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New Equations for Estimating Glomerular Filtration Rate

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Guest: Dr. Anthony Killeen is a professor and vice-chair for clinical affairs in the Department of Laboratory Medicine & Pathology at the University of Minnesota in Minneapolis.

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. For approximately 15 years, U.S. clinical laboratories have been encouraged to report estimated glomerular filtration rates, or eGFR, with creatinine measurements in adults. This recommendation was based on the relatively high prevalence of chronic kidney disease, which affects approximately 14% of the U.S. adult population, and which often goes undetected in its early stages. Changes in serum creatinine concentration may not appear significant and may even be within typical population-based reference intervals and therefore not flagged on laboratory reports, while the eGFR may more effectively demonstrated a change.

The Chronic Kidney Disease Epidemiology Collaboration has recently published new equations for calculating eGFR based on serum creatinine and cystatin C concentrations. A perspective article appearing in the April 2022 issue of *Clinical Chemistry* presents the new equations and discusses their origins and their accuracy. We are pleased to have one of the authors of that article as our guest in this podcast.

Dr. Anthony Killeen is a professor and vice chair for clinical affairs in the Department of Laboratory Medicine and Pathology at the University of Minnesota in Minneapolis, and he has served in numerous leadership positions in several laboratory medicine societies. First of all, Dr. Killeen, what is eGFR and when is it used in clinical practice?

Anthony Killeen: So eGFR stands for estimated glomerular filtration rate and the glomerular filtration rate itself is considered widely to be the most useful overall marker of renal function. And the "e" in eGFR is, as I said, estimated. So, these are estimates of glomerular filtration rate. Typically, they're based on single measurements of a serum or plasma creatinine and in some instances, they're based on cystatin C measurements, but for the most part, creatinine is one that's used. And estimates of glomerular filtration rate are used very widely. I said already that it's considered to be the most reliable marker of

renal function. So, it gives clinicians an idea of a patient's renal function status. It tends to decline with age.

There are differences based on disease state, of course, which are the ones that are most interesting to clinicians but some applications of eGFR measurements would be confirming that a potential kidney donor is suitable for donation of a kidney, drug dosing--there are a number of drugs that are used in medicine where the dose of the drug will depend on the patient's renal function. In some setting, patients may be eligible or not eligible for enrollment in clinical trials depending on their GFR. There are some situations where a radiologist will or will not use radio contrast imaging dyes in preparing patients for those sorts of studies, decisions on when to refer patients to a nephrologist, and kidney dialysis. All of these depend on the glomerular filtration rate and what we usually provide of course, which is the estimate of that number.

So, the eGFR is a number. In absolutely healthy people, it's usually greater than 90 and the units are mLs per minute for 1.73 square meters of body surface area, so that the units are a mouthful, but I just go with the number. So, over 90 is considered to be absolutely healthy. And then below 60, anything below 60 is considered to be mild to moderate renal impairment. So, that value is sort of an important number here, and then as you get down to lower numbers, such as less than 15, that's considered to be kidney failure. So, there's a grading system consisting of five stages and two sub-stages that nephrologists and clinicians use in this, and these are all based on estimated GFR.

Bob Barrett: So why were new eGFR equations published last year?

Anthony Killeen: So, eGFR equations have been used really since at least the 1970s. The first equation that became in any way popular was an equation derived called the Cockroft-Gault equation, which was derived by those two authors. And it was a way of getting a handle on the glomerular filtration rate from a simple measurement of serum creatinine. So, the formal way to get a glomerular filtration rate, or GFR measurement, is to infuse a patient with a filtration marker, such as inulin or more people today use iohexol, and to measure the concentration of that marker in the blood and its excretion in urine over a timed interval. That kind of formal measurement, which we call the measured GFR, is as I think I've described, a difficult and fairly costly and time-consuming thing to do. So, simple measurement of creatinine and the application of creatinine to determining the GFR became very popular.

It became really popular after the 1990s, roughly when the first widely used equation became available, which was an

equation called the Modification of Diet in Renal Disease equation, the MDRD equation, and that came out of a study of the same name: the Modification of Diet in Renal Disease. And then in 2009, there was a new equation that came along from a group called the Chronic Kidney Disease Collaborative Group and they produced an equation for estimating GFR, again based on creatinine. And then there were some later equations using cystatin C as well.

