Kidney Interagency Coordinating Committee Meeting

Use of Race Corrections in Estimating Glomerular Filtration Rate: Part 2

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 across the federal agencies. Dr. Mendley explained that the agenda includes an overview of the NIDDK June 2021 Home Dialysis Workshop and will continue the discussions on the use of race corrections in estimating glomerular filtration rate (GFR). She noted that the meeting summary will be posted to the NIDDK website. Dr. Jenna Norton invited meeting attendees to introduce themselves.

Summary of Home Dialysis Workshop, June 2–3, 2021
Kevin Abbott, M.D., M.P.H.
NIDDK, NIH

Dr. Kevin Abbott remarked that the NIDDK convened a virtual 2-day workshop on home dialysis on June 2–3, 2021. He explained that in the United States, home dialysis—which consists of two types, hemodialysis (HD) and peritoneal dialysis (PD)—has been becoming much more prevalent in the recent cohort of incident dialysis patients. Per the End Stage Renal Disease Quality Reporting System data, from 2010 to 2021, the increase in the utilization of home dialysis has been attributed primarily to ambulatory PD, whereas HD utilization has remained unchanged. Currently, nearly 15 percent of patients are on home dialysis, including more than 20 percent of prevalent patients who are less than 2 years removed from dialysis initiation. Although utilization has been sustained among patients with end-stage renal disease (ESRD), this increase is slowing, despite the launch of the Centers for Medicare & Medicaid Services (CMS) ESRD Treatment Choices (ETC) model. COVID-19 likely has been a factor in this slowed growth. The ratio of PD to home HD decreased to 5.3 but remains high by international standards. Growth of continuous ambulatory PD has been significantly sustained during the past 30 months.

The theme of this workshop was empowering home dialysis and the purpose was to better understand how to advance the field, understand the present state, and promote increased utilization of home dialysis. Dr. Abbott emphasized that although it is unclear whether the national target goal of having 80 percent of ESRD patients start home dialysis by 2025 is achievable, the aim is to make progress. The workshop revealed that some of the key issues, as well as the present state of home dialysis, are not well understood, and it overlapped the discussion of GFR estimation that this KICC meeting will continue. Workshop participants discussed several unanswered questions: When is the decision to start dialysis made? When are patients counseled about the need for dialysis and the choices and options that they would have? What and how are patients informed, and what are the criteria? Workshop participants suggested a way forward—precision dialysis—that includes partnering with multiple stakeholders and advancing new technologies. Dr. Abbott noted that the American Society of Nephrology (ASN) will have a clinical session on this topic at its 2021 Annual Meeting during Kidney Week; the U.S. Renal Data System (USRDS) will publish a new ESRD chapter in 2022. A full summary of the workshop soon will be posted to the NIDDK website.

Discussion

- Ms. Nilka Ríos Burrows commented on revisiting the objectives of the Advancing American Kidney Health initiative, which encourages 80 percent of ESRD patients to have a kidney transplant or start home dialysis by 2025. Dr. Abbott pointed out that achieving this goal also speaks to the question of how patients on dialysis are considered candidates for different types of therapies and patient choice in a modality (e.g., home dialysis or transplant), recognizing that 80 percent of these patients may prefer in-center services.

- Ms. Miriam Godwin announced that the National Kidney Foundation (NKF) has been working for more than a year to gain stakeholder consensus on legislation that would authorize Medicare coverage for staff-assisted home dialysis. The bill is expected to be introduced to the House in the coming weeks, and the stakeholders and the NKF anticipate that this policy change will be impactful on initiation and retention of patients on home dialysis. Dr. Susan Crowley expressed appreciation to the NKF for advancing this legislation that will benefit the veteran population of patients with ESRD, who are older than the general ESRD patient population, and also will help expand the U.S. Department of Veterans Affairs (VA) Caregiver Support Program.

- Dr. Murray Sheldon inquired about monitoring the quality of life (QoL) and other complications in new home HD patients. Dr. Paul Kimmel highlighted that the patient panel at the June 2021 home dialysis workshop revealed that many of the characteristics that allow some patients to be successful at home dialysis, as well as those that suggest which patients would not be interested in this modality, are not well understood. The patients mentioned fear of complications from home HD and being unmonitored by health professionals as concerns, while many remarked on the freedom home dialysis affords. He continued that rigorous, systematic evaluations of the QoL in patients on home dialysis compared with those on in-center dialysis in past 10 to 15 years are limited. Dr. Godwin called attention to the CMS ESRD Quality Incentive Program, which has an in-center focus, suggesting the need for a specific quality strategy and measures for home dialysis that extend beyond access to treatment.

