Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Reporting of estimated glomerular filtration rate calculated from serum creatinine and patient demographics is considered by many to provide a useful estimate of kidney function over and above the creatinine concentration alone.

Dr. Thomas Hostetter addressed how such reporting influences clinical practice in a perspective published in the September issue of *Clinical Chemistry*.

Dr. Hostetter is the Abraham Levitt Professor of Medicine and Director of the Nephrology Division at Albert Einstein College of Medicine in New York. He continues discussing the clinical impact of reporting estimated glomerular filtration rates in this podcast.

Tell us, Dr. Hostetter, why exactly should eGFR be reported every time a serum creatinine is determined?

Dr. Thomas Hostetter: Because it gives the clinician who ordered that test the real information that he or she wants. When you order a serum creatinine, you're really asking what the patient's kidney function is, and in particular the kidney function called glomerular filtration rate, or GFR.

Clinicians often just think that globally as kidney function, but that's the particular function that you are looking for, and the serum concentration of creatinine is a reflection of that kidney function, the GFR. So when the GFR, or its estimate, the eGFR is reported, you're really giving the person to order the test information closest to what they really want to know, namely, the kidney function.

Host: So, isn't reporting serum creatinine concentration good enough?

Dr. Thomas Hostetter: Well, it has been what we have used. The problem is that creatinine is produced in various rates by different people. So, in general people who have more muscle mass, so younger people and men make more creatinine every day. Women and older people make less creatinine every day. So they are at the same level of that kidney function, the GFR, they can have quite different serum creatinines.

So clinicians can be misled by seeing, for example, a serum creatinine that maybe just above the reference range, let's say 1.4 milligrams per deciliter. But if it's in

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an elderly woman, that denotes an estimated GFR or kidney function that's substantially reduced.

On the other hand that same level in a young muscular male maybe a GFR or kidney function that's in the normal range.

So because of those different rates of creatinine production, the serum creatinine when used by itself can be misleading as an index of GFR.

Host: Now, lots of people, especially the elderly have eGFRs in a range that some would classify as some stage of chronic kidney disease. Shouldn't there be an age adjustment in the reporting?

Dr. Thomas Hostetter: Well, that has been a suggestion, because we know that this creatinine production tends to go down with age as muscle mass goes down, but we also know from independent measurements of GFR, that is independent than creatinine, that it also tends to decline with age. The net effect of that is that serum creatinine can stay kind of stable even though GFR is going down as people age.

I am leery about age-adjusting in the reporting of estimated GFR for a couple of reasons. One, as I mentioned, as we age everybody's GFR goes down, and then probably in some circumstances is worth knowing. We also know I am a nephrologist who takes care of people with chronic kidney disease and kidney failure. We also know that the elderly are a group that's growing rapidly in terms of having kidney failure and requiring dialysis or even transplantation. So, it's clinically pertinent that elderly people who have a GFR that's reduced be noticed.

Then lastly many other things that people are treated with and tested with have damaging effects on the kidney and should be either avoided or things like non-steroidal anti-inflammatory drugs, or at least reduced in amount or used sparingly. For example, certain antibiotics are even some of the contrast agents that are used for x-ray studies.

So, since the elderly get more drugs and more testing, we think it's very important to know that someone has a low GFR and not just entirely ascribe that perhaps to something that's "normal" for age.

Host: In your opinion what should clinicians do when they receive a report of eGFR less than 60 milliliters per minute?

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Dr. Thomas Hostetter: A couple of things. One, it depends a little bit on how much less than 60 milliliters per minute, but to take the most common circumstance where it's only a little below it, let's say in the 50 ml per minute range. One first step is to look back at the past record of what the patient's creatinine and estimated GFR have been.

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If this is a new finding then I think you need to take another couple of steps. One is to look at the context or what other things are going on with the patient. If the patient has diabetes or high blood pressure, then there may be very strong reason why they are developing kidney disease.

In general, the test probably should be repeated in most circumstances within a week or two to make sure that that value below 60, really is below 60, and it's a good time to actually check the urine albumin excretion, or one can really measure the urine albumin to urine creatinine concentration ratios as another index of how important that depressed level of 60 may be or not. If there is albuminuria then it's probably more important than otherwise.

But I think it's also—once those are done, it's important to have a discussion with the patient. Again, taking the example, which is probably the most common, that it's a minor depression in the 50s to let that person know that it needs to be followed, and it may be quite stable with no other ramifications, but that they probably should avoid drugs like the non-steroidal anti-inflammatory drugs and things like Advil and Motrin and that kind of thing, and other drugs that can damage the kidney.

