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Optimal Use of Biomarkers for Chronic Kidney Disease

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Guest: Dr. Greg Miller is a professor in the Department of Pathology and Director of Clinical Chemistry at Virginia Commonwealth University.

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.

Chronic kidney disease, or CKD, affects approximately 15% of the U.S. population. People with diabetes, hypertension, cardiovascular disease, family history of CKD, as well as several ethnic groups are at increased risk for CKD. There are two primary laboratory tests for diagnosis of CKD. The first is serum creatinine concentration, along with a calculation of estimated glomerular filtration rate, called EGFR based on that creatinine result.

The second is performed with urine samples, and here both albumin and creatinine are measured and the ratio of those two tests calculated. A challenge for care of people living with chronic kidney disease has been poor awareness of having the disease, because there are no symptoms until advanced stages and people at risk are not adequately screened with the laboratory tests. In the 2013-2016 U.S. National Health and Nutrition Examination survey, only 8% of the population with abnormally low EGFR results were aware of having CKD.

In the August 2019 issue of *Clinical Chemistry*, a Q&A feature titled "Optimal Use of Biomarker for Chronic Kidney Disease" asked five experts in laboratory medicine and nephrology to examine laboratory ordering, testing, and reporting practices, and recommend how those practices should be optimized to better serve patients with CKD.

In this podcast, Dr. Greg Miller from the Department of Pathology at Virginia Commonwealth University in Richmond who moderated the Q&A will summarize the expert advice from his colleagues. So first off, Dr. Miller, just what is a kidney profile and when should it be ordered?

Dr. Greg Miller: Well, a kidney profile is an order set consisting of serum creatinine and urine albumin and creatinine. The main reportable results are the estimated GFR and the urine albumin creatinine ratio that are most useful to identify

people with chronic kidney disease and to classify the risk status. There is not currently a CPT code for billing the kidney profile in the United States, but the individual measured test values are billable irrespective of how they are ordered.

A Laboratory Advisory Group convened by the U.S. National Kidney Foundation recommends implementing the kidney profile for targeted testing of risk groups such as patients with hypertension, diabetes, cardiovascular disease, rheumatic conditions, or who have a family history of CKD. The kidney profile is also useful for patients with known CKD to evaluate the progression which is defined as a change in GFR over time.

Bob Barrett: I'm wondering, how does a kidney profile differ in use from a renal function panel?

Dr. Greg Miller: The kidney profile includes only tests to detect CKD, or chronic kidney disease, and to classify its severity based on the levels of the estimated GFR and albuminuria. The renal function panel consists of a larger number to tests: serum glucose, creatinine, urea nitrogen, calcium, phosphorus, albumin, sodium chloride, potassium, carbon dioxide and anion gap. The renal function panel is used to detect complications of CKD such as abnormalities of mineral metabolism, nutrition status, hyperkalemia, or acidosis, that typically occur when the EGFR falls below 30 to 40 mL per minute per 1.73 m^2 of body surface area.

A renal function panel is also useful at higher eGFR values to set a baseline to evaluate progression of complications. A renal function panel can also be used to evaluate side effects of medications such as hyponatremia, hypokalemia, or metabolic alkalosis from diuretics. Glucose concentrations are important as hyperglycemia can cause acute kidney injury as well as increased risk for CKD progression.

Bob Barrett: What is the preferred equation to estimate eGFR from serum, plasma, or blood creatinine?

Dr. Greg Miller: Well, the two common eGFR equations for use of creatinine are the IDMS traceable version of the modification of diet and renal disease--we call that the MDRD Study equation--and the chronic disease epidemiology collaboration equation, referred to as the CKD-EPI equation, which was developed using IDMS-traceable creatinine results. Both of these equations are valid for patients over the age of 18 and contain variables that adjust the eGFR to account for creatinine differences due to age, gender, an African-American versus non-African-American ethnicity. Use of

these variables improves agreement of the estimated GFR with GFR measured using inulin or iohexol clearance.

The CKD-EPI equation is more accurate and less biased than the IDMS-traceable MDRD Study equation in the population with EGFR near and above about 60 mL/min/1.73 m^2. The IDMS-traceable MDRD Study equation underestimates GFR when values exceed 60. Therefore, such values should be reported as ≥ 60 mL/min/1.73 m^2 when using the MDRD equation. With the CKD-EPI equation, there is no increase in error at higher levels of GFR and therefore the eGFR can be reported through the full range of GFR.

