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Individual Inaccuracy in Glomerular Filtration Rate Estimation

Dr. Butler:
Although population-level differences between estimated glomerular filtration rate, or eGFR for short, and measured glomerular filtration rate are well-known, the individual-level differences are not. So what clinical implication can this have for our patients?

Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Dr. Javed Butler. And here today to discuss a recent study from the *Annals of Internal Medicine* that explored this exact topic is Dr. Tariq Shafi, who is the John D. Bower Director of the Division of Nephrology and Professor of Medicine at the University of Mississippi Medical Center.

Dr. Shafi, welcome to the program.

Dr. Shafi:
Thank you, Dr. Butler, and it's a pleasure to be here.

Dr. Butler:
Great. So we are all really excited about your study, but before we get into the specifics of the study, just to start us off, can you tell us how renal function is currently measured and assessed in the clinical practice?

Dr. Shafi:
As you know, most of the times when there is a chemistry panel, renal function panel, or basic metabolic panel done anywhere in the clinic or in the inpatient setting, there is an estimated GFR that is reported alongside a serum creatinine value. So this estimated GFR is one way of how the renal function is assessed these days. There are other methods, such as measuring a cystatin C level and calculating an estimated GFR from that, and some of the guidelines recommend cystatin C as a confirmatory test for GFR. And then the other method for measuring GFR is the 24-hour urine collection. Now if any time we have ordered a urine collection for 24-hour urine creatinine clearance, it is to really measure GFR. In some specialized centers, direct radioisotopic GFR is also measured. It can be quite cumbersome, but there are some specialized uses for it, such as if you want to know what the split kidney function is. And in a handful of specialized centers, now these modern methods of direct GFR measurements are also being used.

Dr. Butler:
So can you tell us a little bit about the strengths and weaknesses of these current methods, and along with that, if you can opine a little bit about the cystatin issue and how common the cystatin C is being measured in the clinical setting, as well?

Dr. Shafi:
So I think the biggest advantage of estimated GFR is if you remember the time before estimated GFR, there was a serum creatinine that was reported, and people would try to guestimate what somebody's kidney function was, and that could be subjective. So the estimated GFR gives a more scientifically valid way of assessing how the creatinine level relates to somebody's GFR, but this is still a ballpark estimate of what the GFR is. So its advantage is that it only requires the serum creatinine that has been measured eight and six at this

point, so really any lab that has collected these demographic data can report it.

The disadvantage that people overlook is that the estimated GFR is really the population average GFR of people that were in the equation cohorts, and CKD-EPI is the most commonly used equation in the United States and worldwide. The other disadvantage has been that in the zeal to make estimated GFR widely available we have started reporting this number even for patients where it may not be valid. So the results of any study are generalizable to the patients that were actually included in these cohorts, so these cohorts did not include people that were hospitalized or acutely ill for example, people with decompensated heart failure, cirrhosis, or sickle cell. For us, a kidney transplant is a big group as well.

Cystatin C is another filtration marker. It is produced by all nucleated cells in the body. It's also freely filtered, not reabsorbed, not secreted, so we can use its level to give us an approximation of what the kidney function may be. And just like with creatinine where we have estimating equations that calculate an estimated GFR, we have estimated equations with cystatin C, as well. It is not widely available, but in the majority of the health centers in the United States it's a send-out test, so the results are not available right away.

Dr. Butler:
Great. So with that in mind, what were the exact questions you were trying to address in your study? Can you tell us a little bit about the backbone of your study?

Dr. Shafi:
So we started off with a simple question: what is the range of directly measured gold standard GFR in my patient who has a given or a calculated eGFR result? And the reason this was important is that when we looked at the lab report with a serum creatinine value of 1.5, if the test is repeated 100 times, the range will be between 1.4 to 1.6. Right next to it is an eGFR number that is reported. Take an example of 60. So most of the time when people are looking at these numbers, the implication is that this is a gold standard and a highly accurate number of 59 to 60 with a range of 59 to 61. So we wanted to understand this a little bit better and see whether that's really the true range or wider. We also wanted to know how likely large errors in the studies are and how people are classified as CKD versus not CKD using measured versus estimated GFR.

