Utilizing Longitudinal Within-Individual Changes of Serum Creatinine, Cystatin C, and/or eGFR to Optimize Clinical Sensitivity and Eliminate Race and Gender Corrections

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Guests: Dr. John Toffaletti from Duke University Medical Center and Dr. George Bayliss from Brown University and the Miriam Hospital in Providence, Rhode Island.

Randye Kaye: Hello, and welcome to this edition of JALM Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

In September of 2021, a Joint Task Force of the National Kidney Foundation and the American Society of Nephrology recommended the adoption of a new estimated glomerular filtration rate, or eGFR, equation that estimates kidney function without a race variable. Historically, the goal of eGFR equations has been to use serum creatinine and/or serum cystatin C concentrations to calculate an eGFR that would agree with the directly measured GFR, which is a much harder test to perform.

However, it is important for laboratorians and clinicians to remember that the "e" in eGFR stands for "estimated" and that even the newly recommended 2021 eGFR equation has limitations.

In an opinion article in the May 2022 issue of *JALM*, the authors call for eliminating further efforts to improve eGFR equations and instead advocate for longitudinal monitoring of patient's serum creatinine and/or serum cystatin C concentrations to determine clinically relevant within-individual changes. With this approach, monitoring from the patient's baseline values could obviate the need for correction factors based on the patient's race, sex, or age.

Today, we are joined by two authors of this article. Dr. John Toffaletti is a professor of pathology and director of The Blood Gas Laboratory, The Clinical Pediatric Laboratory, and several outpatient laboratories at Duke University Medical Center. Dr. George Bayliss is an associate professor of medicine at Brown University and an attending nephrologist at the Miriam Hospital in Providence, Rhode Island. Drs. Toffaletti and Bayliss, welcome.

We'll start with you Dr. Toffaletti. Longitudinal monitoring of patient's lab values seems to make sense. Is following longitudinal creatinines on a patient a common practice for the monitoring of kidney function?

John Toffaletti: Well, maybe surprisingly, this appears to be a fairly common practice among nephrologists when you ask them. Let me first of all say, I do appreciate *JALM* for taking on this controversial subject because I think it's something that definitely needs discussion.

So, continuing on with my answer, this longitudinal monitoring has been done for decades for acute kidney injury, or AKI, but on a shorter time scale like hours for AKI, versus weeks or months for chronic kidney disease. Also, I add that the timing criteria for chronic kidney disease is really an area that needs both further research and standardization.

Randye Kaye: And Dr. Bayliss.

George Bayliss: So, each has its role in clinical practice. GFR is a steady state equation that's useful for measuring changes in function over time and assessing where people fall in the categorization of their degree of kidney disease. Each stage has a certain action plan of things we need to think about, things we need to do. Measuring longitudinal creatinine is useful within each stage to see how quickly they're progressing. It's also the only thing we can use to assess acute kidney injury since that's of a dynamic process and the eGFR equation doesn't capture that.

Randye Kaye: All right. Thank you and I appreciate that each of you are answering each question. So, we'll continue along these lines starting with Dr. Toffaletti and then Dr. Bayliss. My next question is this: a provider could longitudinally monitor a patient's creatinine or they could longitudinally monitor the patient's eGFR, calculated from the creatinine or cystatin C. Is one approach better than the other?

John Toffaletti: Well, there is certainly differences of opinion on this. But I regard them as largely equivalent because the eGFR is really a creatinine or in some cases a cystatin C that had been mathematically manipulated to look like a GFR.

So, the GFR and/or -- actually, the measured GFR as well, that Dr. Bayliss said is really a very useful for initially evaluating or staging a person's kidney function and possibly using that as an aid for referral to dialysis or transplant.

So serial or longitudinal monitoring of creatinine or cystatin C and a patient provides a parameter to reliably detect significant changes in kidney function and another very important point is that with the recent concerns of racial

disparities, let me emphasize that if you can establish a person's baseline creatinine concentrations, followed by serial or longitudinal monitoring of creatinine over time, that eliminates the variables of sex, race, nationality, body size, and largely age. Thus, it really overcomes many of the shortcomings of creatinine.

George Bayliss: So, I'll go back again and say it again. I measure, in seeing an individual patient, I measure the stage of chronic kidney disease with eGFR to look at broad changes over time but I look at the changes in creatinine more acutely to see how quickly somebody may be progressing.

In the transplant setting, we use changes in serum creatinine almost entirely and decide whether there's a problem that we need to intervene in with the biopsy, and they could be rather subtle changes. Someone has a baseline creatinine of 1.1 and stays in a narrow range and suddenly it's 1.3, 1.4. It's not a big change but it tells me that their function is declining and it may be because of either rejection or infection and the eGFR wouldn't tell me anything because they're still within the same, roughly in the same category.

Randye Kaye: All right. Thank you. So, the measured GFR doesn't seem to be the ideal test for a kidney function. So, why is this and what are the limitations?

John Toffaletti: Well, I believe this is a really very important point and that there's no doubt that glomerular filtration is a most important, maybe the most important, physiologic function of a kidney. However, that does not necessarily make it the best diagnostic parameter.

I'd like to give an example, think of the heart. So, cardiac output is clearly the most important function of the heart, but for diagnosing and monitoring cardiac risk and myocardial necrosis, our troponins are clearly superior.

