Kidney Interagency Coordinating Committee Meeting

Use of Race Corrections in Estimating Glomerular Filtration Rate

Virtual Meeting
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Meeting Participants and Summary

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Welcome and Introductions

Susan Mendley, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)

Dr. Susan Mendley welcomed members and attendees to the NIDDK Kidney Interagency Coordinating Committee (KICC) meeting. She reminded participants that the KICC was mandated by Congress in 1987 to meet yearly; however, because of the enthusiasm, the structure changed from a *pro forma* meeting to one that meets twice yearly with the goal of coordinating a federal response to chronic kidney disease (CKD). The aim is to encourage cooperation, communication, and collaboration among all federal agencies engaged in kidney research and related activities. The NIDDK hosts the Federal CKD Matrix, an online resource that summarizes CKD-related activities. Dr. Mendley explained that the meeting would focus on the use of race corrections in estimating glomerular filtration rate (GFR) and noted that the meeting summary will be posted to the NIDDK website. Dr. Jenna Norton invited meeting attendees to introduce themselves.

Race as a Social Construct

Jenna Norton, Ph.D., M.P.H.
NIDDK, NIH

Dr. Norton presented arguments on race as a social construct and set the context for the later discussion on the use of race in calculating estimated GFR (eGFR). She noted that her goal is to present a compelling argument that race is a social construct rather than a biological construct. Dr. Norton called attention to an article published in the November 11, 2020, issue of *Science* in which the authors called on the NIH to confront the use of race in science. The report conveyed two key messages:

- Compelling evidence shows that racism, not race, is the most relevant risk factor, particularly related to coronavirus disease 2019 (COVID-19).
- The use of race as a means to classify biological diversity in both laboratory and clinical research should be eliminated.

The authors also highlighted the urgent need for the NIH to provide scientists with information about what utility racial data has beyond fostering diversity in research. The underlying question is: What is being measured when the medical and research field measures race in health care?

Dr. Norton explained that four concepts are commonly suggested as components of race: (1) underlying genetic differences, (2) culture, (3) social determinants of health (SDoH), and (4) health effects of structural and perceived racism. She presented arguments on each theme.

Underlying Genetic Differences

Dr. Norton posed the argument that racism is an inadequate proxy for ancestry and genetics. Race designations poorly reflect ancestral differences in genotype. Genetic diversity is higher within people from Africa than between Africans and Europeans. Approximately 25 percent of ancestry informative markers for Americans who identify as Black reflect non-African origin. Diverse admixture in Black Americans reflects European colonization, enslavement of Africans in America, and racial classification structures perpetuated by the "one drop rule," which was a legal and social tenet that a single ancestor of African origin classifies the person as Black even if their majority ancestry is white.

While Apolipoprotein 1 (*APOL-1*) variants often are cited as a key genetic difference across race groups relevant to CKD, *APOL-1* risk variants are common in individuals of West African descent but are almost entirely absent in people of East African descent. This suggests that Black race is a poor indicator of the presence of these variants, since people from West and East Africa would both be classified as Black. The Black race classification might be a reasonable proxy for *APOL-1* in the United States, because the United States disproportionately enslaved people from Western Africa. Thus, Black Americans disproportionately reflect people of Western African origin, who are highly likely to possess high-risk APOL-1 variants. On a global scale, however, race does not align well with *APOL-1* risk variant distribution, and assumptions about APOL-1 presence based on Black race will not well serve the global Black population or people originating from other parts of Africa living in America. Dr. Afshin Parsa will return to this point about the disproportionate Western origin of Africans in America when he discusses data on the comparison of the use of race and ancestral origin in GFR estimation from the NIDDK-sponsored Chronic Renal Insufficiency Cohort (CRIC) study.

Dr. Norton noted that these data suggest that race is not a strong indicator of underlying genetic differences and that it is better to measure ancestry or ideally genes themselves, especially as the field progresses toward precision medicine.

Culture

Culture is defined as the customs, art, social institutions, and the achievements of a particular nation, people, or other group. Dr. Norton emphasized that race classifications in the United States often combine groups with very distinct cultures. Black includes descendants of enslaved Africans in America and the Caribbean and people from 54 distinct African countries who speak approximately 1,500 to 2,000 languages. Many people who are the descendants of enslaved Africans in America were robbed of their ancestral roots, as they do not know from what region of Africa their ancestors originated.