If the patient is in that kind of clinical context of having diabetes or high blood pressure, it's really important we know as a clinical action to get control of the blood pressure to use one of two classes of blood pressure medicines, the ACE Inhibitors or the angiotensin receptor blockers, because we know that those will slow progressive damage to the kidney. That's probably the most—in addition to just talking with the patient and reviewing the old records, that's the most important clinical actions.

If the estimated GFR is substantially lower, and there is no real magic threshold, but most people would say, if it's newly depressed, or certainly if the first time it's noticed it's down below 30, then it's certainly time to

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have a kidney specialist, a nephrologist to see the patient.

Host: With that in mind is there evidence that eGFR has had clinical effects?

Dr. Thomas Hostetter: Yes, the reporting of estimated GFR has gradually increased in laboratories around the world over the last five to ten years. So we now are starting to get reports of whether some of those things we just talked about happen after estimated GFR, reporting begins to be put forth by laboratories.

It's one of my guess, this information comes from health systems where they are lots of records are, and most of them have been recently from Canada. A particular one that was reported this summer in the Journal of the American Medical Association. It showed that in one of the provinces in Canada when estimated GFR reporting began to be reported by laboratories, there was an increase in the consultation to nephrologist.

The study was really quite well-done and controlled for other sorts of things that were going on at the same time, and it looked like that was happening. We think that's in general a good thing, not just because nephrologists like to see the patients, but it's a way of reinforcing these points we have been making about avoiding drugs that would further damage the kidney and employing any hypertensives that would reduce damage. And as GFR goes down farther of being able to counsel the patient on what their options are if they actually get to kidney failure.

The final thing I would say on what the clinical effects are, there is starting to be a little bit of information coming out that the use of these ACE Inhibitors and ARBs to slow further damage, that also seems to have a little bit of an uptake in prescribing with estimated GFR reporting goes on.

So it looks like that there are beneficial effects in real tangible clinical actions that occur when the laboratories start to report this parameter.

Host: Well, what about the reliability of eGFR calculation?

Dr. Thomas Hostetter: It's an estimate based on now nearly 10,000 subjects largely in clinical trials who had formal measurements of GFR by infusion of some exogenous substance and then comparing that to the estimates using the serum creatinine.

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We know that the formula that's now most used is a version of the MDRD formula, which stands for the trial in which the formula was first developed, is the most reliable way of estimating GFR from the serum creatinine.

But what we do know is, that assumes that the people have pretty much normal body built for their age and sex. So one place where the estimating equations and hence the reporting can be misleading is someone who has a major reduction in creatinine production, and in practical terms that means somebody who has lost muscle mass.

So in those circumstances, for example, someone who is paraplegic or has had a wasting illness or may have had amputations, the serum creatinine can be misleadingly low and the estimates are said the other way misleadingly high and that the person's true kidney function maybe lower than the estimates.

So when a physician sees the estimated GFR of some particular number, it's important to kind of think quickly does this patient have more or less normal body built for their age and sex and doesn't fall into one of those clinical conditions I mentioned.

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The other place where the formula is not useful is when kidney function is changing rapidly. A typical clinical example would be a patient in an Intensive Care Unit who may lose 50 to 90% of kidney function over just a few hours, it takes a while for the serum creatinine to rise, to match what we would call a steady state.

So in rapidly changing circumstances of kidney function, again, typically in a hospitalized patient the estimation of GFR by the standard formula or by any formula is not reliable.

Host: Well, finally Dr. Hostetter, what do see on the horizon for renal function testing and the diagnosis of chronic kidney disease?

Dr. Thomas Hostetter: Well, there is a great deal of interest in this now, because we are as the laboratory people know, stuck with a situation where the serum creatinine and that urine albumin, which I mentioned earlier are really the major test we have, and unfortunately it's been around forever and we haven't had really new markers, we've had new ways of expressing them like this estimated GFR and the concentration ratios, but we have been kind

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of stuck with these two measures of kidney function or kidney damage.

But there are increasing interests in investigational studies of looking at markers of injury, for example, protein shed by damaged cells or even the damaged cells themselves being shed into the urine or messenger RNA indicative of damage appearing in the urine as perhaps more sensitive or earlier markers of kidney function.

There has been particularly intense interest in this, in the area of acute kidney injury. But some of these same markers or at least the concepts of looking for markers of injury, of the types I have mentioned seem to be applicable to chronic kidney disease.

So, we don't have one of those now for chronic kidney disease, some of them are close for acute kidney injury, but I am guessing that we will build on that experience in acute kidney injury and have some of those injury markers probably as they are found in the urine as more sensitive markers than estimated GFR or urinary albumin, and then we will have those in not-too-distant future.

Host: Dr. Thomas Hostetter is the Abraham Levitt Professor of Medicine, and Director of the Nephrology Division at the Albert Einstein College of Medicine. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!

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