- Dr. Abbott confirmed that unlike monitoring hospitalizations and effectiveness of home dialysis, QoL is not captured in the USRDS. This area has been noted as a gap in home dialysis implementation that the NIDDK hopes will be addressed in research applications.

- Mr. Siddhartha Mazumdar explained that monitoring is an important aspect of the ESRD ETC model, emphasizing that he will convey the message to the CMS Innovation Center of the need for QoL assessments for patients on home dialysis. Ms. Godwin (in the chat) emphasized better leveraging of the Kidney Disease Quality of Life tool, a resource that details the conditions for coverage for dialysis facilities and requirements for patient assessments.

Where We Left Off at Our Last KICC Meeting
Jenna Norton, Ph.D., M.P.H.
NIDDK, NIH

Dr. Norton recapped the March 2021 KICC meeting, whose agenda included presentations on race as a social construct, an overview of the key issues in using race to estimate GFR, agency perspectives, and a group discussion. She reminded participants of her conclusion that race is a social construct, not a biological one. She highlighted that race is a poor proxy for (1) ancestry and genetics, because it inadequately reflects ancestral differences in genotype, and more genetic diversity exists within people from Africa than between people from Africa and Europe; (2) culture, because race grouping combines people with diverse origins, languages, and cultures; and (3) measuring social risk, because people from diverse racial groups span the socioeconomic status levels in the United States. Conversely, race reflects

experiences of structural and interpersonal racism that affect health in terms of disparities in opportunity, wealth, and social determinants, as well biological effects (e.g., stress, allostatic load, mental health).

In his March presentation, Dr. Afsin Parsa noted limitations of measured GFR (mGFR) that include diurnal variation, variability across methods, and studies demonstrating that estimated GFR (eGFR) might better predict outcomes than mGFR. He also presented soon-to-be-published data from the NIDDK-sponsored Chronic Renal Insufficiency Cohort (CRIC) study. These data suggest that Black race and African ancestry capture differences in serum creatinine (SCr) and eGFR between Black and white Americans. Removing race corrections from SCr and eGFR might induce systemic bias. Cystatin C is unaffected by race or ancestry. Additionally, Dr. Parsa proposed that cystatin C can provide a reasonable alternative to SCr in GFR estimation and emphasized the need to rethink kidney function assessment and whether a single marker can adequately capture kidney function.

Dr. Norton summarized key points of the agency perspectives. The U.S. Food and Drug Administration (FDA) representative questioned the appropriateness of using a single GFR equation for that agency's many distinct purposes (e.g., staging, drug dosing, clinical referral). The Centers for Disease Control and Prevention (CDC) representative noted that changes to the eGFR equations would take time to implement in large, national CDC data sources (e.g., National Health and Nutrition Examination Survey [NHANES]), and any changes would need to be transparent. The CMS representative suggested that modifications to eGFR equations would have minimal impact on CMS quality programs, but they might affect new payment models. The Agency for Healthcare Research and Quality (AHRQ) representatives announced the release of a request for information on the use of clinical algorithms and racial/ethnic biases. The Health Resources and Services Administration (HRSA) representative informed the KICC of a working group established by the Organ Procurement and Transplantation Network to assess potential impacts of changes to GFR estimation on assessment of donor kidney function, priority rankings for kidney allocation, wait time, and transplant performance.

The group discussion highlighted several areas that the KICC will need to consider:

- Continued use of race corrections might perpetuate the issues of structural racism across race groups beyond Black Americans.
- The eGFR is imprecise regardless of the equation used; discrete cutoffs are problematic.
- Education is needed to ensure better understanding of this imprecision.
- The potential opportunity exists for incorporating cystatin C into the basic metabolic panel to increase use.
- The needs for consistency in eGFR methods across NIH research studies and for better measures of kidney function in the aging population were identified.

Are Cystatin C–based Estimated Glomerular Filtration Rate Equations the Best Path Forward? Perspective of the NIDDK Laboratory Working Group
Greg Miller, Ph.D.
Virginia Commonwealth University

Dr. Greg Miller, Chair of the NIDDK Laboratory Working Group (LWG), discussed the uncertainty in estimating GFR and the pragmatic considerations for using cystatin C. Data using the original CKD-Epidemiology Collaboration (EPI) creatinine equation reported by CKD-EPI investigators (Levey *et al.* 2009) showed high variability between eGFR and mGFR and a significant uncertainty around the 95 percent confidence interval. Graphing the same data differently (Miller 2021) using selected eGFR values further highlighted the large uncertainties at different creatinine values using the CKD-EPI

creatinine equation in African Americans (i.e., race-corrected) and non-African Americans. The uncertainty is large at any eGFR, although it is larger at high values and smaller at low values. At an eGFR cutoff of 20 mL/min/1.73 m^2, which is an important decision point for starting dialysis or receiving a transplant, the eGFR values have a large 95 percent confidence interval. Creatinine laboratory measurement variability adds minimally to the variability in eGFR estimates, suggesting that the uncertainty can be attributed to the equation, parameters used to fit the equation, and the non-GFR determinants of creatinine among individuals.

Regarding standardization of creatinine, the College of American Pathologists (CAP) LN24-A Survey examined fresh frozen human samples at two different creatinine concentrations, normal and elevated. The range between the mean values of 11 different commonly used measurement procedures was 4 percent in the normal range and 10 percent at elevated values. Converting data from a 50-year-old non-African American male into eGFR values showed that the creatinine variability contributes very little to the uncertainty in the measurement. In another study (Inker *et al.* 2012), the CKD-EPI investigators reported data introducing a CKD-EPI-cystatin C and a combination CKD-EPI-creatinine-cystatin C equation. The results showed that at higher eGFR values, the CKD-EPI-cystatin C performed better; at lower eGFR values, the CKD-EPI-creatinine equation demonstrated superior accuracy.

Dr. Miller described a study demonstrating the differences in uncertainty between creatinine and cystatin C (Rule *et al.* 2013). The study examined two cardiac disease cohorts (Genetic Epidemiology Network of Arteriopathy, Epidemiology of Coronary Artery Calcification) whose participants had moderate CKD. The data showed variability in the eGFR creatinine and mGFR values similar to those in the original CKD-EPI reports. The uncertainty in eGFR with cystatin C was larger than for mGFR, and the CKD-EPI-creatinine-cystatin C equation was the most accurate. The 2019 CAP CYS-A Survey evaluated the standardization of cystatin C in fresh frozen human serum samples. The survey concluded that normal and elevated values showed that cystatin C results, as practiced in the United States, were more variable across laboratories and methods than were creatinine results, although the uncertainty for cystatin C was overall still low. Translating these data into eGFR showed again that cystatin C variability contributes very little to the uncertainty in the measurement.

It is well known that creatinine is more widely available than cystatin C in the United States. The 2020 CAP proficiency testing surveys showed 5,902 laboratories reporting creatinine and 185 reporting cystatin C. Dr. Miller noted that at his academic medical center, cystatin C is available to clinicians but is ordered infrequently. In one month, his laboratory performed 41,000 creatinine tests and 236 cystatin C tests. Creatinine is more widely used because it is part of the Comprehensive Metabolic Panel (CMP) and Basic Metabolic Panel (BMP) ordered on almost every patient seen at a hospital or clinic, has a Current Procedural Terminology (CPT) code in place that includes creatinine, and is much less expensive than cystatin C. Dr. Miller estimated that replacing creatinine with cystatin C in CMP and BMP panels for his laboratory alone would cost $3 million per year, assuming that the cost to perform this test is half the Medicare reimbursement. In addition, cystatin C is an immunoassay-based test and is not currently offered in point-of-care devices that are used extensively for eGFR, particularly in radiology. Although reagents and standardized calibrators are available for many high-throughput laboratory analyzers to perform cystatin C tests, time is required for manufacturers to increase production capacity. To enable more widespread use of cystatin C for eGFR in the United States, Dr. Miller noted needs for time to implement in the clinical laboratories, time to develop point-of-care applications, and education of providers when to order cystatin C. The current recommendations for the use of cystatin C are as a follow up or confirmatory test for kidney disease when creatinine may be compromised due to non-GFR determinants of its concentration. Note that a CPT billing code exists for cystatin C but does not exist for a BMP or a CMP with cystatin C as a component.

Cystatin- and Cr-based Equations to Span Populations across the Life Course
Derek Ng, Ph.D.
Johns Hopkins University

Dr. Derek Ng reported findings of the Chronic Kidney Disease in Children (CKiD) Study focused on developing and evaluating estimating equations for GFR in pediatric populations. The challenges are that for young adults 18 to 25 years of age with pediatric CKD, the pediatric equations were developed in 2009 and based on SCr underestimate GFR, whereas the adult CKD-EPI equations overestimate this measurement. The previous pediatric equations were based on data with a limited age range (2 to 16 years of age) and moderate to severe CKD. The goal of this study is to develop equations applicable across the life course for pediatric to young adult populations. Dr. Ng and CKiD investigators evaluated 2,655 iohexol-based GFR values from 928 CKiD participants who were 1 to 25 years of age (Under 25 or U25 model). Two U25 equations were developed—one SCr-based and the other cystatin C–based—both with no coefficient for self-reported race, which was consistent with new recommendations from the NKF–ASN Task Force reassessing the use of race in the diagnosis of kidney disease. The data showed a representative age range and GFR distribution that spanned the CKD stages in this subgroup (22 percent Black). The sex-specific values of the CKiD U25 constant (K) demonstrated a smooth transition from childhood to young adulthood, a feature not represented in the previous equations.