Native American, American Indian, and Alaskan Natives include people from more than 600 distinct tribes from different regions within the United States who speak more than 150 languages. The Asian designation includes people from 48 distinct countries, who speak about 2,300 languages. Native Hawaiian and Pacific Islander groups includes people from 25 distinct nations and territories spread across 25,000 islands who speak about 1,750 languages.

Dr. Norton argued that race is not a suitable measure of culture, because race classifications combine groups with diverse and distinct cultures. A better measure would be to focus on the specific cultural aspects of interest (e.g., cultural health beliefs).

Social Determinants of Health/Health Effects of Structural and Perceived Racism

Dr. Norton explained that SDoH and health effects of structural and perceived racism are linked. She described a schematic depicting how structural racism engenders segregation and disparate experiences of SDoH by race. Structural racism underlies segregation in residential, workplace, and school settings and also directly contributes to poverty and low social economic status (SES) among marginalized groups, which reinforces segregation. Segregation, poverty, and low SES lead to differential access and exposure to SDoH, which results in an increased risk of adverse social risks for marginalized groups.

Social risks lead to mechanisms of disease that include barriers to health care access, lower quality of health care, stress, and allostatic load (i.e., wear and tear on the body from chronic exposure to stress).

Mechanisms of disease can lead directly to CKD, ESRD, morbidity, and mortality, and indirectly through various comorbidities and potentially exacerbating factors. SDoH—defined as the conditions in which people are born, grow, live, work, and age—can be responsible for health inequities. Health inequities are unfair and avoidable differences in health status. SDoH include the built environment, access to health promoting resources, and exposure to health impeding factors such as pollution, which are determined by where a person lives.

SDoH are linked to segregation and structural racism. Where a person lives is determined by race through a history of segregating policies. For example, Redlining was a federally supported program active from 1935 to 1968 in which Residential Security maps were drawn up to identify lending risk by neighborhood. High-risk neighborhoods were colored red, thus the term "redlining." The reason given for redlining a neighborhood was often its racial composition. In other words, neighborhoods often were redlined ***because*** they were composed of people of color, particularly Black Americans. Neighborhoods redlined during this critical period of suburbanization in the United States are associated with more poverty and adverse SDoH today.

Racism at interpersonal and structural levels results in perceived discrimination, which increases stress and allostatic load, leading to adverse cardiovascular outcomes and, potentially, poor CKD and ESRD outcomes. Even among people with high incomes, Black Americans have worse outcomes than their white counterparts at the same income level. Upwardly mobile Black and Hispanic Americans are more likely to experience discrimination compared with their socioeconomically stable counterparts and compared with upwardly mobile white Americans. Experiences of discrimination are associated with increased stress, shortened allostatic load, and biological perturbations that contribute to poor cardiovascular and mental health outcomes.

Dr. Norton explained that while SDoH contribute to the disparities seen across race in kidney and other diseases, the field has better ways of measuring SDoH. For example, the recent measures added to the PhenX Toolkit. She continued that although race and social status are highly correlated in the United States, it is better to measure SDoH directly, rather than using race as a proxy. This leaves one with the health effects of structural racism and discrimination if one were to measure race and control for these other factors.

Conclusions

Dr. Norton presented her final conclusions. Race is a social, not a biological construct. The use of race in medicine and research has profound implications that must be accompanied by an understanding of their significance and limitations. Race is a poor proxy for ancestry, genetics, and culture. Although structural racism creates disparities in wealth and SDoH that contribute to health disparities, race is an imperfect proxy for measuring social risk. Race may, however, best measure experiences of racism. Dr. Norton emphasized that the field is left with a problematic and somewhat intractable issue of how to address the use of race in eGFR calculations, which Dr. Parsa will address later in the meeting.

Discussion (Chat)

- Ms. Shannon Bradley Givens noted concern in using genetic ancestry to identify a person's race, especially because it is similar to what early scientists did to determine the hierarchy of races. She also noted that the helpfulness of genetic biomarkers is unclear based on the data from studies such as the APOL1 Long-term Kidney Transplantation Outcomes (APOLLO) and those

investigating sickle cell disease. Ms. Givens remarked on her work on a human papillomavirus study in which the vaccines protected some of the high-risk viral strands but not others; the ones unprotected were the strands found predominantly in Black Americans. She wondered about ways to move science away from connecting genetics, disease, and race. Dr. Norton agreed that genetic ancestry differs from race, reiterating that U.S. race categories group together populations with diverse genetic backgrounds.

