December 16, 2020

The Honorable Richard E. Neal
Ways and Means Committee
U.S. House of Representatives
1102 Longworth House Office Building
Washington, D.C. 20515

RE: Request for Information (RFI) on the Issue of Racial Bias in Clinical Tools Used in the Field of Organ Transplantation

Dear Representative Neal:

On behalf of the American Society of Transplantation (AST), an organization of more than 4,000 transplant professionals dedicated to advancing the field of transplantation and improving patient care, I am pleased to have the opportunity to respond to your important RFI on the issue of racial bias in clinical tools used in the field of transplantation.

The AST unequivocally acknowledges that race/ethnicity and gender disparities exist in many aspects of health care, including liver transplantation, and negatively impact our liver transplant community. It is imperative that any misuse of race/ethnicity and gender should be corrected to promote equity. To appropriately address healthcare delivery gaps, it is imperative that health organizations deconstruct the systemic misuse of race, ethnicity, and gender in the diagnosis, management and treatment of disease. Race and ethnicity are social constructs that, in isolation, are unreliable proxies for significant disease-related genetic differences. As such, in the present-day application of big data, univariate, and multivariate models of poor healthcare outcomes, the use of race, ethnicity, and gender as categorical variables have led to overweighted and oversimplified decision-making algorithms in the everyday management of clinical diseases.

From the Perspective of Kidney Transplant:

1. To what extent is it necessary that health and health-related organizations address the misuse of race and ethnicity in clinical algorithms and research? What role should patients and communities play?

Accurate assessment of kidney function (glomerular filtration rate, GFR) is important to predict progression of chronic kidney disease (CKD) and is vital for appropriate planning for end-stage kidney disease (ESKD) treatment, including timing for referral to transplant evaluation and activation on the national waiting list. Black patients are disproportionately afflicted with kidney disease and have a faster rate of progression of CKD to ESKD. Compared to white patients, Black women are 2-fold more likely and Black men 3.5 times more likely to progress to ESKD over 5 years. Reasons for more rapid progression are multifactorial include genetic risks, differential access to health care, and comorbidities including obesity and hypertension (1).

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Under current allocation policy, patients qualify for waiting time points once they have initiated chronic dialysis or have documentation of a creatinine clearance, GFR or eGFR of ≤ 20 mL/min. Commonly used equations for GFR estimation such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation includes the variables age, sex, and race (specified as black versus non-black), which assigns a race coefficient of 1.16 to patients identified as black, resulting in 16% increases in eGFR for Black patients with the same age, sex and creatinine. However, as Black patients get assigned a higher eGFR for the same level of serum creatinine compared to white patients, use of the equation (as opposed to other measurement tools) exaggerates racial disparity in access to transplant. A higher assigned eGFR lead to a delay in referral and listing of African American patients for pre-emptive kidney transplantation despite having a higher burden and faster progression of CKD to ESRD. The waiting time for kidney transplant is longer for African Americans than white candidates, and living-donor kidney transplantation rate is lowest for African Americans compared to all other racial groups.
Use of current race-based eGFR equations may overestimate the true renal reserve in black potential donors as compared to non-black donors. Although OPTN policy requires confirmatory measurements with mGFR or mCrCl, if eGFR is used in the decision-making process, there remains the potential for its overestimation, thereby increasing donor risk (1).

The use of race in equations also wrongly perpetuate the notion that race is a biological construct rather than a social one and may be a source of continuous mistrust between Black patients and health care providers. We support the motion to readdress the use of race and ethnicity in clinical algorithms and research.

Black patients are not homogenous and hence, GFR equations based on race have a programmed built-in error and can't be claimed to give a completely precise estimation of kidney function. The use of race is also problematic in mixed race patients. We believe that this issue needs urgent attention, but the solution may require more research and time. It took us decades to have a uniform reporting of renal function by every laboratory across the country and that should not be fragmented at any cost due to need for hasty decisions. Patients should not receive different care based on the location of the health care system or lab reporting renal function. It is always good to be transparent about our challenges with patients and community members and should engage them as we seek newer solutions. Engagement starts today by discussing the rationale and flaws of current race-based clinical algorithms and ongoing search for a better tool.

2. What have been the most effective strategies that you or your organization have used to correct the misuse of race and ethnicity in clinical algorithms and research, if any? What have been the challenges and barriers to advancing those strategies?
The serum creatinine based eGFR equations which uses race as an adjustment parameter have become a common use in the field of transplant over the past two decades. Serum creatinine is used by more than 90% laboratories in the country. Hence, changing it overnight is difficult. Although, eGFR can be calculated using the Cystatin C equation in which the black coefficient decreases significantly to 1.06, it still remains race-based equation. Second, Cystatin C is more costly, takes longer to process, and less available. Several hospitals across the country have recently stopped reporting race in serum creatinine based eGFR and are instead reporting e-GFR as a range or are inaccurately assigning the non-black adjusted GFR to all patients. However, reporting a range for a patients' eGFR is not helpful when a specific number is required for

decision making for waitlisting or living kidney donor candidates screening. The measured GFR methods (e.g., iothalmate GFR) are also not available widely or are too cumbersome and expensive. Measured creatinine clearance is more cumbersome than GFR estimation and vulnerable to collection errors.