In terms of validation metrics, the agreement analysis, stratified by self-reported race (Black, white, or other), revealed that the U25 equations designed without the race coefficient showed bias between the eGFR and mGFR values. Specifically, the U25 SCr equation showed significant underestimation in mGFR in the self-reported Black race group, consistent with the adult SCr equations. The U25 cystatin C equation showed no significant bias across the self-reported racial groups. The average of the two equations yielded improved agreement compared with the single equations. Collectively, these data illustrate that the U25 eGFR equation is a valid for clinical use among those under 25 years old and that including the pediatric population is necessary when considering eGFR biomarkers.

Dr. Ng and his colleagues next developed an online web-based calculator and worked with Calculate by QxMD to develop and check a mobile application (app) to translate the U25 data and equations into clinical practice. The CKiD U25 GFR calculator can be accessed from the CKiD website, and the mobile app, Calculate QxMD, can be downloaded at no cost to the user. Dr. Ng concluded that the U25 eGFR with sex- and age-dependent coefficients can be used without bias across the full pediatric age spectrum and into young adulthood up to age 25. The U25 eGFR average based on SCr and cystatin C is more accurate, precise, and unbiased across self-reported racial groups. He acknowledged the CKiD participants and their families and the CKiD investigators.

Experience with Cystatin C in Sweden
Anders Grubb, M.D., Ph.D.
Lund University

Dr. Anders Grubb presented on the use of cystatin C for GFR in Sweden, noting that the discovery of cystatin C as a GFR biomarker began in the 1970s with quantitation in human cells and biological specimens. In 1995, cystatin C was implemented into clinical practice in Lund, Sweden. Since 2010, the analysis has been available in all clinical chemistry laboratories and all hospitals in Sweden. Cystatin C is performed around the clock on the main automated clinical chemistry analyzers, with a turnaround time of 10 to 30 minutes. Dr. Grubb explained that, in Sweden, when new tests are introduced and are based on science and proven clinical experience, approval by a central authority is not necessary. The tests are always reimbursed. The cost of the analysis can vary slightly across laboratories. In Dr. Grubb's laboratory, the cost of enzymatic creatinine is $1, and cystatin C is $1.50. The external quality control of

cystatin C analyses by the External Quality Assessment (EQA) organization began in 2003. To date, 60 laboratories are using EQA services, 15 of which are outside of Sweden.

Dr. Grubb reported data on the utilization of cystatin C and creatinine in Sweden. The Uppsala University Hospital, serving a population of 230,000, performs 50,000 cystatin C and 300,000 creatinine tests annually. In the intensive care unit where accurate eGFR measurements are most critical, the tests ordered were nearly equal between the two assays—slightly less than 3,000 of each.

Dr. Grubb described his work on the Lund model, an interpretation strategy for cystatin C analyses that provides three scenarios. If eGFR creatinine and eGFR cystatin C agree within 15 percent, the average value is reliable, usually more so than an invasive determination of GFR. If eGFR-creatinine and eGFR-cystatin C disagree by more than 15 percent, non-renal influences, such as abnormal muscle mass or use of glucocorticoids, should be checked. If found, the eGFR least influenced by the non-renal condition should be used. If none are found, the patient likely is experiencing shrunken pore syndrome. An internet tool for calculating relative and absolute eGFR can be accessed from the Lund University website: http://egfr.se/eGFRen.html.

Dr. Grubb explained that data from his 1985 studies on the early use of cystatin C showed no differences between males and females, leading to the conclusion that muscle mass was not an interference. Dr. Grubb and members of his laboratory developed and tested in various populations cystatin C–based GFR-estimating equations without correction terms for race or sex. A new cystatin C–based GFR-estimating equation free of race factors has been reported and is in press with the *New England Journal of Medicine*.

Dr. Grubb called attention to the fact that sex factors in the GFR-estimating equations are based on only two sexes and do not take into account LGBTQIA-plus considerations. In several countries, including Germany, Australia, and Sweden, more than two sexes already have been registered. Having cystatin C–based GFR-estimating equations that work well without sex terms is an advantage to the clinical community.