Overview of the Key Issues in Using Race to Estimate GFR

Afshin Parsa, M.D., M.P.H.
NIDDK, NIH

Dr. Parsa presented an overview of the limitations of using measured GFR (mGFR), the association of creatinine with race and ancestry, and the association of race and ancestry with cystatin C versus creatinine. He also addressed questions related to renal function assessment and identifying a substitute for race in eGFR-serum creatinine (SCr) measures.

mGFR Limitations

Dr. Parsa noted that diurnal variation in mGFR has been reported, with significant changes from daytime to nighttime. Different methods for mGFR provide different results and variability in repeat testing. In a 2016 study by Ku *et al.* evaluating the CRIC Cohort, assessment of a subset of 942 CKD patients revealed that eGFR was slightly better at predicting ESRD and cardiovascular disease events than was mGFR by iothalamate clearance. One hypothesized reason for this could be related to the fact that creatinine-based iGFR measures average GFR over a few days, as opposed to the more variable immediate GFR. These data suggest that regardless of the biomarker used, eGFR can never perfectly match mGFR because mGFR itself is highly variable. Last, mGFR falls short as a benchmark (i.e., gold standard) to accurately capture renal function.

Race, Ancestry, Creatinine, and eGFR

Dr. Parsa reminded participants that the CRIC study recruited and characterized a longitudinal cohort of nearly 4,000 individuals with mild to moderate CKD. The cohort is nearly half Black and half white, with a smaller number of Hispanics; half the participants have diabetic CKD. The CRIC cohort has been deeply phenotyped and data have been collected on genetic ancestry and GFR. In terms of race, ancestry, creatinine, and eGFR, the CRIC study asked three questions: (1) It is possible to better estimate GFR using genetically defined ancestry instead of self-reported race in adults with CKD? (2) Are genetic ancestry or self-reporting of Black race independently associated with components of creatinine production, secretion, or excretion, independent of GFR? (3) Are genetic ancestry or self-reporting of Black race necessary for GFR estimation when using cystatin C?

(Confidential Data, Unpublished)

To address question 1, comparisons between self-reported Black and African ancestry Black subgroups were correlated to measures of body composition and muscle mass; dietary intake; creatinine production and extra-renal elimination; and tubular secretion of creatinine. The eGFR was assessed by either serum creatinine (SCr) or serum cystatin C and mGFR was based on iothalamate clearance. Dr. Parsa reported that African ancestry was 82 percent in the African ancestry Black subgroup (n = 460) and 2.2 percent in the non-Black self-reported subgroup (n = 700). The mGFR values were similar between the two groups. The Black race was associated with 11 percent higher SCr. Each 10 percent increase in African ancestry

associated with a 1.3 percent higher SCr. The results using self-identified race versus genetic-based ancestry were similar.

To address question 2, non-GFR determinants of SCr (e.g., body mass index, body surface area, percent ancestry, weight, height, fat-free mass) were used. The results revealed that Black race and ancestry were associated with 24-hour urine creatinine secretion but not with differences in tubular secretion. No difference in dietary protein intake was observed. Adjusting for all variables only slightly attenuated race- and ancestry-based differences in creatinine, suggesting that other factors contributing to race- or ancestry-based difference in creatinine are not being captured by tested measures of body composition and diet.

In response to question 3, evaluation of data from CRIC found no association between Black race or percent ancestry and eGFR in models using cystatin C.

Dr. Parsa summarized this CRIC set of data. Black race and African ancestry, similarly, captured systemic differences in SCr/eGFR in Black Americans compared with white Americans. The differences in quantifiable anthropomorphic measures account for only a small fraction of noted differences. Ignoring race or ancestry will induce systemic bias in the Black American population. Cystatin C is unaffected by race or ancestry. Participants were reminded that these data are confidential, unpublished, and under review.