Observational studies comparing these two widely used equations show the CKD-EPI creatinine equation more accurately predicts adverse kidney, cardiovascular, and mortality outcomes for people with CKD. There is a strong need to harmonize the equation used and thus decrease the variability in eGFR values among different laboratories, supporting uniform use of the best available CKD-EPI equation. For these reasons, the kidney disease improving global outcomes, usually called KDIGO 2012 guideline, and U.S. National Kidney Foundation both supports using only the CKD-EPI equation.

It is important to remember that all estimating equations have errors relative to measured GFR. The 2002 Kidney Disease Outcomes Quality Initiative guidelines concluded that an eGFR within 30% of a measured GFR was satisfactory for clinical interpretation. Errors will be greater for people who have non-GFR determinants that are different than the populations from which the equations were derived, for example, vegetarians, bodybuilders, or people with muscle wasting diseases. In children, the “Bedside” Schwartz equation is suitable for use with creatinine results from IDMS-traceable enzymatic creatinine measurement procedures and is recommended in pediatric patients.

Bob Barrett: Should enzymatic methods replace Jaffe-based methods for measuring creatinine?

Dr. Greg Miller: Jaffe creatinine measure procedures are typically influenced by interferences from what had been called pseudo-chromogens, or non-creatinine chromogens, in the reaction. These include glucose, protein, pathological amounts of acetoacetate, acetone, ascorbate, pyruvate, and many drugs such as dobutamine and cephalosporin present in serum plasma. Attempts to reduce the influence of interfering substances in Jaffe methods by using kinetic measurements and compensated methods are common but only partially successful. The compensation approach subtracts a fixed value from the creatinine measurement to

adjust for the average amount of pseudo-chromogens in adult serum or plasma. When abnormal amounts of pseudo-chromogens are present, the compensation is inadequate and erroneously high creatinine values typically occur. Of particular concern is pediatric testing when proteins in particular is lower than in adults causing falsely low creatinine results and an incorrect assessment of kidney function.

Because of their better analytical specificity, enzymatic creatinine methods have largely eliminated the analytical interferences caused by pseudo-chromogens. However, some enzymatic methods do have some interferences particularly from hemoglobin and bilirubin. Current automated measuring systems automatically check for hemolysis and elevated bilirubin, so a laboratory can easily identify affected creatinine results.

Investigations of patient sample results measured by both Jaffe and enzymatic methods have shown reduced bias for enzymatic methods compared to the IDMS reference measurement procedure and better precision performance than for Jaffe methods. The superior analytic performance of enzymatic method is particularly important that the critical decision value of 60 mL/min/1.73 m^2 of body surface area for classifying patients with CKD and for pediatric patients who have lower creatinine values even in the presence of kidney disease.

So, in summary, laboratories should use enzymatic methods for improvements in all aspects of performance. This is particularly important in pediatric samples and is formally recommended in Australian guidelines. However, in resource-limited parts of the world, the use of Jaffe method is less expensive, but attention should always be given to ensure IDMS-traceability of the calibration.

Bob Barrett: Doctor, when should cystatin C be ordered?

Dr. Greg Miller: Cystatin C is a protein produced by all nucleated cells and is freely filtered through the glomerulus. Its principal advantage over creatinine is that cystatin C is not affected by muscle mass. Consequently, cystatin C is used as a confirmatory test in situations when eGFR from creatinine is less reliable. Creatinine production is abnormally low for example in sarcopenia, in patients with a low muscle mass due to a neuromuscular disorder, muscle wasting disease, limb amputation, malnutrition, or vegetarian diet. Creatinine is abnormally high in situations such as bodybuilders, elite athletes, those taking creatinine supplements or on a high red meat diet. Cystatin C should be considered when a more accurate level of eGFR is needed for clinical decisions. For example, administration or dosing

of toxic medications cleared by the kidneys, such as cisplatin, carboplatin, several antibiotics or contrast agents. eGFR from cystatin C is also useful for decisions for kidney donation or determination of GFR prior to decisions for heart or liver transplant alone or simultaneous with kidneys. In most populations, several studies have demonstrated that the eGFR from an equation that combines creatinine and cystatin C provides the most accurate estimate.