So to answer these questions, we collated data from four cohorts where GFR was measured as part of a research protocol using highly standardized methods in about 3,000 participants, and these participants also had serum creatinine and cystatin C values at the same time. And then we related these measured GFR values with the calculated estimated GFR from creatinine and cystatin C.

Dr. Butler:
That's great that you had the opportunity and the data to look into those not easy things to do. So what did you find?

Dr. Shafi:
So we found that the eGFR calculation was substantially inaccurate, so much so that we felt that it's actually inaccurate to report it as a single number. So just to give you an example, if we take 100 patients with an eGFR of 60—remember, that's the number where we were wondering the range of measured GFR 59 to 61—we found that half of the people with an estimated GFR of 60 would have a directly measured GFR in the range of 50 to 70, and 95 of the people have a directly measured GFR in the range of 36 to 87. Now, this is a substantially wide range where 36 is really a very advanced kidney failure and 87 is a really novel kidney function, so no CKD to severe CKD.

We also found that substantial errors where people's measured GFR was outside of the 15 percent range was high at about 50 percent, and only half the people that were classified as CKD by the estimated GFR were classified by measured GFR. This is really important for the people with what we call the CKD Stage 3A, which is people with an estimated GFR of 45 to 59 and no protein in the urine. And in this group, we found that two out of five, or 40 percent of the patients, had a directly measured GFR greater than 60 which really classifies them at CKD 3. And to put it in context, we're talking about 7.5 million people in the United States that are classified as CKD based on this estimation.

Dr. Butler:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Dr. Tariq

Shafi about a recent study that focused on quantifying individual-level inaccuracies in glomerular filtration rate estimations.

Obviously, CKD stages are important not only for the generic prognostic purposes, but also some of our therapies are targeted towards that, so I want to hear your perspective about the clinical implications of your results.

Dr. Shafi:
I think in terms of clinical implications from the patient care perspective, for a long time we've actually started to tell people that their kidney function number is this, and the number that we are reporting is not really highly precise so we should tell them what the range of kidney function may be. So that's one aspect of things. And then I think we need to sort of modify the way the labs report these tests, and perhaps not report them for people where they are not valid, and when it's supported report the uncertainty as well. I think in terms of the CKD classification system, it is okay if we actually use estimated GFR to classify groups of people for population health studies, population health intervention, and disease epidemiology. But I think it's really problematic at the individual patient level when we classify them as having a disease versus no disease based on a single estimated GFR number, and this is something similar to what we've done with hemoglobin A1c, except that A1c is measured so it's actually a measured test, whereas estimated GFR is not a measured test.

Dr. Butler:
So while there seems to be a lot of clinical implications of your research findings, is it clinically feasible? And what in your opinion are the next steps for your line of research?

Dr. Shafi:
Yes. So I think the new methods for measured GFR are highly clinically feasible. The modern methods of GFR measurements are quite simple. So if you can give a dose of a drug IV that's nonradioactive or give a sub-q injection, and you can draw blood and do bladder scans, you can measure GFR in a period of about two to four hours. Obviously, this is not a simple procedure that everybody would be getting, but it is not a highly complicated procedure that it should not be available to our patients.

So how do we actually make it available? I think education and awareness of both directly measured GFR and the limitations of estimated GFR is extremely important. And finally, I think one of the biggest barriers in the U.S. healthcare system is that we do not have a CPT code for a non-nuclear GFR. One exists for nuclear GFR but not for non-nuclear GFR, so we need to do work to make directly measured GFR available procedure.

Dr. Butler:
Well, I very much appreciate your insights. These were certainly some very important findings when it comes to measuring a patient's renal function. Tariq, thank you so much for walking us through your study and spending some time with us. It was a pleasure speaking with you.

Dr. Shafi:
Yes, and thank you for this very interesting discussion.

Dr. Butler:
I am Dr. Javed Butler. To access this and other episodes in our series, visit ReachMD.com/CliniciansRoundtable, where you can Be Part of the Knowledge. Thanks for listening.