Clinical Implications of Removing Race from Kidney Function Estimates

Dr. Parsa next described a recent study (Diao *et al*., 2021) evaluating the clinical implications of removing race from estimates of kidney function in Black adults with and without CKD using National Health and Nutrition Examination Survey (NHANES) data. The study reported that removing race increased CKD classification by 3.5 percent, equating to a 20 percent prevalence or an estimated 1 million additional Black Americans being classified as having CKD. In addition, removing race will decrease kidney transplant donations and negatively affect other aspects of kidney health care, such as drug dosing, while potentially increasing referral to a nephrologist and shortening the time for renal transplant referral, which could be indirectly helpful.

Dr. Parsa explained that discussions have been ongoing in the NIDDK and other organizations on whether the misclassification toward more disease severity would counter racial-based disparities in health care access and delivery, and, overall, be helpful, harmful, or neutral. He posed three questions: (1) Can the kidney community reliably assess and weigh the perceived pros and cons? (2) When and how should social context modify scientific approach? (3) How might it affect the perception of scientific integrity?

Futuristic Look—Assessing Kidney Function and Cystatin C

Moving forward, Dr. Parsa pointed out that global perspectives urge the kidney community (research and clinical) to find alternative approaches to assessing kidney function. The limitations of eGFR-SCr as a measure of kidney function also provide basis for change. Cystatin C provides a reasonable alternative. Cystatin C costs are higher but are scalable and already much cheaper in other countries (e.g., Sweden), where it is commonly used. He asked about taking this opportunity to rethink kidney function assessment, whether a single marker can comprehensively capture renal function, and whether the field has become too comfortable with subpar measures of kidney function. Dr. Parsa highlighted that the cost of continued inaccurate and incomplete capture of renal function and suboptimal drug dosing likely is much higher than the eventual cost of developing multi-panel biomarkers (glomerular and tubular). Advances in broad

scale metabolomic profiling provide new opportunities for multi-panel biomarker discovery. The field can consider not only benchmarking against mGFR but also tubular function and clinical outcomes.

In closing, Dr. Parsa summarized that ignoring race or ancestry induces a systemic bias in creatinine-based eGFR for Black Americans. The effect of bias is complex, significant, and not globally uniform. Cystatin C appears to provide a feasible alternative, for the time being. He remarked on the opportunity for the kidney community to re-assess and re-imagine its approach and expectation of how to evaluate renal function in a robust and comprehensive manner.

Discussion (Chat)

- Dr. Kevin Abbott asked what it meant that almost 20 percent of Black people did not have African ancestry and asked whether West African or East African ancestry were implied or other groups. Dr. Mendley clarified that these data were indicating the Black people have 82 percent African ancestry, rather than that 20 percent had no African ancestry. Dr. Norton agreed with Dr. Mendley's interpretation, which aligns with other data indicating the average percent of African ancestry among Black Americans. She noted the data indicating that most Black Americans are "mixed race."

- Dr. Anjali Jain commented that these data are impressive and necessary for the current dilemma but they continue to be based on the notion that race is a biologic and/or genetic entity, which goes against current thinking of race as a social construct. She wondered if it would be better to start with a different assumption that race indicates racism (unless proven otherwise) and investigate for racism rather than race and examine where it could be acting to influence health.

- Ms. Nilka Ríos Burrows asked how to improve the use of cystatin C and whether the increase in demand potentially could decrease the cost and make it more accessible. Dr. Norton explained that clinical laboratories in Sweden have successfully driven down per unit cost of cystatin C by increasing its use.

Agency Perspectives
Various Agency Representatives

U.S. Department of Health and Human Services

Dr. Benjamin Eloff called attention to the U.S. Department of Health and Human Services (HHS)/American Society of Nephrology (ASN)–sponsored Kidney Innovation Accelerator (commonly called KidneyX) prize competitions, which would apply to this topic regarding eGFR. He noted plans to sponsor prize challenges that focus on diagnosing and preventing kidney disease and requested input to identify prize opportunities.

