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Which Methods for Determining Glomerular Filtration Rate Most Strongly Associate with Risk of Progression of Kidney Disease?

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Guest: Dr. Anders Berg is the Associate Medical Director of the Core Laboratories at Cedars-Sinai in Los Angeles.

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.

In the March 2019 issue of *Clinical Chemistry*, Professor Andrew Levey and others from a multinational consortium of institutions, published a study titled, "Validation of a Metabolite Panel for a More Accurate Estimation of Glomerular Filtration Rate Using Quantitative LC-MS-MS."

In fact, we have another podcast from one of the authors of that paper available. But today, we're joined by Dr. Anders Berg, the Associate Medical Director of the Core Laboratories at Cedars-Sinai in Los Angeles, who co-authored an editorial that accompanied the paper.

Dr. Berg is here to help us deconvolute the significance of this intriguing study and where this research might lead us in the future. So, first, Dr. Berg, for our listeners less familiar with tests for kidney function, can you give us some review on the significance of glomerular filtration rate?

Dr. Anders Berg: As most physicians and clinical chemists are aware, renal function is monitored by measuring the primary function of the kidney, which is filtration of the blood by kidney nephrons. Estimation of glomerular filtration rate, or eGFR has become the primary means of assessing patients' kidney function. And measurement of creatinine, an estimation of eGFR, thus becomes one of the most widely used and useful tests in the modern clinical chemistry laboratory.

Bob Barrett: How is glomerular filtration rate measured?

Dr. Anders Berg: The gold standard method for measuring glomerular filtration rate, or GFR, is by direct methods. Renal filtration rate was originally measured by administering renally filtered substances such as inulin and measuring their clearance in the urine compared to circulating concentrations. Although this is still the gold standard method, it is not applicable for routine clinical use.

In 1948, Jan Brod and Jonas Sirota proposed that renal filtration rate and function could be evaluated based upon urinary clearance of endogenous creatinine, allowing doctors to measure kidney function without having to administer inulin or other renally excreted tracers.

They demonstrated that renal clearance of creatinine was approximately equal to that of exogenous inulin. Thus, measuring serum and urine creatinine allowed for a reasonable estimation of renal filtration rate. The only limitation to this approach was that it required accurate measurement of urinary creatinine excretion through a 24-hour timed collection of urine, which lessened its practicability for rapid assessments of renal function.

In 1976, Cockcroft and Gault proposed that creatinine clearance could instead be estimated based upon measurement of serum creatinine concentrations alone without measurement of urinary creatinine clearance. This concept was based upon the assumption that most adults produce approximately 1 gram of creatinine per day. And thus, instead of directly measuring urinary creatinine excretion rate, they simply assumed all patients excreted similar amounts of creatinine within a 24-hour period.

They were aware, however, that a number of factors modify this assumption because of differences in creatinine production rate. In order to accommodate these differences, the Cockcroft and Gault equation included modifiers for age, weight, and gender.

In 1999, Levey and other investigators participating in the Modification of Diet in Renal Disease—or MDRD—Study published a new equation which expressed glomerular filtration rate as milliliters of blood per minute per 1.73 m^2 of body surface area. This adjusted for differences in the size of the patient. The new equation also included an adjustment for patients with black ethnic heritage.

Later in 2009, Levey and others published an updated equation for eGFR called “CKD-EPI,” which was based upon a larger data set and which adjusted for age, sex, gender, ethnicity, and was shown to be more accurate than the MDRD algorithm, particularly in patients with GFR values above 60.

Bob Barrett: So, is serum creatinine the only assay method clinically available for estimating GFR, and if not, is it the preferred method?

Dr. Anders Berg: Although Cockcroft and Gault, MDRD, and the CKD-EPI methods for estimating filtration rate based upon serum creatinine concentration have all been clinically useful

approaches, they each suffered from frequent discordance between measured and estimated GFR value in some patients.

For example, 19.4% of MDRD values and 15.9% of CKD-EPI estimated values deviate from the actual measured GFR by more than 30%. This limitation drove the need to develop additional biomarker approaches.

Cystatin C is a small molecular weight protein that is constitutively synthesized by most nucleated cells and freely filtered by the glomerulus. Cystatin C-derived estimated GFR has been shown to be significantly more accurate than creatinine-based estimates. And equations which use both creatinine and cystatin C have been shown to be even more accurate.