So, there's been a history of these equations. All of these equations up until the 2021 equation, which is the newest one, included race. Actually, the Cockroft-Gault didn't include race, but the MDRD and the CKD-EPI 2009 equation included race, along with age and gender as variables in determining or calculating the eGFR, and of course, the serum creatinine. In the last few years, as I think everybody is aware, there's been a lot of questioning about the use of race in medicine, in medical practice. And so race is increasingly seen not as a true biological difference between people but more of a social construct that has all sorts of ramifications and implications and of course historical context as well.

So, the way that we were reporting eGFR using the CKD-EPI equation from 2009, and indeed the MDRD equation before that, was to report a value if a patient was Black and if a patient was not Black. We reported two values. Typically, we didn't know in the lab what a patient's racial group was. We typically had access to their age and their gender, and of course, we measured the serum creatinine. So, we had those three parameters, but we didn't know usually, from the medical record, what a patient's race was. So, we calculated for both Black and non-Black and reported it as two separate values.

And I remember when we first started doing that, probably around 2006 maybe, or something like that. A clinician called us and said that he thought this was racism that we were reporting two separate values, one for non-Blacks and one for Blacks, and we sort of explained that that was the recommendation at the time and the issue kind of seemingly went away for a while. And then in the last few years, this issue of race has come up again and there's been a lot of pressure to eliminate these sorts of racial variables and equations, and it's seen as sort of a healthcare disparity issue. So, there was a lot of pressure to remove race as a variable in the eGFR equations.

So, there was a group of experts convened called the CKD-EPI Collaboration Group, which included experts in nephrology, lab medicine, pharmacy and so on, and they re-examined the data, which was used in derivation of the 2009 CKD-EPI equation. They basically redid the equation, the regression equation, excluding race as a variable, and came

up with a new set of equations. And so this new equation includes, again, age and gender, and of course the serum creatinine, but it excludes race. There's no racial component now in this new equation, the 2021 equation, and so there's no longer a need for clinical labs to report or do a reporting. It's not necessary anymore.

So that was the background to the 2021 CKD-EPI equation, which is the one that we've adopted here at the University of Minnesota. And I should say, I was on a group here that met late 2020 and 2021 looking at this whole issue of race in reporting eGFR. This was before the eGFR new equation came out. And we made some changes to our reporting system to remove the racial component, but now we have new authoritative recommendations from this group, so we've adopted their new equation.

Bob Barrett: So, I want to talk about those equations right now. If a laboratory started reporting eGFR using the standard Cockroft-Gault equation, then switched to the MDRD equation, then switched to the first CKD-EPI equation, and now switches to the new CKD-EPI equation, that would mean possibly using four different equations in a dozen or so years. Could there be some eGFR equation fatigue among laboratories and can we anticipate yet another shortly down the road?

Anthony Killeen: Yeah, that's a good question. The Cockroft-Gault probably was not widely adopted for routine reporting, it was more used in research settings. But the MDRD from 1999 and the CKD-EPI from 2009, and now the 2021 equations were the three that we've been using here, and I certainly understand the concern about this equation fatigue. I think the answer to that is that in each situation, we were adopting equations that were recommended by national expert groups. I think this one may be the last one for creatinine. I don't think there's going to be another CKD-EPI creatinine equation. I would be surprised if that was the case.

When we report estimated glomerular filtration rate, we report what the equation is that it's based on. We also have done some education of clinicians around these changes as they have occurred, but I think it is a useful point to make to understand that if you're following patients longitudinally, you need to know what equation was in use at what time. First of all, I think labs should adopt these equations, but I think there's also a need to indicate on your lab report when you adopted the equation, when you put them to practice for patients who are being followed longitudinally. But I think there is some risk of fatigue but as I say, I think we probably come to the last iteration of creatinine-based eGFR equations.

Bob Barrett: So how accurate are the various eGFR equations for estimating renal function and is there a gold standard?