Opportunities and Obstacles to Cystatin C Implementation at the Veterans Health Administration
Susan Crowley, M.D., M.B.A., FASN
Veterans Health Administration (VHA)
Jessica Wang-Rodriguez, M.D.
Veterans Administration (VA) San Diego Healthcare System

Dr. Crowley described the demographics and kidney testing in the VA. She reminded participants that the VHA is the largest integrated health care organization in the United States and manages care primarily of approximately 7 million military veterans. The average age of veterans is 65, the majority of whom are males, and approximately 15 percent are Black. The prevalence of diabetes is 25 percent. The prevalence of CKD in the veteran population also is approximately 15 percent and presents a challenge to the VA in terms of patient testing. SCr is the predominant biomarker used for assessing kidney function in the VA. Approximately 80 percent of veterans who have had at least one appointment in the VA had serum creatinine levels assessed annually. Nearly 1 million veterans meet the criteria for CKD of having two eGFR measurements less than 60 mL/min/1.73 m^2 separated by 90 days of reporting. Use of cystatin C for eGFR has had low utility in the VA, with high geographic variability across the VA Medical Centers.

Dr. Jessica Wang-Rodriguez described the comparative volume and cost of SCr and cystatin C tests in the VA from October 2020 to June 2021. The data showed that SCr was widely used in CMPs and BMPs and in various settings, at the CMS-calculated cost of $5.12 per test. Cystatin C currently can be ordered but is used at a much smaller percentage within the VA; more commonly, it has been sent to reference laboratories. The CMS reimbursement rate for cystatin C is $18.52, but the cost of performing this test

was $50.14 based on the VA workload calculation. The overall cost of performing both tests during this period was $47.6 million. If the VA were to switch to cystatin C alone, the overall cost would increase tenfold to $460.9 million based on the VA's calculation model. Dr. Wang-Rodriguez could not speak directly to why the VA's costs for the cystatin C assay exceed the Medicare reimbursement rates, but she suspected that the low volume, output rates and labor costs, instrumentation costs, maintenance, and proficiency testing are major factors.

Dr. Wang-Rodriguez detailed some perceived obstacles to implementing cystatin C testing within the VA laboratories. There is an increase in the cost with a questionable number of increased diagnoses of CKD. The test's utility is limited in a primary care setting, and it may not be available as a rapid assay, thus affecting the timeliness of eGFR reporting. Additionally, there is an overall lack of awareness of the indications for cystatin C testing and its potential predictive utility. Although the 2019 VA/DoD CKD Primary Care Guidelines recommend cystatin C to assess eGFR in specific instances, adoption has been limited. Last, the VA laboratory capacity is limited.

Dr. Wang-Rodriguez proposed four options to assist implementing cystatin C testing within the VA laboratories: (1) a targeted approach in utilizing cystatin C for specific patient populations (e.g., people with low muscle mass or altered body habitus) in which SCr has been shown to be a unreliable test, (2) a national clinical protocol and accompanying electronic health record decision support tool to guide appropriate use of cystatin C, (3) a medical provider education campaign on the indications for cystatin C testing, and (4) a VA laboratory outfitting necessary to perform the test.

Coding and Payment under Medicare
Sarah Shirey-Losso
CMS

Ms. Sarah Shirey-Losso provided an overview of the Medicare coding and payment structure and the Clinical Laboratory Fee Schedule (CLFS) relevant to cystatin C. She reminded participants that Medicare Part B, which includes a variety of outpatient services, covers medically necessary clinical diagnostic laboratory tests ordered by a physician. Medicare reimburses the laboratory that performs the tests without coinsurance or deductible applied. The Medicare CLFS was first adopted in 1984 and has been updated annually, according to an inflation factor. The Protecting Access to Medicare Act (PAMA) enacted April 1, 2014, revamped the CLFS to base the fees on private payor rates. PAMA Section 216 requires CMS to collect data from clinical diagnostic laboratories every 3 years, resetting the fees to the median (weighted by volume) private payor rates. Medicare payments have been based on these data effective January 1, 2018.

To date, more than 1,800 tests are on the CLFS. CMS is required to set a payment rate for any new or revised Healthcare Common Procedure Coding System (HCPCS) code, but not all tests on the CLFS are covered. Payment rates are determined via crosswalk or gapfill methodologies during the CLFS Annual Public Meeting process, with input from industry stakeholders and an Advisory Panel. Cystatin C is represented by CPT code 82610, with a Medicare reimbursement of $18.52.

