May 4, 2021

David Meyers, MD
Acting Director
Agency for Healthcare Research and Quality
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Meyers:

The American Society of Nephrology (ASN) thanks the Agency for Healthcare Research and Quality (AHRQ) for the opportunity to provide comments on AHRQ's "Request for Information (RFI) on the Use of Clinical Algorithms That Have the Potential to Introduce Racial/Ethnic Bias into Healthcare Delivery." ASN applauds AHRQ for commissioning an evidence-based review on the use of race within clinical algorithms.

Reaffirming that race is a social, not a biological, construct, ASN remains committed to ensuring that racial and ethnic biases do not affect the diagnosis and treatment of kidney diseases. As stated in a letter to ASN membership in March 2021, **ASN asserts that 1) race modifiers should not be included in equations to estimate kidney function and 2) current race-based equations should be replaced by a suitable approach that is accurate, inclusive, and standardized in every laboratory in the United States**. Any such approach must not differentially introduce bias, inaccuracy, or inequalities.

In this letter, ASN outlines the historical development of estimated glomerular filtration rate (eGFR) equations and the Kidney Donor Risk Index (KDRI), two clinical algorithms in nephrology. ASN discusses implications of the use of race variables on quality of care and health disparities. Through efforts across our organization, ASN is committed to health equity and eliminating disparities in care. Our September 2020 response to US Representative Richard Neal, Chairman of the House Committee on Ways and Means, further details these far-reaching efforts.[1]

Use of Race in Estimated Glomerular Filtration Rate (eGFR)

Accurately assessing kidney function is critical for diagnosing kidney diseases, dosing medications appropriately, ensuring timely care delivery, and prognosticating clinical outcomes. Methods to directly measure kidney function (glomerular filtration), using iohexol or iothalamate clearance, are expensive and cumbersome and impractical in routine clinical care. As a result, kidney function is typically estimated by measuring serum (blood) levels of biomarkers that are filtered by the kidney.

Serum creatinine is the most common biomarker used to estimate kidney function. Estimated glomerular filtration rate (eGFR) is most often calculated using an equation that incorporates serum creatinine, age, sex, and race. Over the past year, the inclusion of race in eGFR has been questioned given that race is considered a social, not a biological, construct.[2-4] With a clear need to comprehensively evaluate this issue, a joint task force between ASN and the National Kidney Foundation (NKF) was created, comprised of a broad group of experts and patients, to make recommendations for a national evidence-based approach to assess kidney function using GFR

estimating equations. An interim report summarizing the initial findings of this task force was published in April 2021.[5]

Development and Validation of eGFR Equations

In addition to kidney function, there are several non-GFR determinants of creatinine levels, such as diet, physical activity, and degree of hydration. Historically, GFR estimating equations have attempted to account for these factors by incorporating age, sex, and race as surrogate markers for creatinine generation. More recently, race has been recognized as a social construct – not a biological one – making it not appropriate for use in clinical algorithms.

Two equations are widely used in the United States to estimate GFR based on serum creatinine levels: the older Modification of Diet in Renal Disease (MDRD) Study equation[6] and the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[7] Both equations use a race variable, dichotomized as “Black” and “non-Black.”

The MDRD Study equation was derived using baseline data from a randomized controlled trial that evaluated dietary protein restriction and blood-pressure control interventions.[8] Race was recorded by study team personnel during a baseline in-person patient visit and was classified as white, Black, Hispanic, Asian, Native American, Pacific Islander, Other, or Unknown.[9] There was no designation for mixed race or multiracial individuals. The original MDRD eGFR equation used data from 1,628 individuals in the MDRD Study who had a measured GFR (mGFR) by iothalamate clearance, with 1,070 of these participants used in the training sample and 558 used in the validation sample.[10] A total of 197 (12%) participants were Black and 1,304 (80%) were white. Black race was associated with an on average 18% higher eGFR in a six-variable eGFR equation (that additionally included serum urea nitrogen and serum albumin level). An abbreviated four-variable MDRD eGFR equation that did not include physical activity and diet showed an on average 21% higher eGFR in Black participants at any given serum creatinine, age, and sex.[6] The MDRD equation subsequently was validated in 1,703 African Americans participants in the African American Study of Kidney Disease and Hypertension study.[11]

The CKD-EPI equation was developed in 5,504 participants pooled from 10 studies, internally validated in 2,750 participants, and externally validated in 3,896 participants from 16 studies. The race/ethnicity composition of the cohorts is presented in Table 1. Multivariable linear regression was used to model mGFR, with predictors including serum creatinine, age, sex, and race. Race was classified as Black vs. non-Black in the regression model. On average, individuals identified as Black had a 16% higher eGFR value compared to non-Black individuals at any given age, sex, and serum creatinine level. The CKD-EPI eGFR equation using creatinine achieves an estimate that is within 30% of the mGFR 80-85% of the time, highlighting that eGFR is limited in precision.