Bob Barrett: So, with all the methods available for measurement of creatinine and cystatin C and the equations for estimating GFR, what was the motivation by this group to develop a new method for estimation of GFR?

Dr. Anders Berg: Despite steady progress toward an optimal test for estimation of GFR, the analytical accuracy of even the best available methods are still comparably poor compared to assays used in other clinical areas. Even when GFR was estimated based upon both creatinine and cystatin C, 8.5% of the values showed more that 30% bias compared to directly measured GFR values.

It's not unreasonable to expect that diagnostic assays should normally be within 30% of the true value 100%, of the time. The authors of this new study suggested that there may be unavoidable challenges to developing a perfect GFR based upon creatinine or cystatin C measurements, however.

Creatinine assays based on the Jaffe method have been shown to be limited in their accuracy and precision. Creatinine-based eGFR measurements may be affected by Asian or Hispanic race, muscular versus obese body habitus, chronic illness, meat enriched or a vegetarian diet. Also, cystatin C-based eGFR measurements may be affected by corticosteroid use, weight, height, smoking status, the level of C-reactive protein, and relatively common genetic variants of the cystatin C gene.

Bob Barrett: And how did these authors circumvent these challenges?

Dr. Anders Berg: They reasoned that there may be other renally excreted biomarkers that accumulate in the blood of patients with reduced kidney function, and which may more accurately reflect filtration rate. They developed a multiplex assay in

high-performance liquid chromatography and tandem mass spectrometry that measures a novel panel circulating the serum biomarkers of renal filtration.

Each of these biomarkers are independently correlated with GFR. By combining all four markers into a single model, they were able to estimate GFR with greater accuracy than creatinine or cystatin C-based methods alone. And when creatinine and cystatin C values are also incorporated into their model, it produced the most accurate eGFR values of any of the approaches.

Bob Barrett: Doctor, what conclusions did the authors make from the results of their study?

Dr. Anders Berg: The authors concluded that their new method may be clinically useful for confirmation of abnormal kidney function. In other words, they suggested that when a patient's eGFR is measured using creatinine or cystatin C-based methods and the values are near an important clinical decision point, the results could be confirmed using their multiplex assay method.

Although this is a reasonable suggestion, further studies are needed before this could be recommended in a clinical setting. Their mass spectrum metric assay is an LDT and would be difficult to implement in a local hospital setting. As an alternative, it could be argued that patients with abnormal GFR values instead deserve to have their GFR measured using a direct method, although it should be pointed out that this approach too would have to be validated and go through FDA review for routine clinical use.

Bob Barrett: Why do you think these alternative biomarkers of renal function more accurately reflected GFR compared to creatinine and cystatin C?

Dr. Anders Berg: The fact that the accuracy of this test improved with each additional independent renal function biomarker suggests an important principle. Individually, each marker is an indicator of renal function, but it's also affected by other patient-specific variables, limiting its accuracy. Together, however, the combination of multiple markers seemed to have an additive effect on the accuracy of the assay.

Bob Barrett: Well, finally, Dr. Berg, are there any other conclusions you would like to add regarding the study?

Dr. Anders Berg: The relationship between this novel panel of biomarker in renal function deserves further investigation. One of the markers that correlate with eGFR was serum tryptophan, but it was negatively correlated with GFR.

Tryptophan is an essential amino acid whose physiology is unlike creatinine or cystatin C. It is taken in through the diet and actively reabsorbed by the kidneys. The fact that it correlates negatively with eGFR actually suggests a problem with tubular reabsorption, which is a different pathophysiology entirely.

Future studies are needed to understand how this novel biomarker panel may relate to renal physiology disease progression and how well it predicts clinical adverse outcomes related to kidney disease.

It may be that retention of these specific renally excreted metabolites are more predictive of clinical outcomes and response to specific therapies. Thus, instead of looking for assays which are best correlated with measured GFR, perhaps we should be asking which of the many methods of determining GFR and assessing kidney function are most strongly associated with risk of progression of kidney disease and expand our understanding of renal physiology.

Bob Barrett: That was Dr. Anders Berg, the Associate Medical Director of the Core Laboratories at Cedars-Sinai in Los Angeles, who co-authored an editorial in the March 2019 issue of *Clinical Chemistry* on the development of a new method for estimation of glomerular filtration rate. I'm Bob Barrett. Thanks for listening!