospective cohort by Zelnick et al.[15] Their group examined the association of eGFR with and without the race

coefficient with the time to eligibility for kidney transplant (eGFR <20 mL/min/1.73 m^2). Their study estimated that the time to achievement of an eGFR of less than 20 with race was not used was 13.9 years (95% Cl, 13.0−13.9 years) compared to 12 years (95% Cl, 10.9−13.0) when the race coefficient was not used.[15]

As the Organ Procurement and Transplantation Network notes, “perhaps the most significant barrier to preemptive kidney transplantation is timely referral for transplantation evaluation.”[16] Similar concerns exist about the timeliness of referrals to see a nephrologist, where Black patients wait longer to be referred.[17] Unfortunately, poor access to timely donation, racially-based clinical bias, and lower rates of referrals are only a few factors driving healthcare disparities affecting Black patients that are candidates for kidney transplantation.[18] In a study utilizing population data from National Health and Nutrition Examination Survey between 2001 and 2018, Diao et al[11] estimated that removing race from the eGFR equation could potentially raise the proportion of adult Black patients eligible for kidney transplant by 0.05%. Conversely, the proportion of “Not Acceptable” kidney donor candidates would increase by 2.1%.[11] Any potential harm that might be experienced by Black patients related to differential misclassification of kidney function by a race-adjusted GFR estimating equation could be eliminated either by allowing all patients to be listed for deceased donor kidney transplantation at an eGFR of 20 mL per min or below using the equation for non-Black patients, or by allowing listing for Black patients at a higher eGFR (eg, 25 mL/min). Doing so would seem reasonable, particularly since Black patients with CKD tend to progress to ESKD more rapidly than do non-Black patients.

ESTIMATING KIDNEY FUNCTION IN THE CARE OF UROLOGIC CANCERS

Bladder Cancer

When caring for a patient diagnosed with urothelial carcinoma, a clinician considers the eGFR when ordering contrast enhanced imaging to evaluate the presenting hematuria, when dosing anesthetic medications during the TURBT procedure, when considering cisplatin-based chemotherapy regimens for patients with muscle-invasive disease, and when considering the type of urinary tract reconstruction at cystectomy. Under-estimating kidney function could result in fewer patients undergoing radiocontrast-enhanced imaging and receiving lower doses of cisplatin-based chemotherapy.

Urinary Diversion

Kidney function is an important consideration in the decision to proceed with continent, conduit, or orthotopic urinary diversions. Incorporating bowel to reconstruct the urinary tract creates a unique scenario where bowel mucosa is exposed to excreted urinary electrolytes requiring the kidneys to manage an increased acid load. Patients unable to manage this metabolic acidosis due to compromised function are likely to experience metabolic derangements along with other associated symptoms such as nausea and dehydration.”[19] Skinner et al demonstrated that patients with lower preoperative eGFR undergoing two types of neobladder reconstruction exhibited increased risk of further eGFR decline.[20] Most urologists recommend that a patient have a baseline eGFR greater than 35 to 40 mL/min/1.73m^2 to consider continent diversion.[19]

The current use of race in eGFR equations should increase the number of Black patients considered candidates for continent urinary diversion. Choosing to remove race as a factor might lead to fewer Black patients receiving continent diversions. Unfortunately, there are significant disparities in the surgical treatment of Black patients with muscle invasive urothelial carcinoma. Black patients have delays in receipt of cystectomy, are less likely to receive a lymph node dissection and have fewer total lymph nodes removed at the time of cystectomy, and have inferior overall survival.[21] Conversely, white men are two times more likely to receive a continent urinary diversion than Black men.[22] Removing the race coefficient from eGFR equations may further exacerbate these disparities.

Renal Cell and Upper-Tract Urothelial Cell Carcinoma

Partial nephrectomy is the preferred standard for management of small (clinical T1a) renal masses, when feasible. While the use of partial nephrectomy is increasing, it has been preferentially adopted in younger and healthier patients − and in those with better baseline kidney function.[23] Maintaining the race coefficient in eGFR equations may misrepresent Black patients as having better kidney function influencing the decision towards nephron sparing approaches. Conversely, removing race from the eGFR calculation would result in Black patients having a lower estimated baseline kidney function which may influence whether Black patients are offered a partial nephrectomy. The same thought process may be extended to the management of upper tract urothelial carcinoma (UTUC). Over the past decade, the incidence of UTUC has increased in Black patients, and Black patients have been shown to have higher mortality compared with other racial groups.[24] The use of endoscopic ablation, instead of radical nephroureterectomy, may offer an opportunity to preserve nephron-mass and improve outcomes in patients with upper tract urothelial carcinoma. For patients with UTUC that would otherwise be appropriate candidates for endoscopic treatment, failure to eliminate race as a factor in eGFR might expose Black patient to more radical nephroureterectomies and thus permanent loss of kidney function.