Table 1. Race/ethnicity Composition of CKD-EPI eGFR equation cohorts.[3]	**Development (n = 5,504)**	**Internal Validation (n = 2,750)**	**External Validation (n = 3,896)**
Black	1728 (32%)	857 (31%)	384 (10%)
Hispanic	247 (5%)	106 (4%)	67 (2%)
Asian	62 (1%)	38 (1%)	67 (2%)
White and other	3467 (63%)	1749 (64%)	3378 (87%)

The measures selected for use in the GFR estimating equations are limited to laboratory data and demographic data that would be available in a clinical or laboratory database to facilitate automated reporting of estimated GFR. Although social determinants of health (SDOH) may impact non-kidney

determinants of the serum creatinine level (diet, physical activity, and degree of hydration) and were collected in some cohorts,[12] measures of SDOH were not widely available in clinical and laboratory databases employed, and therefore were not included as candidate variables in these models. ASN supports research on how SDOH can impact both creatinine and eGFR, and additionally other kidney-related clinical measures and outcomes.

Estimated Impact of Race-based eGFR on Quality of Care, Clinical Outcomes, and Health Disparities

Kidney diseases, particularly kidney failure (also known as end-stage kidney disease or ESKD), disproportionately impacts people who are Black, Hispanic, American Indian or Alaskan Native, Asian, and Hawaiian and Other Pacific Islanders compared with non-Hispanic white individuals.[13] One in every 12 Black men develop kidney failure requiring dialysis during their lifetime – 2.4-fold higher than is seen among white men.[14,15] Black women similarly have a 3-fold higher lifetime incidence of kidney failure than white women. Black patients have worse outcomes with respect to blood pressure control, timely nephrology referral, home dialysis uptake, hemodialysis fistula or graft placement prior to dialysis initiation, waitlisting for transplantation, and receiving a transplant compared to other groups.[16-19]

ASN's written testimony in June 2020 to the House Committee on Ways and Means further discusses the disproportionate impact of kidney diseases on minoritized people.[20] It is a national urgency to address these major disparities in health care, and these disparities extend beyond the scope of this RFI on the use of race in clinical algorithms.

Removing the eGFR race coefficient could potentially have multiple effects on care delivery, including diagnosing more people with kidney diseases, earlier referrals to nephrologists, and waitlisting for Black people for transplants earlier.[21,22] Several empirical analyses have quantified the impact of including versus omitting the "race-correction" in eGFR equations:

- Among 2,225 Black patients in the Partners HealthCare System Chronic Kidney Disease registry, removing the race coefficient leads to 16% more individuals having an eGFR below 60 mL/min/1.73 m^2, a threshold consistent with CKD stage 3, and reclassifies 33.4% of patients to a more severe stage of CKD, with 3.1% more individuals attaining an estimated GFR < 20 mL/min/1.73 m^2 for transplant waitlist eligibility.[23]
- Analyses of National Health and Nutrition Examination Survey data found that removing the race coefficient would increase the prevalence of kidney diseases among Black adults from 14.9% to 18.4%, while reducing the number of eligible kidney donors and having significant implications for medication dosing and contraindications.[24]
- An analysis of the Chronic Renal Insufficiency Cohort found that removing the race coefficient would result in a shorter time to achieve an eGFR < 20 mL/min/1.73 m^2, a level that qualifies one for transplant waitlisting.[25]

However, addressing health disparities and inequities requires identifying and confronting racism on a systemic level. Health status closely correlates with racism and socioeconomic status (as does allostatic load), which is further stagnated by a lack of upward mobility through multiple generations. In addition to health and health care, these social determinants of health include economic stability, social and community context, neighborhood and built environment, and education.

Nephrology Professional Standards and Guidance

The interim findings of the join ASN-NKF Task Force published in April 2021, outline the problem and evidence in five domains:

1) eGFR and measurement;
2) race, racism, and genetic ancestry;
3) body composition and populations used in eGFR;
4) standardization and guidelines; and
5) patients' perspective and shared decision making.[5]

In its interim report, the task force enumerated an inventory of 26 possible approaches for estimating and reporting GFR, including creatinine-based and non-creatinine-based methods that do and do not use race; sought counsel about dissemination and development of guidelines as is discussed in the interim report.[5] The task force is continuing its deliberations and a final recommendation regarding a race-free approach to calculating and reporting kidney function is anticipated in summer 2021 at the latest.

The ASN leadership is tasked with the dissemination of education on changes to eGFR clinical algorithms, including trainee and continuing medical education. ASN continues to prioritize the education of trainees related to health disparities in persons with kidney diseases through venues such as Town Halls with Training Program Directors and ASN's TREKS (Tutored Research and Education for Kidney Scholars) program for medical school students.

