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# Optimizing Estimation: Perspective on Drug Dosing Using New CKD-EPI Equations

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**Guest:** Dr. Walter Kraft is an internist and clinical pharmacologist at Sidney Kimmel Medical College in Philadelphia, Pennsylvania.

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 an essential role in many biological processes, and diminished renal function leads to complications ranging from anemia to cardiovascular disease and ultimately death. Not surprisingly, renal function is routinely assessed during annual physicals and at more frequent intervals in patients diagnosed with kidney disease.

The gold standard evaluation of glomerular filtration involves administration of an exogenous substance and measuring its removal from the body, but this is cost-prohibitive and impractical to perform at scale. As an alternative, several equations that estimate glomerular filtration have been integrated into routine clinical practice, serving as mostly adequate surrogates for measured GFRs.

The first of these, the Cockcroft-Gault formula, was established in 1976 using a non-standardized assay that is no longer routinely available, but despite the development of new assays and better formulas, Cockcroft-Gault is still used to guide medication dosing decisions in many clinical settings.

A perspective article, appearing in the October 2025 issue of *Clinical Chemistry*, focuses on the new National Kidney Foundation position paper recommending replacement of Cockcroft-Gault with the 2021 CKD-EPI equation, with particular attention paid to the pitfalls and challenges likely to be encountered during this transition.

In this podcast, we are joined by the article's senior author. Dr. Walter Kraft is an internist and clinical pharmacologist at Sidney Kimmel Medical College in Philadelphia. He has research interests in early-phase drug development, anticoagulants, and opioid exposure in neonates. He is the current chair of the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee.

So Dr. Kraft, first off, why is the working group suggesting use of EGFR to dose drugs when many drugs were approved using the Cockcroft-Gault equation?

Walter Kraft: So that's a good question, and Cockcroft-Gault is interesting in its longevity. It is an estimator generated in a relatively homogeneous small number of individuals, and it was designed to measure, or to estimate, creatinine clearance, when in fact, it is glomerular filtration rate that is more closely linked to drug disposition for renally eliminated drugs. So, creatinine is a proxy for GFR, but our estimator that goes to look at the actual parameter that is more predictive of the thing we're interested in, drug clearance, is one of the primary reasons that we are more interested.

Secondly is that the assay itself was quite variable. The values, in fact, for serum creatinine has decreased 12% over that time, and those standards for which were used at various labs no longer exist. So what we had defined in a drug label using Cockcroft-Gault, that is no longer the same standard that we would get now from that value of creatinine and the other parameters that we put into the equation.

Bob Barrett: What about body surface area de-indexing? Should that be done routinely, and if not, are there specific patients for whom this makes sense?

Walter Kraft: Yeah, so the output that we automated with the current eGFR is standardized to a body surface area of 1.73. Interestingly, that correlates about to a BMI-- they're different, of course-- of about 20, and this makes it easy to report, right? We don't need a patient's weight on our lab report forms. It is standardized to that 1.73. We know that the typical BMI of the United States inhabitant is much higher, and in fact, by 2030, we estimate that a large proportion of individuals will be substantially larger than that.

So, as we get higher in body mass, it makes sense to de-index to a value that is actually more normalized to what the actual body surface area would be. So the advantage of that standardized 1.73 is reporting out, but the end-user, the further that you vary from that standard value, the more accurate you will be in the de-indexing, essentially subtracting by 1.73, multiplying by their actual body surface area.

Bob Barrett: What are the circumstances in which cystatin C could aid an estimation of glomerular filtration?

Walter Kraft: So the standard, of course, right now is a creatinine-based estimator, but creatinine, the source, is muscle mass. So if you have large variations in muscle mass, and we use body weight as our proxy for muscle mass. So if you have

somebody that has an amputation, let's say, or has severe cachexia, their body weight is not as reflective of the amount of muscle secreting creatinine, then that estimator, or biomarker, will not be as accurate. And in these cases, cystatin, as a product from all nucleated cells, is more accurate.

Now, it's not perfect itself. Certain conditions, such as hypo- or hyperthyroidism, smoking, inflammatory diseases, or glucocorticoid excess, all can vary the cystatin values also. The best, if it's available, is the estimating equation that incorporates both. And in that way, you minimize any particular covariate that would impact this estimation of glomerular filtration rate.

Bob Barrett: Well, finally, Dr. Kraft, let me ask you this. What is the difference between estimation of creatinine clearance and estimation of glomerular filtration?

Walter Kraft: Yeah, so getting back to that Cockcroft-Gault, this was generated at a time in which the actual measurement of glomerular filtration was more difficult. Now, we can still do that. It is inconvenient. It's expensive. It's not done quite a bit. And in fact, that's probably one area in which perhaps me and the other editorialist had differed a little bit from the working group in how much we would suggest the use of an actual measurement of glomerular filtration using an exogenous substrate.

But in the case of the difference between the creatinine clearance and estimated glomerular filtration, it's really a reflection of the fact that the equations were optimized for two different things. One, creatinine, the proxy for the thing we're interested in, which is glomerular filtration rate. And second, our modern equation, which actually is optimized for glomerular filtration itself as an estimator.

Bob Barrett: That was Dr. Walter Kraft from Sidney Kimmel Medical College in Philadelphia, Pennsylvania. He wrote a perspective article in the October 2025 issue of *Clinical Chemistry,* discussing the impact of new glomerular function equations on drug dosing, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.