3. What strategies would you propose to build consensus and widely used guidelines that could be adopted broadly across the clinical and research community to end the misuse of race and ethnicity in clinical algorithms and research?

Since, race is a social construct rather than biological one, we need research for identification of more precise biological markers that will replace race in equations and other tools. One of these biological markers is APOL-1 gene which can potentially supplant race but remains unexplored. Additional markers to assess GFR including cystatin C, β-trace protein, and β-2 microglobulin are less influenced by race and should be evaluated.

The AST's Kidney and Pancreas Community of Practice has designed a survey to gather opinion of transplant clinicians across the country on use of race in eGFR equations, which is under IRB review and anticipated to launch within December 2020. This survey, once conducted, will provide important insight into the perception and practice of transplant centers on use of race in eGFR, important for building consensus. We also hope to survey potential living donors and recipients not on dialysis about their opinion regarding use of race based clinical algorithms.

We acknowledge that current equations have limitations, but change should await more research for development of race independent eGFR equations, and development of consensus and guidelines to improve access to transplant for disadvantaged racial minorities. We need a national plan that is adopted by every lab and institution so that patients receive uniform diagnosis (CKD staging) and possibly uniform care (pre-emptive listing for transplant) no matter where they seek care.

Last, but not the least, we must continue to assess the other factors that may exaggerate racial disparities in access to transplant. For example, a larger proportion of African American patients compared with whites depend on Medicare, especially in Southeastern states (2). The lower income/socioeconomic status and having noncommercial insurance have been shown as the reasons for lower waitlisting of African Americans for transplant (3). Hence, racial and ethnic differences in insurance coverage exacerbates disparities in access to transplantation in the end stage kidney disease population. We recommend expanding Medicare eligibility to people aged <65 years of age if they have CKD with an eGFR <20, which will allow more pre-emptive transplants, especially among black indigent patients.

From the Liver Transplant Perspective:

Specific examples include the use of race in the Modification of Diet in Renal Disease (MDRD) equation for estimation of glomerular filtration rate (eGFR) raises the eGFR for black recipients, unfairly disadvantaging them from meeting eligibility criteria for simultaneous liver-kidney listing and post liver transplant safety net criteria. Similarly, the utilization of serum creatinine in the Model End-Stage Liver Disease (MELD), the numerical scoring system used to calculate a patient's chances for survival in the next three months that is used in organ allocation, unfairly

disadvantages women compared to men as it does not adequately reflect similar degrees of deterioration of renal function.

There is universal agreement that health care organizations and specialty societies need to play a leading role in demonstrating such disparities and recommending solutions to end them. Currently, many researchers are focused on disparities relating to access to health care as well as racial differences in disease and therapy. It is important for our society to focus on all areas where race may impact access to transplant, such as in OPO performance metrics. Removal of race from formulas estimating eGFR may allow for equal access to SLK and post-LT safety net listing for black recipients, and changes in the calculation of the MELD score to utilize a non-race based eGFR equation rather than serum creatinine may mitigate the disparities in access to liver transplantation for women.

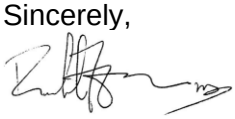
The Pediatric Perspective

For children, this misuse is manifested over a lifetime as a determinant of health that impacts cognitive development, risk for late diagnosis, inadequate patient follow up, inopportunity for preventative care, delayed referral for tertiary care, and difficulties with access to best treatments. Further perpetuating the initial impact of misuse is the lack of consistent social work support services to assist the disadvantaged and disempowered (4). Patients and communities have the unglamorous responsibility of highlighting these social injustices to drive political support for focused public health research, physician training, and insurance company payor reform. Scientists should help reconfigure the community-identified resource needs into new clinical care algorithms that are free of unproven racial and ethnic biases.

Thank you for the opportunity to provide feedback regarding this challenging topic. In addition to the comments I share above, it is important to note that there are many social determinants at play that contribute to medical conditions that are beyond the scope of the medical community. The AST believes that it is important to remember that issues of race cannot be simply ignored or silenced, when determining health care or health care research because this "would blind us to the ways race and racism structure society (5)." It is also important to recognize the need for financial support to truly address this problem, including support to facilitate the enrollment of Black individuals in related research studies. Things such as travel costs, visiting nursing, and even pill organizers are small items that will help. The AST sees this as both a social issue as well as a medical issue.

Please let Mr. Bill Applegate, AST's Director of Government Relations, at bill.applegate@bclplaw.com, or Ms. Shandie Covington, AST's Executive Director, at scovington@myast.org, know if you have any additional questions or if we may be of continued assistance as you consider this complex issue.

Sincerely,



Richard M. Formica, Jr., MD
President

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