Awareness of Race-based eGFR

The eGFR equations to estimate kidney function are used widely across clinics, hospitals, clinical laboratories, and research studies by health professionals in a multitude of specialties. The eGFR equations are also used by researchers and clinical decision support developers who are additional stakeholders. Since 2017, medical students, residents, nephrology fellows, and faculty across the nation have increasingly called for the removal of race from eGFR calculations.[26] As referenced earlier, ASN and NKF formed a joint Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases in August 2020.

Patient perspectives on race-based eGFR reporting have not been formally studied. To capture patient perspectives, the ASN-NKF Task Force conducted dedicated sessions with patient discussants and testimony.[5] Most laboratories automatically report eGFR as two values "if African American" and "if non-African American;" these lab results are often viewable by patients. How clinicians currently communicate race-based eGFR results to patients has not been systematically examined. Similarly, there have been no studies of how application of the race multiplier is explained to patients.

Updating eGFR Equations and Current Challenges

There are several alternatives to creatinine-based eGFR that have various strengths and limitations.[27] For example, Cystatin C, β_2-Microglobulin, and β-Trace Protein are other biomarkers that can be used in equations to estimate kidney function without a race coefficient.[28] The ASN-NKF Task Force is comprehensively reviewing these alternative approaches as it finalizes its recommendations.

Cystatin C is a stronger predictor of incident kidney failure, cardiovascular events, and death than creatinine.[29-31] Although many nephrologists across the country utilize cystatin C testing, current challenges to large scale universal adoption of cystatin C include lack of laboratory standardization, lack of in-house testing, high cost, and low clinician education. Because cystatin C is not currently widely used, it is not included in common laboratory panels such as the basic metabolic panel and is often a send-out test that increases laboratory turnaround time from hours to days.

As with other new biomarkers, greater clinician education and electronic health record integration can facilitate more widespread implementation of cystatin C. Notably, the adoption of new eGFR algorithms within laboratories has been historically slow. Current guidelines recommend using the 2009 CKD-EPI creatinine equation to report eGFR.[32] However, only 31% of laboratories in the United States currently utilize CKD-EPI, indicating a need to accelerate implementation of equations that reflect improving standards of care.[33] Any new recommendations regarding eGFR calculation and reporting would benefit from federal support to overcome these implementation barriers.

Estimated Impact of KDRI on Quality of Care, Clinical Outcomes, and Health Disparities

KDRI is a composite measure of 10 clinical characteristics of deceased donors that provides a reasonable estimate of the relative risk of allograft (kidney transplant) failure. KDRI was developed using the Organ Procurement and Transplantation Network (OPTN) dataset that includes all kidney transplants performed in the United States.

This score is converted into a percentile, referred to as the kidney donor profile index and used as part of the current kidney allocation system since 2014 by transplant centers as a surrogate for organ quality. This measure includes race, classified as African American or non-African American, based on population level data that has demonstrated lower long term allograft survival rates for kidneys from Black donors. More recent efforts attempted to replace donor race with high-risk G1 and G2 genetic variants in APOL1, which are associated with worse allograft survival and almost exclusively present in the individuals of recent sub-Saharan ancestry, such as African Americans.[34] Additionally, there is an ongoing national prospective study of outcomes for kidneys from deceased African American donors funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) named APOLLO. APOLLO is an observational study addressing critical questions in kidney transplantation consistent with outlined federal initiatives following the new Kidney Allocation System implementation in 2014. In the APOLLO Protocol, the authors write:

[APOLLO] will determine whether replacing deceased-donor race/ethnicity in the current KDRI with APOL1 genotype better describes organ quality. Deceased-donors are tested for viral infections using polymerase chain reaction–based technology and results are available in hours. APOL1 genotyping also can be performed within hours to permit results to be included in decisions on allocation of kidneys. APOLLO results could lead to fewer discarded kidneys, improved donor and recipient selection, additional kidneys transplanted, longer renal allograft survival, and substantial savings. In addition, APOLLO and LETO hold great promise for determining the safety of living-kidney donation from African American individuals with APOL1 high-risk genotypes. Additional ancillary studies will be performed.[34]

ASN is encouraged by this work and hopes it will provide improved guidance in kidney transplantation. ASN is advocating for additional resources to be applied and research to be conducted to achieve greater equity and understanding in transplantation.

ASN is committed to ensuring that racial and ethnic biases do not affect the diagnosis and treatment of kidney diseases. ASN is also committed to education efforts on changes to eGFR clinical algorithms, including educational efforts targeted at trainees and expanding continuing education to health professionals, including nephrologists.

Again, thank you for the opportunity to provide comments on AHRQ's "Request for Information (RFI) on the Use of Clinical Algorithms That Have the Potential to Introduce Racial/Ethnic Bias into Healthcare Delivery." To discuss this letter further, please contact David White, ASN Regulatory and Quality Officer, at dwhite@asn-online.org or (202) 640-4635.

Sincerely,

Susan E. Quaggin, MD, FASN
President

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