U.S. Food and Drug Administration

Dr. Aliza Thompson commented that the field is using one eGFR estimating equation for multiple purposes (e.g., to define and stage CKD and estimate kidney function for the purpose of drug dosing). From a Center for Drug Evaluation and Research (CDER)/U.S. Food and Drug Administration (FDA) perspective, eGFR is used in drug labeling to specify the level of kidney function at which a dose adjustment should be made (for drugs that are cleared by the kidney) and to define who should and should not be treated with a particular drug. Estimating equations also are commonly used to specify who can and cannot enroll in a drug development clinical trial (i.e., to select patients for enrollment). Drug labeling

is FDA's primary tool for communicating drug information to the public and recommendations to the community on how to use a drug safely and effectively. From a drug dosing perspective, the goal is to use an equation that provides the best estimate of kidney function in the population. Dr. Thompson noted that the estimating equations used by the community change over time as the science evolves. She therefore has advised internal CDER workgroups that, as a general practice, labeling should not specify a particular equation. She explained that using an equation that underestimates kidney function in Black Americans (i.e., an equation that is biased on a population level) could result in underdosing of drugs such that, on a population level, Black Americans may not receive an effective dose or obtain the full benefit of a drug; if such an equation is used in particular settings in which labeling does not recommend drug use below some level of kidney function, patients may not be offered an effective treatment for their condition. Using an equation that underestimates kidney function in Black Americans also could impact eligibility for clinical trials and reduce diversity in trials.

- Dr. Star noted that the accuracy of the creatinine eGFR equation and that of cystatin C (without the race term) appear to be similar.

- Ms. Givens asked whether using genetic biomarkers to include or exclude patients from trials represented a systemic racism issue. Dr. Thompson noted the need to enhance the diversity of clinical trials and clarified that she was addressing only how FDA generally uses estimating equations (to estimate renal function for the purpose of drug dosing and to determine eligibility for drug development trials).

- Dr. James Oliver highlighted the issue: using the estimating equations for multiple purposes rather than tailoring to the intended use and purpose. He suggested focusing on an eGFR of 60 mL/min/1.73 m^2. Assessing drug dosing should not include equations for normal renal function or evaluations for a kidney transplant. Using one equation to evaluate all ranges is a weakness of the current approach.

Centers for Disease Control and Prevention

Ms. Burrows pointed out the CDC Chronic Kidney Disease Surveillance Project, which depends heavily on various data sources—such as the National Health and Nutrition Examination Survey (NHANES), the U.S. Department of Veterans Affairs (VA), and Medicare—to estimate prevalence of CKD across racial and ethnic groups. Any changes regarding the kidney function estimating equation would take time to implement in these data sources, particularly for the national survey data, and would need to be transparent. She noted that NHANES field operations paused because of COVID-19 and are expected to resume in summer 2021. Methodology questions, including the modifications to the laboratory protocol, the number of years to be included in the survey cycles, and the weighting parameters for the survey data, would need to be addressed.

- Dr. Mendley suggested thinking about data harmonization across years if substantial changes are made to the eGFR calculations. Dr. Star anticipates that the effects from switching from creatinine-eGFR to cystatin C-eGFR would be minor. Dr. Parsa called attention to the role of the National Kidney Foundation (NKF)–ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases to address some of these issues. Drs. Parsa and Mendley noted likely effects of changes to acute kidney injury assessments with modifications to the estimating equations.

Centers for Medicare & Medicaid Services

Dr. Jesse Roach explained that the Centers for Medicare & Medicaid Services (CMS) Center for Clinical Standards and Quality (CCSQ) reviewed the potential impact of modifications to the eGFR-estimating equations in the CMS quality measures programs and found that effects would be minimal. The use of eGFR in these measures is rare. From a nephrologist's perspective, Dr. Roach noted the importance of any changes to the equations for classifying additional individuals with CKD and having them evaluated for a kidney transplant.

Mr. Tom Duvall pointed out that changes to the eGFR equations likely would impart a downstream impact on the Center for Medicare & Medicaid Innovation new payment models, particularly the International Statistical Classification of Diseases, 10th revision, (ICD-10) codes built into the payment models.

From a CMS policy and Office of Minority Health perspective, Dr. Loida Tamayo (in the chat) suggested using a measure of implicit bias, given that use of race in eGFR affords little to the overall kidney function analysis.

- Dr. Star inquired on the effects of the cost differences of using the more expensive cystatin C-eGFR equation. Confirming that the impact of removing the term "race" from eGFR to CCSQ programs would be limited, Dr. Roach noted that any impacts to the CMS payment structure would be best addressed by those CMS specialists.