Anthony Killeen: So, the gold standard is a measured glomerular filtration rate. And as I indicated earlier, that requires bringing the patient in and infusing iohexol typically would be the agent that's used today. Collecting blood samples, measuring iohexol concentration in blood and urine. That's the gold standard. It is used and it's necessary in some situations where a truly accurate number is required, but it's impractical for most patients. The accuracy of the estimated glomerular filtration rate, so, some specific numbers around this are that if you look and compare measured glomerular filtration rate coming out of research studies with estimated glomerular filtration rate in those same research participants, the median difference is somewhere around 3 to 4 mLs per minute per 1.73 square meters from the measured value.

So, the median includes 50% of the observation. So, 50% of the observations will be within 3 or 4 mils of the measured value. And for the other 50% of subjects, the values can get quite different. The spread between measured GFR and estimated GFR can increase. A metric that's actually used to describe that is called the P30, which describes the number of patients whose values fall within 30% of a measured GFR. And for the new equation, and also for the 2009 equation, somewhere between 85 and 90% of all patients will have a value that falls within 30% of a measured value. So, that's kind of the accuracy standard.

Now, you can say that's reasonable or you can say maybe it's not so reasonable because 30%, if you have a patient who's got a true measured GFR of 60, a 30% variation and the estimated value could range from 42 to 78 mLs per minute per 1.73 square meters. So that's quite a range and that would put the patient squarely into very different categories of renal function. And then for 10 to 15% of patients, the difference between the measured GFR and the estimated GFR is going to exceed that 30% range. So, these are not deadly accurate equations. In most patients they are reasonable, but there are certainly patients where you're not going to get a great number out of an estimated GFR. And if there's any question, that's when we would use a measured value.

But the final way in which the authors of this new document assess the accuracy of the equations is by looking at how many patients fall into the correct stage of CKD. As I said earlier, there are five major stages of CKD. With a new equation, something around 60 to 66% or so of patients will be correctly classified into their stage of CKD based on these estimated formulas. And that's only marginally different from what was seen with the 2009 equation. So, we think that

probably, most of those who are misclassified are sort of around the border of these cutoff ranges.

Bob Barrett: So, doctor, what about expenses involved for laboratories to make these changes?

Anthony Killeen: So, the expense for the lab really has to do with reprogramming the lab information system or the hospital's electronic medical record. There is no cost involved in the assay because we're not changing the assay. So, any cost would involve IT personnel time and validating these new equations. So, the cost to the lab and the hospital system should be fairly minimal. It shouldn't take more than I don't know how many hours of IT professional time to rewrite the equations and validate them.

Bob Barrett: Are physicians aware of the changes in those calculations when interpreting results?

Anthony Killeen: So that's a really good question. So, we sent out information bulletins to our clinical staff about the change. And when we report eGFR today, we always indicate on every report that we changed the equation on a specific date. Actually, I remembered the date. It was the Winter Solstice. It was December 21. That goes on every report and it says we changed it to the new 2021 CKD-EPI equation. So yes, so we have done and we say, of course, that the new equation does not include race as a covariate.

Bob Barrett: Well, finally, Dr. Killeen, what should clinical laboratories do with these new equations and what are labs outside the U.S. doing?

Anthony Killeen: So, the recommendation is that clinical labs in the United States should adopt the new 2021 equation. We did a survey in the College of American Pathologists as recently as 2019 and it turned out that only a minority of clinical labs who are participating in a C.A.P survey just a few years ago were actually using what was then the current equation, which was the 2009 equation. So clinical labs today should adopt these new equations. That would require also, of course, some education of their clinicians who use the lab, awareness. There is no need to report duo by race results anymore. That's no longer a part of these equations.

So, the recommendation for U.S. labs is to adopt these equations immediately, effectively, or as soon as practical. For labs outside the U.S., it should be borne in mind that most of the datasets that were used to derive these equations come from U.S. individuals and it may be necessary, and this is something that labs outside the U.S. have to figure out for themselves, it may be necessary to revalidate the equations

and see if they're actually suitable for use in other countries with different ethnic makeup.

Bob Barrett: Dr. Anthony Killeen is a professor and vice chair for clinical affairs in the Department of Laboratory Medicine and Pathology at the University of Minnesota in Minneapolis. He has been our guest in this podcast on the new equation for calculating eGFR. He is a co-author of a perspective article on that new equation that appears in the April 2022 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.