Ms. Shirey-Losso explained that CMS and the NIDDK previously discussed the process to include cystatin C on existing CPT panels; she provided a list of the current CPT panel with rates, ranging from $7 to $18, such as the CMP or BMP. The CMS recommends that the KICC work with the CPT advisors to either revise existing panels or develop a new panel to incorporate the cystatin C test. The CMS regularly attend the CPT Panel meetings, and Ms. Shirey-Losso volunteered to share contact information with the KICC for those meetings. Any new HCPCS coding associated with cystatin C tests would be reviewed during the CLFS Annual Public Meeting process.

Reflections from the National Kidney Foundation–American Society of Nephrology Task Force
Neil Powe, M.D., M.P.H., M.B.A.
University of California, San Francisco

Dr. Neil Powe explained that the National Kidney Foundation (NKF)–American Society of Nephrology (ASN) Task Force recognized that the solution to the problem—reassessing the use of race in kidney function equations and its use to diagnose kidney disease—would take time. The 12-member Task Force, composed of members with broad expertise and diversity (e.g., nephrologists, patients, pharmacologists, geneticists, experts in racial and ancestral diversity) from across the country were selected by the NKF and ASN. He acknowledged the members of the KICC and LWG who had participated. The Task Force, seeking to be transparent in its activities, invited community input. The Task Force reviewed a wide range of evidence and opinions with diverse representation, hosted 16 sessions with more than 90 experts from 19 U.S. states and 7 countries, and convened 3 community forums (i.e.,, one each for trainees, clinicians, and the general public).

In April 2021, the Task Force members published an interim report, titled "Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report from the NKF–ASN Task Force," in which they detailed the process, activities, and evidence. The Task Force developed 30 statements, with 97 references, a cornerstone in forging a path forward. These included statements of evidence and value in terms of equity, disparities, race, and racism; GFR measurement estimation equation performance; laboratory standardization; and patient perspectives. The Task Force next assembled 26 different approaches to estimating and reporting kidney function and solicited new research ideas by engaging panels on emerging and new investigations; participants from around the world presented their new research. In its interim report, the Task Force formulated a set of attributes to be considered in making final recommendations on alternative approaches to estimating kidney function. Dr. Powe explained that the Task Force has completed its work, and a final report is being refined and soon will be released to the public.

Discussion

- Dr. Mendley asked whether the Task Force discussed cystatin C. Dr. Powe pointed out that cystatin C has not been studied widely nor has it had the years of scrutiny that creatinine has had. The Task Force recognized that although cystatin C is a reasonable GFR marker, it has not been studied widely in non-ambulatory populations and the very ill; the concern is with regard to performance. Additionally, an economic concern remains in terms of health equity and covering costs for the analyses. Roughly 85 percent of people in the United States do not have kidney disease; having a more accurate and precise measure of kidney function in the 15 percent of people who are being diagnosed is critical. The kidney community is debating whether to incorporate another marker into the BMP.

Interagency and Panel Discussion: What Is the Message to the Broad Health Care Community?

Cystatin C as a GFR Marker

- Dr. Norton observed two divergent pathways on the use of cystatin C as a GFR marker: (1) use of cystatin C more narrowly in the populations who really need it and (2) use of cystatin C more broadly to reduce costs. She asked whether using cystatin C in a smaller subset of patients who really need it would be sufficient to begin to improve infrastructure such that costs would decrease. Dr. Powe noted that having multiple markers increases the chances of accurate prediction. In fact, supporting evidence suggests that the combined creatinine-cystatin C equation is the most accurate measure, yielding a coefficient of 1.08, but includes race corrections. He further commented that economists have shown that scale in health care does not always reduce

costs. Additionally, health care does not follow regular market economics largely because of the insurance payment structure.

- Dr. Crowley asked Dr. Grubb to comment on Sweden's model of offering the cystatin C test, scaling, and then reducing cost for those services. Dr. Grubb first clarified that cystatin C is not an inflammatory marker and highlighted the published data supporting this claim. Regarding the low cost of cystatin C in Sweden, he explained that this test and creatinine are performed using the same automated laboratory equipment and determination parameters. The cost differences in the United States are most likely administrative and due to the requirement to request permission for reimbursements for the analyses. Proof that a test is scientifically valid and has sufficient clinical experience is immediately reimbursable in Sweden. Dr. Mendley pointed out that these costs are reimbursed in the United States, but concerns remain on enhancing the use of this test.