NEPHROTOXIC AND RENALLY CLEARED CHEMOTHERAPY REGIMENS

A patient’s baseline kidney function plays a significant role in the selection and dosing of chemotherapy regimens for patients with urologic cancers. For example, patients with urothelial carcinoma of the bladder and reduced kidney function are not eligible for cisplatin-based neoadjuvant chemotherapy − the only chemotherapy regimen shown to improve overall survival for patients with muscle-invasive urothelial carcinoma. Guidelines also recommend potentially nephrotoxic agents for patients with advanced testicular and penile cancer both for metastatic disease and in the neoadjuvant and adjuvant setttings.[25,26] For agents that are dosed using the eGFR equation, removing race as a coefficient would expose patients to a lower, and potentially less effective chemotherapy regimen. Conversely, keeping the race coefficient could mask subclinical CKD and increase the likelihood of exposure to nephrotoxic agents. Again, we are faced with a dilemma - keeping race in the equations to estimate kidney function for Black patients would increase access to these critical agents but removing race would limit access or potentially reduce the dose to a less effective level.

CONTRAST ENHANCED IMAGING

Urologic care relies heavily on the use of contrast enhanced imaging (eg, CT or MRI). Contrast enhanced imaging is the gold standard method of evaluating patients with hematuria, in the evaluation of patients with renal masses, adrenal masses, and in the use of MRI for patients diagnosed or screened for prostate cancer. The main criteria to qualify for contrast imaging is an acceptable eGFR. What does this mean for Black and non-Black patients in the context of eGFR? Currently, the inclusion of race in the eGFR equation gives Black patients a perceived advantage. For two male patients age 60 with serum creatinine of 1.4 mg/dL, a Black patient would receive an eGFR of 63 mL/min/ $1.73m^2$ (CKD 2) while a patient labeled as non-Black would demonstrate an eGFR of 54 mL/min/1.73m2 (CKD 3). Using the current eGFR equations, one would expect that Black patients would be more likely to obtain diagnostic urologic imaging compared with white patients. However, Black patients are currently at-risk of experiencing both over- and under-use of contrast enhanced imaging. Washington and Deville[27] evaluated health disparities and inequities in the utilization of diagnostic imaging for prostate cancer and found that African-American men had higher odds of experiencing overuse of standard pelvic CT/pelvic MRI. Nonetheless, African-American and Hispanic men were less likely than their white counterparts to obtain a prostate mpMRI. Alabee et al analyzed 2080 patients treated with cystectomy and found that Black race was associated with reduced utilization of radiographic follow up after surgery.[28]

SURGICAL MANAGEMENT OF STONE DISEASE

Urinary stone disease affects 1 in 11 persons in the U.S.[29] and is the cause for roughly 2 million emergency room visits in the U.S. each year.[30] Urinary stone disease can affect long-term kidney function through episodes of infection, obstruction, or volume depletion.[31] Consequently, delays in management of clinically significant urinary stone disease increase risks of complications such as pyelonephritis, urosepsis, and AKI.[29] Assessing kidney function is paramount in the evaluation of patients presenting with symptomatic urinary stone disease. In the presence of a solitary kidney or compromised kidney function, urologists immediately focus on urinary decompression or definitive stone surgery in order to preserve renal function. Brubaker et al[29] evaluated the role of race/ethnicity in the timing of surgical management of clinically significant urinary stone disease. Over this 2-year time frame, they identified more than 15,000 patients who were discharged from the emergency department with a diagnosis of urinary stone disease who later underwent definitive stone surgery. The study found that patients identifying as Black or Hispanic, as well as underinsured patients, experienced longer wait times to definitive stone management. Similarly, Kirshenbaum et al[32] found that Black and Hispanic patients were less likely to undergo definitive stone management in an inpatient setting. While these studies were not able to assess whether baseline kidney function estimates were associated with delays in management, the decision to keep or remove race from eGFR equations may lead to changes in the use of medical expulsive therapy, increased use of temporizing procedures such as ureteral stenting, and expedite or delay timing of definitive stone surgery.

ESTIMATED GFR AND MANAGEMENT OF URINARY TRACT INFECTIONS

Managing urinary tract infections is an integral component of urologic practice. Recent consensus guidelines provide recommendations for managing recurrent urinary tract infections in an otherwise healthy female[33] but do not address the management of patients with impaired kidney function. While the guidelines do not explicitly recommend obtaining baseline labs such as eGFR prior to antibiotic management, the choice of antibiotics and therefore antibiotic effectiveness may depend on presence/absence of impaired kidney function, especially in older patients. Commonly prescribed antibiotics such as fluoroquinolones, trimethoprim/sulfamethoxazole, most cephalosporins, all consider kidney function when adjusting dosing.[34] Consequently, treating patients with impaired kidney function and urinary tract infections creates a difficult challenge with serious complications if not managed appropriately. Ahmed and colleagues[35] performed a retrospective study collecting data from linked health records over 6 years to evaluate the risk of adverse outcomes following UTI in older patients with impaired kidney function. Among 123,607 patients over the age of 65, patients with an eGFR <60 mL/min/1.73m^2 had higher odds of being hospitalized for UTI and AKI. Worse kidney function (as measured by the eGFR) was directly associated with clinical outcomes. Patients with an eGFR <45 mL/min/1.73m^2 were more likely to be admitted for sepsis, and those with an eGFR <30 mL/min/1.73m^2 had higher odds of death. It is important to consider how patient outcomes would change when the eGFR is calculated differently. Would a lower eGFR attributed to Black patients confer worse outcomes? Black patients may not be directly affected if race persists in eGFR however removing it may unnecessarily place them in an at-risk category.