Agency for Healthcare Research and Quality

Dr. Jain expects that any eGFR changes would have minimal direct effects on the Agency for Healthcare Research and Quality (AHRQ) programs or policies but could affect how the agency synthesizes studies in future reviews. She called attention to a new Evidence-Based Practice Center (EPC) Program effort to review this topic. A request for information (RFI)—Use of Clinical Algorithms That Have the Potential to Introduce Racial/Ethnic Bias Into Health Care Delivery—has been released and posted in the *Federal Register*. This RFI will inform a task order and subsequent AHRQ systematic review (SR).

Dr. Christine Chang encouraged responding to the RFI and noted that the SR is scheduled to start in May 2021. She anticipates a draft report mid-2022 and an update to the KICC in a future meeting.

Dr. Elise Berliner recommended developing and validating algorithms for eGFR and in diverse populations representative of the U.S. populace. She posed a question on whether race, a social not a biological construct, should be ignored in such algorithms.

- Dr. Parsa explained the issue in eGFR calculations: creatinine is not a suitable biomarker across populations. Use of improved biomarkers, such as cystatin C with less race and/or ancestry-based differences, will be one approach to resolving this issue. Dr. Jain reiterated her previous comments on the use of a biologic model to address a social construct, race.

- Dr. Mendley suggested exploring, more broadly, innovative ways to assess kidney function that extend beyond cystatin C and consider other factors (e.g., SDoH).

Health Resources and Services Administration

Dr. Marilyn Levi first provided a brief overview of the Health Resources and Services Administration (HRSA) Healthcare Systems Bureau, Division of Transplantation. This division provides oversight of solid organ transplantation through the Organ Procurement and Transplantation Network (OPTN) in the United States, as well as the blood stem cell transplantation program. The impact of eGFR modifications on these programs were reviewed. This national program consists of solid organ and blood stem cell implants. Any eGFR changes will have minimal effect on blood stem cell transplantation. The OPTN organizes the HRSA organ transplant program based on sound medical judgement and equitable allocation policies, with the utility of the eGFR. The Scientific Registry of Transplant Recipients (SRTR) uses the OPTN data to inform developing simulation models.

Dr. Levi detailed the potential impact to the HRSA solid organ transplantation program if the eGFR were to be modified: (1) OPTN policies incorporate eGFR for clinical assessment of donor kidney function; (2) the OPTN uses eGFR to establish priority rankings for donor kidney allocation; (3) ESRD diagnosis is based on eGFR, which affects wait time; and (4) the SRTR uses eGFR and CKD factors in performance assessments for transplant. The OPTN established kidney transplant and minority affairs committees and then formed a joint working group to begin to address this impact.

- Dr. Kimmel noted that the NIDDK-funded APOLLO study uses race determinations via assessment of *APOL1* variants rather than eGFR in evaluating acceptability of donor kidneys by the OPTN.

- Dr. Mendley remarked on a comment posted in the chat by Dr. John Williams emphasizing that personalized medicine treats an individual based on the average value from the estimating equations, lending to clinical variability if outside of this range. She noted the need for equations validated in the normal eGFR ranges.

Indian Health Services

Dr. Ann Bullock noted that the Indian Health Service (IHS) mission is to provide health care services to American Indian/Alaska Native people. As such, removing race from the eGFR equation would have minimal impact on IHS programs. Additionally, because issues with systemic racism have been and remain prevalent is these communities, with links to worse health outcomes, Dr. Bullock noted that using a clinical equation that singles out one racial group inadvertently serves to perpetuate these issues.

Dr. Andrew Narva pointed out that primary care physicians are using the eGFR equations to be alerted to CKD in an individual patient who has normal creatinine levels. He continued that a lack of educating clinicians in using the estimating equations have resulted in performance measures with discrete cutoffs based on eGFR values, with low accuracy (P30) and high margins of error.

- Dr. Norton asked about data on the performance of the existing eGFR equations and the race corrections in other race and ethnicity groups. Dr. Parsa explained that creatinine-eGFR equations are variable regardless of the group.

- Dr. Narva clarified that his preference is to eliminate the race correction from eGFR equations. Although cystatin C is more precise than creatinine, it is unlikely to be universally adopted and will not address the issue: lack of measures to increase the sensitivity of disease identification in a group with much higher rates of that disease with less access to appropriate care.