George Bayliss: So, nephrology moved from looking at serum creatinine and creatinine clearance as the main assessment of kidney function on the basis of -- there are differences in serum creatinine's among people. It's not really a good population measure because different people metabolize it at the same rate.

John Toffaletti: Absolutely, yes.

George Bayliss: So, a 220-pound football player, 6'2", has a lot of muscle mass. They may have a creatinine of 1. The real function is clearly better than a sarcopenic 90-year-old who has a creatinine of 1. So, what the GFR did was allow us to say, all right, let's calculate this in a way that can show the difference on a population basis. But within individual, that football

player may have a dynamic creatinine that's your result of some underlying disease. The sarcopenic patient may have had a stable creatinine for many months, many years, and so, that tells me at least within the individual that somebody is stable. But in terms of trying to stage their disease, the eGFR is really the standard for staging chronic kidney disease.

Randye Kaye: All right, thank you. Now, I noticed in your article it notes that several studies have shown that both physiologic and methodologic variation with measured GFRs. Why are the measured GFRs so variable?

John Toffaletti: Well, a person's GFR has both physiologic and diurnal variations. Plus, there is considerable methodologic variation. That is, our GFR varies from hour to hour and from day to day, but that is as it is supposed to be. Our GFR is not supposed to stay constant. The kidneys are trying to maintain the homeostasis of our blood. So, glomerular filtration along with tubular reabsorption, tubular secretion. They do those as needed for this purpose.

For methodologic variation of measured GFR, several studies have shown that methods for measuring GFR have large analytical variation, and often really do not agree with each other. Whether done by iothalamate, by iohexol, by inulin even, or by creatinine GFR. Basically, we should not regard measured GFR as gold standards, even though that seems to be a very, very common sight that quote in the publications.

George Bayliss: Yeah, I agree that variation in GFR over time depends on a lot of things. The patient's volume status, how much fluid they're taking in, how much salt they're taking in. It could be affected by fever. It could be affected by any other pathologic process that's going on. But even somebody who's healthy is going to vary based on changes in blood pressure.

Randye Kaye: All right, thank you. So, serum creatinine and cystatin C do not seem to exhibit this degree of daily variation. So, why is that?

John Toffaletti: Well, that's a great question that I can only speculate on an answer. I'd like to know if somebody's really studied that in great detail as to why. But I'm guessing that our blood concentrations of these markers kind of average out over the hourly fluctuations of our GFR. That is GFR changes rapidly while serum markers may react more slowly to these changes.

George Bayliss: Yeah, the serum markers are simply reflect the amount of clearance. We're breaking down muscle at a steady rate. Cystatin is going to be present in the blood at steady rate but the clearance from the blood is going to vary as renal blood flow varies. So, it's really the change in renal blood flow and

renal clearance that determines what the serum level is going to be.

Randye Kaye: All right, thank you. And finally, your article closes with some future needs for further improving the utility of serum creatinine and cystatin C testing and interpretation. So, can you each describe what are some of those future needs?

John Toffaletti: Yes. For detecting changes in longitudinal monitoring of creatine in a person or a single individual, I believe that analytical precision should be the highest priority for creatinine methods. And this is not going to be easy because it may require manufacturers to redevelop their creatinine methods to achieve that goal of higher precision. That may be things like changing the time of measurement, maybe go into more enzymatic creatinine methods, things like that. It's not going to be easy.

Finally, let me emphasize that we do not need more equations, which is one of the recommendations of that major NKF ASN report in 2021. Let me say again, we do not need more equations in attempt to make the eGFR agree with a measured GFR. Which has always required accepting a plus or minus 30% difference and if you look the plus there always a huge amount of scatter there and I want you to think about what a plus or minus 30% difference can mean. For example, if your actual GFR is 80, that would mean to accept anywhere from 56 to 104, which would be anywhere from possibly significant kidney damage to totally healthy.

So, being largely based on creatinine, the eGFR is a more reliable parameter, is certainly far less expensive, less invasive, and much faster. So, I believe we should try to make that as good as we can.

George Bayliss: Cystatin C is going to take some time. Still in clinical practice it's more of a research tool. So, not all of us -- not every lab runs it, and so, for those of us who work in a healthcare setting that only uses creatinine, that's what we're familiar with. But if cystatin C becomes more widespread and as we use the two of them in combination, that's going to take some time for clinical nephrologists to get used to looking at the variations in cystatin C. Independent of the standardization of labs. But the standardization of labs is going to be essential as well.

John Toffaletti: Right. I believe that cystatin C and creatinine would make a great pair of tests to have all the time, but there's a matter of cost and, more immediately availability, and we do not do cystatin C yet here at Duke. We certainly thought about it and may do it one day but I think if it was no extra cost, I think it would be a great combination to have all the time.

Randye Kaye: Thank you so much. Doctors, thank you so much for joining us here today.

John Toffaletti: Certainly welcome.

George Bayliss: Well, thank you very much. Thank you for inviting me to participate.

Randye Kaye: That was Drs. John Toffaletti and George Bayliss, describing the *JALM* Article "Utilizing Longitudinal Within-Individual Changes of Serum Creatinine, Cystatin C, and/or eGFR to Optimize Clinical Sensitivity and Eliminate Race and Gender Corrections."

Thanks for tuning into this episode of JALM Talk. See you next time and don't forget to submit something for us to talk about.