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Validation of a Metabolite Panel for a More Accurate Estimation of Glomerular Filtration Rate Using Quantitative LC-MS/MS

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Guest: Dr. Josef Coresh, Professor of Epidemiology, Biostatistics, and Medicine at the Johns Hopkins University Bloomberg School of Public Health in Baltimore.

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

Glomerular filtration rate, or GFR, is generally accepted as the best overall index of kidney function, and a decrease in GFR has important implications for prognosis in patient management. GFR is most commonly estimated by calculation, using the serum concentration of an endogenous filtration marker such as creatinine and demographic variables such as age, sex, and race.

In the March 2019 issue of *Clinical Chemistry*, a paper investigated the possibility of developing a more accurate estimate of GFR, using a panel of metabolites measured by quantitative liquid chromatography, tandem mass spectrometry without creatinine, cystatin C, or demographic variables.

As our guest in this podcast, we have one of the authors of that paper, Dr. Josef Coresh. He is the George W. Comstock professor of epidemiology, biostatistics, and medicine at the Johns Hopkins University Bloomberg School of Public Health in Baltimore. He has been involved with his co-workers at Hopkins in developing equations used for estimating kidney function that have been applied globally.

So Dr. Coresh, estimates of glomerular filtration rate calculated from serum creatinine are reported by nearly all clinical chemistry laboratories. What are the strengths and limitations of current GFR estimates?

Dr. Josef Coresh: Serum creatinine-based estimates of GFR are powerful predictors of a wide range of clinical outcomes. They define over a one thousand-fold risk gradient for kidney failure and are strong predictors of other outcomes including acute kidney injury, cardiovascular disease, and hospitalization. Therefore, they are reported by nearly all clinical chemistry laboratories. However, we do know that estimated GFR can be imprecise and in some settings, biased. In general population studies, the overall accuracy of estimated GFR is

80 to 90 percent of the estimates being within 30 percent of the measured GFR.

The main limitation comes for patients with large, non-GFR influences on serum creatinine, such as loss of muscle and chronic kidney disease. In addition, more accurate estimates are desirable in settings where estimated kidney function leads to major decisions, such as eligibility for kidney donation, dosing of medications cleared by the kidney with a narrow therapeutic range, or decisions in chronically ill patients such as advanced liver or heart failure.

Bob Barrett: In your paper, you appear to be taking a completely different technique. How does your publication use metabolomics to advance GFR estimation?

Dr. Josef Coresh: What we did is we used untargeted metabolomics to identify promising, additional filtration markers beyond serum creatinine. Serum creatinine is a small metabolite. And now, we were able to work with Metabolon to screen over one thousand different other metabolites. We then took the most promising metabolites, and we worked with Metabolon to develop targeted mass spectrometry assays with high precision to quantify the leading candidates. We then developed a GFR estimating equation, which combines the information from four metabolites, to estimate measured GFR.

The new equation was developed in a random subset of 1,615 participants, and evaluated in an independent sample of the remaining 809 participants. And then we looked at usual metrics of accuracy.

Bob Barrett: How does GFR metabolite estimate compare to current estimates?

Dr. Josef Coresh: The newly-developed GFR estimate based on four metabolites can provide an estimate without demographics. That means that this estimate no longer needs adjustment of the lab measurements for age, sex, or race. In terms of accuracy performance, if we look at the 1-P30, or the percentage of the time that the estimate has errors greater than 30 percent, the metabolite estimate without demographics has an error rate of 10 percent, which was more accurate than the 13 percent error rate with estimated GFR from creatinine and demographics in the most commonly-used state-of-the-art equations.

It was also more accurate than estimated GFR by cystatin and demographics at 12 percent. However, it is noteworthy that it was not more accurate than a combined equation which used creatinine and cystatin, which had an error rate

of 8.7 percent. In fact, if we want to make a fairer comparison and allow the metabolites to be enhanced by creatinine, cystatin, and demographics, then we did have an equation presented in the paper which led to the most accurate error rate of 7 percent of estimates being outside of 30 percent of the measured GFR. And these equations performed well across different subgroups of the population.

So, in summary, we can get an estimate for metabolites that is a pure estimate that can be a follow-up estimate to a creatinine, when creatinine is not performing well, that will give better accuracy than creatinine would have performed, had it done well, and better accuracy than cystatin alone. However, if creatinine and cystatin are doing well, this estimate will not do better than they would have done themselves in populations where they do well.

Bob Barrett: Well finally, doctor, let's look ahead. What do you see as the next steps in this line of investigation?

Dr. Josef Coresh: I see two lines of future work. The first natural extension is to take the current assay to clinical use. This would involve both scientific and commercial considerations. Scientifically, one needs to make sure that the lab conducting the assay maintains the high accuracy and stability shown in this research study. And then, if one goes to a commercial, making the assay available, one needs to define the target clinical uses, show that you perform well in those populations, and understand reimbursement mechanisms for actually getting the assay into the market.

Independently, we're actually pursuing further improvement of the assay itself, in that we think that if we develop an assay that's even better, then the commercial case would be easier. So we submitted a grant to screen more metabolites with the goal of developing an even larger panel of metabolites. Having more than just the four metabolites should get us greater accuracy as well as better generalizability.

We're hoping that with advanced statistical algorithms, like machine learning that has been done for other things, we could then have lower reliance on any one metabolite, and it would mean that we would have also robustness if one metabolite did not agree with the other ones in estimated GFR, it could receive a lower weight or be discarded altogether, and therefore we would get to a much more robust estimate.

So, our eventual goal is to have an easy-to-conduct blood assay that provides similar accuracy and generalizability to the more labor-intensive direct measurement of GFR. This would provide a follow-up procedure that is much needed to

the initial estimate of GFR by serum creatinine, which is widely used, but in many cases has an elevated error rate where patients have altered muscle mass.

Bob Barrett: That was Dr. Josef Coresh, Professor of Epidemiology, Biostatistics, and Medicine at the Johns Hopkins University Bloomberg School of Public Health in Baltimore. He has been our guest in this podcast on a potentially new way to estimate glomerular filtration rate using a panel of metabolites. He is a co-author of the paper describing that approach that appears in the March 2019 issue of *Clinical Chemistry.* I'm Bob Barrett. Thanks for listening!