Dr. Parsa pointed out that random error and systemic bias are different and agreed that a referral for nephrology care should not be based on medically classifying an individual differently, as opposed to addressing any underlying issues directly (e.g., access). He emphasized that mGFR is not the gold standard, has its own variability, and the field can improve on the P30. Better solutions are feasible that could be applied or developed without introducing systemic bias.

- In response to comments to consider that cystatin C could be included in the chemistry screen, SMA-6, in the future, Dr. Narva expressed that his concerns are pragmatic.

U.S. Department of Veteran Affairs

Dr. Susan Crowley commented on the KICC's messaging to primary care colleagues about the concerns with eGFR in terms of accuracy. Because it is used in screening for CKD in routine clinical practice, Dr. Crowley suggested retaining and continuing to promote eGFR as a required measure for kidney function assessment for high-risk individuals. Efforts to identify an optimal marker can continue. She agreed the cystatin C, if incentivized properly, is one place to start and that a numeracy campaign educating health care providers on eGFR would be helpful. Dr. Crowley also suggested engaging clinical laboratories to advise on incorporating cystatin C into the chemistry screen and updating SMA-6.

- Dr. Norton noted that similar discussions on race and eGFR are ongoing with the NIDDK Laboratory Working Group.

U. S. Department of Defense

Dr. Oliver informed the KICC that the U. S. Department of Defense (DoD) does not have a centralized enterprise–wide standard for laboratory reporting. Approximately 80 percent to 90 percent of DoD clinical laboratories have switched to using the CKD Epidemiology Collaboration (CKD–EPI) equation and are reporting GFR along with brief background information. Dr. Oliver explained that race correction in eGFR is major topic among DoD trainees who are prompting change, including residents at the Walter Reed National Military Medical Center. He suggested (1) weighing the pros and cons of eliminating the race correction; (2) considering an eGFR reporting range; (3) ensuring no undue harm to the public; and (4) developing a responsible, ethical approach to implementing any changes.

Dr. Oliver underscored the importance of explaining eGFR to non-nephrologists in a way that is easy to understand. Regarding a change in activities in if eGFR is changed, Dr. Oliver pointed out that the nephrology referral patterns differ in the DoD from the civilian sector. The DoD does not have chronic dialysis facilities and focuses more on early CKD and disease progression, which relies heavily on eGFR changes. With active duty personnel, including young Black American males more likely to be referred with mildly elevated creatinine levels and no CKD, the DoD's standard approach would be evaluation.

From a broad perspective, Dr. Oliver expressed that the DoD is thinking about two questions: What is the logic to use of the eGFR race correction in clinical medicine and research? How to accurately measure kidney function? Although cystatin C would be a long-term solution, some short-term solutions would be to improve the exiting equations and have a tiered assessment approach (e.g., function, drug dosing, and transplant). Dr. Oliver suggested assessing clinical outcomes according to the equation used and emphasized interpreting study data in the context of the diversity of clinical trial enrollment.

NIH—National Heart, Lung, and Blood Institute

Dr. Diane Reid explained that the National Heart, Lung, and Blood Institute (NHLBI) has a robust research portfolio of clinical trials, observational studies, and registries. Research includes investigations

into pulmonary, hematologic and sleep disorders and the full spectrum of cardiovascular disease (CVD), including coronary heart disease, hypertension, heart failure, and carotid, renal and lower extremity peripheral artery disease. CKD is a common comorbidity among study participants, especially in CVD research studies. Going forward, this existing NHLBI portfolio might offer opportunities for integrating a proposed alternative method of estimating the GFR alongside currently used methods in well-phenotyped participants who collectively span the CKD stages from normal to end-stage renal disease. The NHLBI's efforts also would focus on communicating the rationale for proposed changes in the eGFR calculation to investigators and prospective applicants who are in the process of designing new studies that will require renal function monitoring.

- Dr. Mendley commented on the potential of merging data across existing NIDDK clinical trials using eGFRs calculated using different methodologies and asked whether harmonization would be necessary. Dr. Parsa noted that most of the existing data sets contain eGFRs calculated using both creatinine and cystatin C. The researcher would need to ensure comparison data are matched to the respective method.