- Dr. Mendley asked Dr. Miller to comment on the use of an automated analyzer capable of determining creatinine enzymatically and cystatin C via immunoassay. Dr. Miller noted that, like Dr. Grubb's, his laboratory uses a fully automated measuring system equipped to determine creatinine and cystatin C simultaneously. The cost of reagents in the United States tends to be higher than in Sweden.

- When asked whether the higher cost of cystatin C reagents in the United States compared with Sweden could be attributed to a supply and demand issue, Dr. Grubb noted that the suppliers are the same in the two countries. Dr. Powe added that health care costs, including of pharmaceuticals, tend to be higher in the United States than in other countries.

  Dr. Parsa asked about the actual cost differences between the clinical laboratories in the United States (e.g., Dr. Miller's laboratory) and Sweden (e.g., Dr. Grubb's laboratory) for the cystatin C assay and wondered whether price negotiations had been considered. Dr. Miller could not share the actual cost of tests performed at his hospital, noting that differences across laboratories could vary depending on how the costs (e.g., reagents, labor, overhead, accreditation, proficiency testing) are being estimated. Dr. Grubb noted that in Sweden, introducing new tests that are based on the science and proven clinical experience does not require approval by a central authority and these tests are always reimbursed. He added that state hospitals in Sweden pay for the reagents and the services, with no profit. The cost of cystatin C varies across hospitals from $1.50 to $4.00. An open-access price list can be viewed on a hospital's (e.g., Region Östergötland) website.

- Dr. Aliza Thompson sought clarity on whether the question is to measure both creatinine and cystatin C to provide the most accurate assessment of eGFR and to address the race issue or whether the KICC being asked to evaluate the cost of switching from one measurement to the other. Dr. Grubb noted that in Sweden, both tests are performed in patients, significantly reducing the number of invasive measurements used for assessing eGFR. Dr. Powe remarked that a variety of measurements (e.g., albumin, albumin-to-creatinine ratio, proteinuria) rather than one test for eGFR are needed for the 15 percent of the population who have kidney disease, thus triggering a threshold for treatment and its management. He emphasized using the various tests holistically for managing kidney disease, rather than relying on any one measurement of GFR.

- Dr. Crowley (in the chat) commented on using the combined creatinine-cystatin GFR equation for assessing kidney function in children because of its increased accuracy. Dr. Mendley expressed concern in recommending cystatin C testing for all assessments of kidney function in children, noting that it likely is not the best option. She reminded participants that the narrow range of creatinine values Dr. Miller reviewed were normalized in adults; the accuracy would be lower for measurements in children, for whom the range is 0.1 to 0.6 mg/L.

- Dr. Miller pointed out that 70 percent of U.S. clinical laboratories still use the Jaffe method for measuring creatinine, which, in his opinion, is unreliable in children because of the manner in which the technology is used. The recommendation in the field has been to use enzymatic methods, especially for the pediatric and diabetic populations in which the assay interferences are more common.

- Dr. Crowley whether the VA should consider the more accurate creatinine enzymatic assay as a confirmatory test for individuals with spinal cord injuries and low muscle mass, suggesting low creatinine levels below the reliable range of the assay. Dr. Miller explained that the Jaffee assay is more reactive to protein at low creatinine levels, magnifying the bias. Dr. Grubb added that cystatin C is used for sarcopenia patients in Sweden because of the low muscle mass and inconsistencies in the creatinine test.

Implementation into Clinical Practice

- Dr. Robert Star, observing that the transition from creatinine to cystatin C for eGFR will be complicated, noted the need to educate the broader health care community and patients about such a shift. He asked how the change in calculating eGFR would be implemented.

- Dr. Powe commented on the 15-year time frame to implement reporting eGFR values in the clinic, as well as use of the Modification of Diet in Renal Disease (MDRD) equation, which both took a unified approach.

- Dr. Norton emphasized a systems-based approach that encompasses policy changes, in addition to education.

  Dr. Miller noted two ways to accomplish the desired goal: (1) altering the laboratory accreditation standards to require use of the equation and methodology considered scientifically most appropriate for patient care and (2) being consistent and discontinuing reimbursements for laboratory tests that are not the most appropriate for the patient's care.

- Dr. Abigail Ryan agreed with including both measurements in a metabolic panel, enabling evaluations across all age groups and genders. The CMS procedures would be similar to the process for new drugs or the "focus on dialysis" assessments. Incurring costs or increasing base rates for the eGFR changes would be beneficial to avert new dialysis cases.

