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Rethinking Albuminuria in Low-Risk Patients and a Call for Urine Albumin Standardization

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Guest: Dr. Jesse Seegmiller is an Associate Professor in the Department of Laboratory Medicine and Pathology at the University of Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. The kidneys play a central role in many biological processes, including maintenance of fluid and electrolyte balance, acid base homeostasis, endocrine hormone production, and removal of waste from the blood. One of the first signs of chronic kidney disease is the presence of protein in urine and clinical guidelines suggest measuring urine albumin and creatinine to help diagnose disease and establish a prognosis.

In fact, long-established categories use the albumin to creatinine ratio, or ACR, to determine risk of disease progression, with A1 (low ACR) indicating minimal risk and A3 (high ACR) indicating severely increased risk. These standard guidelines are applied throughout the world at hospitals using a variety of albumin test methods and assume that albumin assays are interchangeable and generate identical results.

But what if urine albumin assays are not interchangeable? What implications would this have for patient care? A new perspective article, appearing in the February 2025 issue of *Clinical Chemistry*, summarizes the current state of urine albumin assay standardization and describes the impact of assay bias on the implementation of universal guidelines.

In this podcast, we welcome the article's lead author. Dr. Jesse Seegmiller is an Associate Professor in the Department of Laboratory Medicine and Pathology at the University of Minnesota. He is a board-certified clinical chemist and his primary research focus involves the study of kidney disease.

So, Dr. Seegmiller, in your recent publication, you briefly cover creatinine but really focus on urine albumin. Every time I get a blood draw from my primary care provider, I see the serum creatinine results on my lab report, but not urine albumin. Why don't they collect urine for an albumin measurement on me?

Jesse Seegmiller: That's a great question, Bob. Providers generally order a panel of tests for your yearly routine checkup. Creatinine is

an endogenous biomarker removed by the kidneys that is primarily used to estimate your glomerular filtration rate. This is also known as the GFR.

So, the GFR has proven to be one of the best overall measurements of a patient's kidney function. So, if your estimated GFR is considered healthy or normal, for example, say above 90 milliliters per minute or more, and you do not have a previous diagnosis of a disease such as diabetes, then a provider will likely not test your urine for protein, or specifically urine albumin, routinely.

Bob Barrett: Doctor, your article also mentions the urine albumin to creatinine ratio. Why do they calculate the ratio of albumin to creatinine and are they using serum creatinine to do this?

Jesse Seegmiller: Yeah, that's another great question. So, laboratories will measure urine albumin and urine creatinine to come up with the urine albumin to creatinine ratio and this is commonly referred to as the ACR. So, they're not using your serum creatinine result for this ratio, and the reason why they measured the ACR is that as we just discussed earlier, the creatinine is a marker of GFR and cleared typically by the kidneys.

The amount of creatinine in the urine provides a general assessment for how concentrated the urine is. For example, if you're dehydrated, the kidneys will likely compensate and retain water from your blood, which will make your urine more concentrated in solutes like metabolic products such as creatinine. Conversely, if you drink a bunch of water, you're likely going to dilute your urine.

If you measure the amount of urine albumin in either case, you're going to get this really conflicting result as the dissolved concentration of substances found in the urine will be at the extremes. With dehydration, substances the most concentrated and overhydration, you'll have urine solutes be most diluted.

So, by ratioing the urine albumin to creatinine, you in a way account for how concentrated the urine is in a patient without being tricked by, say, a healthy patient who just ran 10 miles and has concentrated urine with a small amount of albumin present in their urine. The same person will likely have a larger than normal amount of creatinine in the urine. This is why clinicians employ urine albumin to urine creatinine ratios.

Bob Barrett: Okay. Well, let's move on to some of the more interesting points in your manuscript. You highlight that urine albumin tests from different manufacturers could be off by 56%. How can these different methods be off by so much if they were approved by the FDA?

Jesse Seegmiller: Yeah, that's a really troubling point. I think it's a really unfortunate consequence of the FDA's approval process and diagnostic products. Typically, when a manufacturer goes through the FDA's approval process, they'll compare the results of their test to a predicate device, currently or previously that was on the diagnostic market and approved by the FDA. In the case of urine albumin, there are several manufacturers available. So, the diagnostic manufacturer, whoever they may be, they're going to work with the device that best represents their system and shows the best correlation of a diagnostic test that's already been approved by the FDA.

So, the manufacturer does not have to prove unambiguous accuracy through the FDA's process. It's more of a relative accuracy to a predicate device rather than an absolute accuracy for truth. So, if the FDA-approved in vitro diagnostic is off, this is going to be perpetuated through the new generations of the tests that come through the FDA's process.

Bob Barrett: Well, that's a bit of a conundrum for diagnostic medicine. Won't this cause issues with clinical laboratories using many different assays? And if so, how can this be fixed?

Jesse Seegmiller: Yeah, that's correct. One of the issues that we highlight in the paper is one manufacturer system, you can be diagnosed with albuminuria and another system you would not be. It's really a travesty for trying to monitor a patient's progression, which we highlighted in the manuscript that we wrote, that watching progression of even these small amounts of albumin can change and it's going to show progression.

So, if you switch from one manufacturer, let's say you moved, and the hospital system has a different manufacturer, they could be off by like 76%. Additionally, these diagnostic classifications are not driven by the manufacturers. They're really driven by guidelines, clinical guidelines, and these guidelines are not manufacturer-specific.

So, by having these differences so large between manufacturers is certainly going to result in misclassification due to the use of particular manufacturers. It's really an enormous problem. They can likely be fixed through test standardization of urine albumin.

Most people do not know this, but most FDA approved tests are not standardized. Fortunately, creatinine has been standardized years ago. So, the nephrology community has really been on the forefront of accurate diagnostic testing.

The problem with that is they do not know that many of these other diagnostic testing systems, which are approved by the

FDA, are not standardized. However, when you look at standardizing things like albumin that are using antibody-based systems, it's really not practical to characterize antibodies and it's really challenging, and it's really -- to be quite honest, impossible to do entirely.

Therefore, these standardization efforts are underway that are focused on using antibody-free technologies such as mass spectrometry-based assays that are considered laboratory developed test, or LDTs.

Bob Barrett: So, finally, doctor, we've seen all sorts of articles about the FDA's final rule for laboratory developed tests. Why would you use an LDT to fix an FDA approved test?

Jesse Seegmiller: Yeah, this is quite ironic, I think, that researchers need to develop methods in order to standardize current FDA approved tests. Really in my opinion, the FDA would better serve the public and our nation by turning their attention to the deficiencies and fix the systems that they have created and already approved rather than focusing on LDTs in the clinical laboratories.

The LDTs developed by researchers in clinical labs are being used for a reason. That reason is either there's a problem with the current FDA approved test, if one exists, or an FDA approved test does not exist. Every lab director or medical director I know would only use a test that is valid and performs well for their patient population.

We are bound to this through the Clinical Laboratory Improvement Amendments, also known as CLIA regulations. These tests have all underwent strenuous validation by the CLIA regulations and guidelines. These LDTs are then inspected by diagnostic experts, such as my certified and trained colleagues, in the field during regulatory inspections.

In the case of urine albumin, many approved diagnostic tests exist and none of which are standardized, thus requiring researchers to create a reference measurement procedure that is an LDT along with forming laboratory working groups to work at standardizing urine albumin measurements, with really the overall goal of improving patient care globally.

Bob Barrett: That was Dr. Jesse Seegmiller from the University of Minnesota in Minneapolis, Minnesota. He wrote a new perspective article calling for the standardization of urine albumin assays in the February 2025 issue of *Clinical Chemistry*, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.