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Is it Time to move on? Reexamining Race in Glomerular Filtration Rate Equations

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Guest: Dr. Anais Ovalle is an instructor of medicine at Geisel School of Medicine and an infectious disease fellow and preventive medicine resident at Dartmouth-Hitchcock Medical Center. Dr. Joe El-Khoury is Associate Professor of Laboratory Medicine at Yale School of Medicine, Director of the Clinical Chemistry Laboratory and co-director of the Clinical Chemistry Fellowship Program at Yale New Haven Health.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Glomerular filtration rate is the best overall index of kidney function. Since it is difficult to accurately measure GFR in clinical practice, it is commonly estimated using equations that incorporate serum creatinine concentration which is easier to measure and is routinely available. Several equations for estimating glomerular filtration rate or eGFR have been developed. The most widely used equations in addition to creatinine also factor in the patient's age, sex, and controversially, race. Separate equations for African-Americans and for non-African-Americans are in part based on small, not so well-designed studies that suggest a higher baseline serum creatinine concentration in black individuals.

Nonetheless, there are also data to suggest that a separate equation for blacks does better reflect the gold standard measured GFR value. Those data suggests that the use of a separate coefficient for black patients is a well-intentioned act designed to improve the accuracy of the eGFR for a subset of the U.S. population. However, we cannot be blind to the reality that those data come with caveat. A Q&A feature appearing in the April 2021 issue of Clinical *Chemistry* re-examined race in glomerular filtration rate equations and asks: is it time to move on? That Q&A spoke with a group of five global experts in the fields of nephrology, laboratory medicine and public health, to share their perspectives on this topic.

The moderators for that feature are Joe El-Khoury, Anais Ovalle and Mark Cervinski. We are pleased to have two of those moderators in this podcast. Dr. Anais Ovalle is an instructor of medicine at Geisel School of Medicine and an infectious disease fellow and preventive medicine resident at Dartmouth-Hitchcock Medical Center. Dr. Joe El-Khoury is Associate Professor of Laboratory Medicine at Yale School of Medicine, Director of the Clinical Chemistry Laboratory and co-director of the Clinical Chemistry Fellowship Program at

Yale New Haven Health. And Dr. Ovalle, I want to start by asking you, what is the history of using race in glomerular filtration rate equations?

Anais Ovalle: Well, in the nephrology realm, the glomerular filtration rate is very difficult to exactly measure. So, they use an estimated glomerular filtration rate and that's through the measurement of creatinine, which is what's most commonly performed in the United States. So, at the bedside, this eGFR is used in a multitude of clinical decisions from medication dosing, approaches to diagnostic testing, where you're going to use contrast or not in procedures, and also surgical risk. So with that, you have in the mid-1970s to the 1990s, yet, Cockcroft-Gault that equation was utilized and then research from the National Institute of Diabetes and Digestive and Kidney Diseases noticed that there are higher same concentrations in non-Hispanic blacks compared to non-Hispanic white adults. And then there was further research done and ultimately in the modification of diet in renal disease or the MDRD group, they saw that in 197 patients that were identified as black, they had persistently high levels of creatinine, that was back in 1999. And so utilizing logistic regression, they basically came up with the 1.212 multiplier that was created.

That multiplier was justified with the fact that there was the assumption of higher average muscle mass and creatinine generation was in African-Americans. They didn't really explore other factors that affect creatinine such as nutrition and protein intake. So that kind of snowballed into where we're at today and then you know, the CKD-EPI group also created an estimated GFR calculation back in 2009 that didn't use the multiplier of 1.159.

And so, you know when you think about race being a group of humans that share these physical or social qualities, you know, you think about it and we really started measuring race in the 1790s and that was back when slavery was really the use for it. And you kind of assigned it for those that you thought looked a certain way. There's a lot of heterogeneity in that practice and then you have 2003, The Human Genome Project that confirmed that there is actually no biological difference between races. So you have this moving target of race that we socially define and then you have biological evidence showing that there's no difference with it. So this approach where we're utilizing race as the surrogate marker for something is I think at this point antiquated.

Bob Barrett: So has the use of race in GFR equations contributed to racial disparities in medicine and if so, how?

Anais Ovalle: So, there are health disparities with kidney disease and management. Underrepresented racial groups and ethnic

groups are disproportionately affected by social determinants of health. And you know with that, it makes it difficult to attribute the equation itself, as it's multifactorial and it involves different levels of structural barriers. Social determinants of health are conditions in the environment that affect where people -- how people -- basically their health and where people are born, live, learn, play, worship. And with that in mind, you know, there is a wide disparity present with these. The CDC website has a really great example where people who don't have access to grocery stores with healthy foods are less likely to have good nutrition. And so when I think of the historical context of redlining and neighborhoods, it would be difficult for some communities to find healthier meals that then raises the risk for health conditions such as heart disease, diabetes, obesity. And then that could even lower life expectancies compared to those who do have access to healthier foods.

And then another thing I think of is access to specialty care. We have these food deserts. And then there also exists specialty deserts. So, you have community centers that only could do so much and then you have black patients who live in, you know, I think it's Chicago, inner cities where they have a lot of community centers but they don't really have the subspecialty care or the access to subspecialty care such as nephrology or transplant, and I feel like I've touched it very superficially, but all of these then contribute to black patients having advanced kidney disease at younger ages and also they progress more quickly to end stage renal disease. Again, this could be to higher rate diabetes, hypertension, less access to nephrology or transplant. There's also ancestry where the alpha-1 gene or allele is more present in those of African ancestry, which is distinct from being a black race. And then black patients are also less likely to be treated with home dialysis therapies and they're more likely to be wait-listed for transplants and even fewer people get transplanted. So all of this kind of leads into, you know, there are racial disparities present in this, however, I'm not sure how much to attribute to the equation itself.