THE PATH FORWARD

Removing race from the equation should be carefully considered and compared with alternatives. As elaborated by Dr. Powe and a recent report by Diao et al,[36] there are several alternative approaches, each with inherent advantages and disadvantages. One alternative approach is using cystatin C as a marker of renal solute clearance that is independent of creatinine generation. When deriving equations to estimate measured GFR using serum cystatin C rather than serum creatinine, Black versus non-Black race did not improve the fit of the regression equations.[5] However, at present, serum cystatin C testing is not yet widely available. Moreover, serum cystatin C concentrations are known to vary with inflammation, and our understanding of its role in patients with urologic disease is unknown. Another approach is to use a blended race standard that would require developing a new equation using multiple weighted average race coefficients. The approach removes the Black vs non-Black race coefficient and recognizes the limited participation of Black patients in prior studies. However, this would need to be done for all races/ethnicities and require agreement on the appropriate weights.[5] Finally, another approach could incorporate prediction intervals alongside eGFR reporting to acknowledge the imprecision of current eGFR equations.[12] Providing intervals instead of relying on a single value may be helpful to clinicians in assessing patients with better nutritional status, fitness, and muscle strength (therefore more likely to have a higher GFR) compared to patients who are more frail.[12] There may be other alternatives, but regardless of the approach, the time and opportunity to address how these factors effect Black patients in urology is now.

CONCLUSION

Evaluating kidney function is important to urologic care. Black patients suffer disproportionately when it comes to cancer screening and treatment choices, CKD, and transplant allocation. Removing race from eGFR could provide a needed shift in how clinicians/urologists (should) deliver care to Black patients. Overestimating or underestimating eGFR could lead to serious unintended consequences in the management of urologic conditions. Therefore, urologists should be aware of the imprecision of using race to estimate kidney function, as well as the potential effects removing race from GFR estimating equations will have on their Black patients. As the conversation continues, we should embrace the opportunity to revisit equations for estimating GFR, and to improve clinical tools and evidence-based solutions that inform our decision making. As urologist Randy Vince states, “racism in medicine exists, and bold and decisive actions are needed to solve this problem.[37] All urologists should recognize that race is a social construct, that Black kidney function matters, and that much work is needed to personalize and improve the care of Black patients with urologic conditions.

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Table 1.

Urologic conditions where the estimating the glomerular filtration rate is used in medical decision making.

Urologic Condition	If you have a higher eGFR you are:	If you have a lower eGFR you are:
Overall Health Assessment	Assigned earlier CKD stage Viewed as "healthier" More likely to receive aggressive treatments (eg, surgery)	Assigned more advanced CKD stage Labeled as "less healthy" Less likely to receive aggressive treatment
Imaging *Bladder Cancer:* Diagnosis/Staging *Renal Mass:* Diagnosis/Staging *Prostate Cancer:* Diagnosis/Staging	More likely to get contrast imaging which affects: 1. Diagnosis of disease (earlier diagnosis) 2. Staging of cancer (proper staging and informed management plan). 3. Surveillance of Disease (catch early complications, recurrences)	Less likely to receive contrast studies
Systemic Therapy *Bladder Cancer:* Chemotherapy *Advanced testicular/penile cancer:* Chemotherapy *Urinary Tract infection:* Antibiotic choice and dose	More likely to be eligible for a drug; receive (or require) higher dose of drugs such as: 1. Chemotherapy 2. Anesthesia medications 3. Antibiotics	Less likely to be eligible for a drug or may receive lower dose
Surgical Intervention *Bladder Cancer:* Urinary Diversion *Kidney Cancer and Upper tract Urothelial Cancer:* Nephron-sparing approaches *Urinary Stone Disease:* Timing and type of intervention	More likely to receive a continent diversion May affect decision to recommend partial nephrectomy May affect decision to recommend endoscopic ablation More likely to receive trial of passage or upfront ureteroscopy	Less likely to receive these surgical approaches. More likely to receive temporizing procedure (e.g., ureteral stenting)
Kidney Transplant	Less likely to be referred for Kidney Tx	More likely to be referred
Progressive CKD	Less likely to be referred to Kidney Specialist	More likely to be referred

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