- Dr. Abbott noted that in the United States Renal Data System creatinine-based eGFR is used to initiate dialysis, but other measures could be adopted.

NIH—National Institute on Aging

Dr. Susan Zieman pointed out that the National Institute on Aging (NIA) would take this opportunity to identify a better measure of kidney function for aging adults and understanding what the trajectories would be. Just removing the race correction from eGFR still leaves a poor measure of kidney function and has several repercussions, such as no good predictor of clinical trial outcomes, reduced participation in trials, and less availability of donor kidneys. Dr. Zieman explained that the NIA could begin to review its clinical trial data of longitudinal cohorts to assess the effects of a proposed change to the eGFR and consider harmonizing those data across studies.

Group Discussion

Dr. Mendley opened the discussion, noting the chat comments.

- Dr. Norton pointed out that her comments on genetic ancestry are not from a geneticist's perspective. She clarified that ancestral informative markers used in research and by genealogy companies (e.g., Ancestry.com) can track the region of origin (e.g., West Africa, East Africa, Europe) with confidence. Race categories group people from different parts of the world. The United States has a unique subsample of people of West African ancestry because of the patterns of enslavement. U.S. ancestry studies of Black Americans (e.g., CRIC) will not reflect the genetic diversity of the Black population and data should be interpretated carefully.

- Dr. Parsa responded to questions in the chat regarding interpreting 80 percent African ancestry and noted that it represents the percentage of genome linked to complementary ancestry, which is more specific than race.

- Dr. Paul Kimmel pointed out the relationship to use of reference data for estimating ancestry and interpretating those results. For example, in HapMap data, African ancestry, defined as modern members of the Yoruba tribe, genetic maps were constructed based on 49 members. The chip used in the analysis in the Human Heredity and Health in Africa (commonly called H3Africa) had a wider representation of African ancestry spanning across the continent. The consensus is that genetic ancestry markers outperform self-report but remain approximate tools.

- In response to a query by Dr. Abbott on the variability of eGFR by ancestry, Dr. Parsa explained that the assumptions of the markers hold true for an American population of Black or African ancestry, but not necessarily across other Black populations or different regional ancestries across Africa, because African ancestry itself is diverse across the continent.
- Dr. Zieman (in the chat) remarked that a one-size estimating equation is unlikely to fit all, specifically for older adults and more so for factors like age, sex, and gender due to age-related changes in body composition (for whom this is a particular problem with medication modification due to polypharmacy). Dr. Norton (in the chat) commented that age, sex, and age–sex interactions could be addressed with correction factors or biological markers of age because chronological age may not equal physiological age.
- Dr. Oliver commented on a recent DoD study evaluating GFR changes in self-identified Black individuals without the race coefficient, noting that the preliminary results are similar to the Diao *et al.* study and NHANES data.
- Dr. Mendley summarized that discussions suggest a strong desire to move away from a race-based equation for eGFR, with definitive reasons and shortcoming highlighted. She posed several questions: What could we do better? How would we want it to happen? Can we move to a cystatin C-based system and can we afford it? Dr. Star asked what the government agencies represented can do to facilitate the process?
- Dr. Zieman noted the pragmatic clinical trial platforms such as the NIH Collaboratory and the NIH Health Care Systems Research Collaboratory would be models to assist with testing and implementation.
- Dr. Thompson pointed out that the FDA endorses the concept of using an estimating equation that best assesses renal function, but does make recommendation on any specific equation.
- Dr. Roach commented that incorporating cystatin C into the SMA-6 panel likely will increase uptake and reduce the associated costs.
- Dr. Crowley suggested gathering information from the laboratories and other groups on the applications of the eGFR equations regarding implementation.
- Dr. Oliver commented on the timeline to incorporate cystatin C into the SMA-6 and noted the opportunity for the DoD and the VA to consider implementation strategies.
- Participants expressed appreciation to the NIDDK for organizing this meeting and discussion to address this challenging issue.

Around the Table: Agency Updates

Centers for Disease Control and Prevention

Ms. Burrows expressed appreciation to the KICC members for their input and feedback on the Chronic Kidney Disease in the United States, 2021 fact sheet released just before World Kidney Day.

Adjournment

Dr. Mendley thanked the presenters and attendees for their participation and noted that the next meeting is scheduled for September 17, 2021. She adjourned the meeting.