- As a health disparities and kidney disease researcher, Dr. Powe remarked on the lack of evidence that performing one test over another prevents people from going on dialysis because of other underlying factors. For example, it is not well understood why African Americans progress faster and have a higher incidence of ESRD. The myth is that the eGFR measurement is causing the disparities; however, these disparities existed before race was incorporated into the eGFR. Eggers *et al.* published a study in 1992 showing that African Americans and other ethnic groups were less likely to be placed on the transplant waiting list. The MDRD equations with the race correction were published in 1998 and broadly adopted after 15 years. Dr. Powe emphasized investing in resources that will achieve health equity. Dr. Ryan explained that CMS is conducting an in-depth review of the existing payment and health equity measures, which are expected to be completed at the end of 2021.

- Dr. Parsa remarked that implementing two different eGFR calculations into clinical practice would be confusing to patients and health care providers. He suggested minimizing the choices to include eGFR cystatin C for all.

- Dr. Miller highlighted the uncertainty of estimating GFR that should be conveyed to the broader community. Tests should be performed in duplicate and averaged, regardless of whether they are creatinine- or cystatin C–based.

GFR Reporting

- Dr. Mendley asked whether a range for eGFR should be reported, in addition to the single value. Dr. Miller explained that most computer systems used in clinical laboratories and electronic medical records do not support this functionality. Dr. Ng added that an interquartile range has been included in the U25 calculators to obtain an understanding of the precision of the estimate and determine the level of uncertainty of the point estimate.

- Dr. Crowley commented on separating the eGFR reporting information provided to the patients from the information sent to health care professionals and agreed with stating GFR ranges.

Referrals

- Dr. Star remarked that providing GFR ranges would be disruptive and suggested using thresholds for clinical decision making or using a trajectory concept.

- Dr. Powe suggested moving away from a waitlist to using risk of disease progression to decide who should be referred for a transplant.

- Dr. Susan Zieman asked Dr. Grubb about an age limit to using cystatin C that would affect older age groups, calibration parameters, and prognosis. Dr. Grubb explained that because of the other health complications older age groups experience, cystatin C is a better biomarker for these groups.

- In response to Dr. Crowley's comment on the challenge in developing a risk prediction tool for clinical decision making in the VA systems, Dr. Powe noted that these tools can be developed and should reflect what is being measured. He added that the existing prediction calculators (e.g., MDCalc) are being used and are providing useful results.

- Dr. Norton highlighted that many biomarkers are not available to support risk prediction equations and noted that risk prediction would work well for nephrology referrals in the context of disease progression, but not necessarily for drug dosing. Dr. Thompson asked whether the aim is to predict risk of progression to define a disease or assess renal function to inform drug dosing; a single estimating equation for both purposes presents a challenge. Dr. Powe agreed and reiterated the need to take a holistic approach to kidney care because the estimating equations affect access to care, as well as medication management decisions for clinical trial enrollment. Dr. Star called attention to discussions in the NKF to develop patient personas as educational tools to address some of these issues.

What Is Missing?

- Dr. Crowley suggested broadly engaging health professionals (e.g., pharmacists, dieticians, nurses) in CKD care and seeking guidance from implementation science experts.

- Dr. Sheldon asked to what extent the patient communities in the United States and globally are involved in these discussions on race and the GFR estimating equations. Dr. Powe clarified that the Task Force was not charged with implementation but with providing recommendations of alternative approaches to estimating kidney function. The NKF and ASN will take the next steps.

Around the Table: Agency Updates

Agency for Healthcare Research and Quality

Dr. Christine Chang informed the KICC that the public comment period for the request for information on the use of clinical algorithms and racial/ethnic bias has closed, and responses are being reviewed. AHRQ launched a systematic review on this topic and anticipates that the preliminary scope will be ready for public comment in October 2021.

Centers for Disease Control and Prevention

Ms. Burrows announced that the CDC and National Center for Health Statistics has worked with the NIH to update the NHANES USRDS data linkages. These data will be available to researchers in the coming weeks, and proposals will be required for access. Further details can be accessed from the CDC website: https://www.cdc.gov/nchs/data-linkage/esrd.htm.

NIH—National Institute on Aging

Dr. Zieman pointed out (in the chat) that the National Institute on Aging (NIA) has launched Clinician-Scientists Transdisciplinary Aging Research (Clin-STAR), a virtual community of transdisciplinary clinician-scientists of all disciplines focusing on aging/geriatric research. Clin-STAR aims to promote interactions within and among the specialties of the clinician-scientists to accelerate collaboration, networking, mentoring, and career development. KICC members were encouraged to visit the website.

Adjournment

Dr. Mendley thanked the presenters and attendees for their participation and noted that the next meeting is scheduled for March 2022. She adjourned the meeting.