Bob Barrett: Well, we could get into it a lot deeper, but this would be a 12-hour podcast then, so I don't think we could do that. Dr. El-Khoury, let's bring you in on this. What are some potential solutions to these issues?

Joe El-Khoury: Thank you Bob. There are several general approaches that could solve this problem and these fall under two broad categories. One is where we continue to use creatinine as a biomarker and two is where we stop using creatinine and switch over to ones that are not affected by race, they are more race neutral. In the first category where we choose to continue to use creatinine, the suggested solutions are removing the race coefficient entirely from the equations.

Another solution is reporting a range of eGFR values instead of a single value. For example, where we remove race and state it's from low muscle mass to high muscle mass and again, each of these having advantages and disadvantages and that specifically has not had significant evidence to support its use. And last in that category is using a single coefficient that is weighted for the percentage of African-Americans in your specific population and then reporting it for everyone, so it's not biasing African-Americans one way versus none.

In the second category where we stopped using creatinine and look for these other markers, they're race neutral like Cystatin C is one example where equations already exist. That is being looked at strongly. In addition, measuring GFR directly using these exogenous filtration markers like iothalamate or iohexol is also being looked at as an option, however, that is much more tedious and again, that's not something you can screen patients with. So, it's something that we could look at for a reflex mechanism potentially, to do that if needed, but for screening, kind of these are the general broad categories that would sum up what could be approaches that could apply to address this major issue.

Bob Barrett: So Dr. Ovalle, back to you. Let's discuss what would some of the intended and unintended clinical consequences of removing race from GFR equations be?

Anais Ovalle: When I think about this, I think that intentionally, you know, if we remove it, you're going to have earlier detection of CKD for a larger portion of those who otherwise aren't categorized as such in the U.S. And with that, you're going to be able to be more aggressive when it comes to treatment of hypertension, diabetes, and other conditions that could contribute to renal disease. And so, if you also modify it to remove that, that coefficient, you would expand the amount of people that okay, you classify with chronic kidney disease, and you're able to treat their comorbidities and then also give them education on how to prevent progression and then that can also lead to early nephrology referral and nephrology care and then you can ideally delay or avert adverse outcomes with that. And then also, you would have early transplant referral.

On the other side of that coin, you can lose a substantial portion of people who would be eligible for certain medications that would be helpful to treat those with CKD later on. And then you also lose those individuals who initially were eligible to donate their kidney to others because of that removal of the race coefficient.

Bob Barrett: So Dr. El-Khoury, earlier you mentioned Cystatin C being a kidney biomarker that is race-neutral. What are some of the

challenges associated with transitioning from creatinine to Cystatin C-based GFR equations?

Joe El-Khoury: So in a nutshell, there are three major issues with moving to Cystatin C. One is lack of standardization between existing assays, second being cost, and third being lack of worldwide availability that was noted by some of our experts who are more international. So, on the lack of standardization front, that means essentially that what the patient is getting-- their sample run on one assay will get a different result on another assay. So, it's almost like you need an equation for every single method if you can't achieve standardization. Cost: Cystatin C have assays have been reported to be at least twentyfold more expensive than creatinine assays. That can be a problem for areas which are countries that lower income or cannot afford the higher expense and the value is not as significant except, you know, in this case trying to address this issue. So it's something to be looked at on the cost-benefit as well.

And lastly, again, lack of worldwide availability that continues to be an issue, but the main issue to be addressed right now is standardization that could then potentially lead to more use of Cystatin C.

Bob Barrett: So, it sounds like there were challenges with either approach. What action do you and the experts in the Q&A feature recommend clinical laboratories and clinicians take to improve their calculation, interpretation, and reporting of GFR equations?

Joe El-Khoury: So, that is the key question and hopefully the main take-home from the podcast today is this is a complicated issue with no straightforward solution and all experts noted that as well. And the current recommendation is to wait for the report from the National Kidney Foundation and the American Society of Nephrology Task Force and their recommendations. So they've just published their first interim report summarizing that approach and how they plan to address this issue and we are looking forward to seeing their final recommendations hopefully in the upcoming year. I know this is hard. We recognize that the current equations are not doing well in light of all of the discussions that was presented by Dr. Ovalle already today and mentioned in the Q&A article. However again, making a decision and choosing one solution, there may be unintended consequences. We don't know yet what each of these can do and how they will affect our patients. So there's a more thorough evaluation that's occurring by the NKF-ASN Task Force and because we do not want to have different centers choosing or acting differently by choosing different approaches to deal with this. So, we want to maintain standardization between different hospitals as well. So we want to all make the best decision

we can and the same decision instead of having one hospital choose option A, and the other one choosing option B and having completely different treatment and consequences to the patients. So, again, the recommendation is right now to wait for the NKF-ASN Task Force.

Bob Barrett: That was Dr. Joe El-Khoury, associate professor of laboratory medicine at Yale School of Medicine, Director of the Clinical Chemistry Laboratory and co-director of the Clinical Chemistry Fellowship Program at Yale New Haven Health. He was joined by Dr. Anais Ovalle, an instructor of medicine at Geisel School of Medicine and an infectious disease fellow and preventive medicine resident at Dartmouth-Hitchcock Medical Center. They are two of the moderators that participated in the Q&A feature in the April 2021 issue of *Clinical Chemistry* on re-examining race in glomerular filtration rate equations. I'm Bob Barrett. Thanks for listening.