The 2012 KDGO CKD Guideline recommends assessment of cystatin C in persons with creatinine-based eGFR between 45-59 mL/min//1.73 m^2 without any albuminuria based on data showing that the eGFR from creatinine may misclassify CKD.

Persons with eGFR based on creatinine between 45 and 59 without albuminuria and whose eGFR from the combined creatinine cystatin or from cystatin alone values are above 60 have a very low risk for CKD complications. Estimating equations that incorporate cystatin C require standardized calibration of serum cystatin C measurement procedures to the certified reference material ERMDA471/IFCC Human Serum (Cystatin C) introduced in 2010.

Bob Barrett: When should urine albumin and/or urine total protein be measured in patients with chronic kidney disease?

Dr. Greg Miller: Serum creatinine is a measure of a number of functional nephrons. Albuminuria allows assessment of the quality of the glomerular membrane itself. Urea albumin and urine total protein tests are often used interchangeably in practice. The urine albumin creatinine ratio is a more sensitive and specific measure of kidney damage. Moreover, only the urine albumin is currently being standardized whereas the urine total protein will probably never be standardized. For these reasons, urine albumin is the preferred test for routine screening of targeted risk groups such as diabetes, hypertension, cardiovascular disease, relatives of patients with end-stage renal disease, systemic vasculitis, recurrent urinary tract infections, and in patients with a history of chronic non-steroidal anti-inflammatory drug intake.

For glomerular disease, urine albumin should be approximately 60%-70% of the urine total protein present. Most kidney diseases, such as diabetes or hypertension, affect the glomerulus. Consequently, for most causes of kidney disease, theoretically both albumin and protein can provide similar information. However, because assays for albumin are more accurate and can detect lower concentrations, urine albumin is recommended as the primary test to detect CKD. However, there are conditions where the presence of non-albumin proteins is important to

detect. The most important are immunoglobulins which could indicate myeloma or more generally monoclonal gammopathy of renal significance. Thus, both total protein and albumin should be ordered when physicians are concerned about these conditions, and if the total protein is more than 30% greater than the urine albumin, it might indicate non-albumin proteins in the urine, and further diagnostic tests should be considered.

Bob Barrett: Well finally then doctor, how should urine albumin and the albumin creatinine ratio, or urine total protein and protein creatinine ratio, be reported?

Dr. Greg Miller: Historically, the urine albumin excretion rate calculated from a 24-hour urine collection was the gold standard test used for assessing albuminuria. Due to frequent incomplete collection of 24-hour specimens, the urine albumin to urine creatinine ratio (UACR) is now recommended by most practice guidelines including the KDIGO 2012. The urine albumin creatinine ratio from a first morning void has been shown to have equivalent diagnostic accuracy to a properly collected 24-hour urine albumin excretion.

Physicians need to know the quantitative amount of the urine albumin creatinine ratio to properly manage risk and progression of CKD, as well as the effectiveness of treatment. When urine albumin values exceed the upper limit of the analytical measuring range for that measurement procedure, the urine should be diluted, re-measured and a quantitative value reported. If a result is obtained that exceeds the extended measuring interval for diluted samples, a result for the albumin and the urine albumin creatinine ratio should be reported as “greater than” the maximum value that could possibly be obtained for the upper limit of the extended measuring interval after the dilution procedures.

The terms “microalbumin” and “microalbumin” also caused confusion since practitioners may incorrectly conceptualize that microalbumin testing is for excretion of a small albumin molecule rather than elevated level of urinary albumin excretion. Recent clinical practice guidelines recommend that the term “microalbumin” be replaced with “urine albumin” as the name for the test, and the result always be reported as a ratio of albumin to urine creatinine.

The units for measuring urine albumin and creatinine are not uniformed and can cause confusion for physicians. Reporting units for urine albumin should be mg/L and for urine albumin creatinine ratio should be mg/g creatinine or mg/mmole of creatinine depending on in what country a laboratory is located.

Bob Barrett: That was Dr. Greg Miller from the Department of Pathology at Virginia Commonwealth University in Richmond. He has been our guest in this podcast from *Clinical Chemistry* on "Optimal Use of Biomarkers for Chronic Kidney Disease." That Q&A feature appears in the August 2019 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening!