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# Toward More Accurate Detection and Risk Stratification of Chronic Kidney Disease

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**T**HE TERM *CHRONIC KIDNEY DISEASE* (CKD) WAS FIRST PROPOSED and systematically defined in 2002, and the 5 incremental stages for the degree of severity of CKD were described based on the estimated glomerular filtration rate (GFR) (stage 1,  $\geq 90$ ; stage 2, 60-89; stage 3, 30-59; stage 4, 15-29; and stage 5,  $< 15$  mL/min/1.73 m<sup>2</sup>). Stage 1 is the least severe and stage 5 is classified as kidney failure.<sup>1,2</sup> The estimated GFR (calculated from the Modification of Diet in Renal Disease [MDRD] Study equation)<sup>3</sup> can be derived automatically from a single serum creatinine measurement, combined with the easily available age and sex data, plus a qualifying statement on race, and without a need for patient weight.

The automated estimated GFR calculation has rapidly become a routine component of virtually every laboratory report of serum creatinine concentration. This has occurred even though estimated GFR is not based on an accurate timed urine specimen, is only a rough estimate of a patient's actual GFR, and is more applicable to the population than to the individual. An estimated GFR lower than 60 mL/min/1.73 m<sup>2</sup> has been flagged as indicating moderate to severe kidney disease<sup>3</sup> and physicians, following the guidelines,<sup>2</sup> sometimes inform patients of this finding. The prevalence of CKD using the MDRD equation in nationally representative surveys has been estimated at 10% to 12% of the population, with CKD stage 3 (estimated GFR 30-59 mL/min/1.73 m<sup>2</sup>) comprising the largest category. Population-based studies have consistently reported a strong and incremental association between CKD stages and risk of cardiovascular events and death,<sup>4,5</sup> suggesting that an individual with low estimated GFR (ie, stage 3, 4, or 5) might be at increased risk.

The use of the term "kidney" along with the new CKD staging and its expanded spectrum based on estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup> has increased awareness about and the apparent prevalence of a once underappreciated and confusing disease state.<sup>1</sup> Consequently, nephrologists have had an unprecedented increase in consultations to verify the diagnosis of "CKD stage 3+" primarily because of a calculated estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup>. Many patients with this alleged diagnosis are anxious until they see a nephrologist, whereas the specialist feels compelled, perhaps in part because of concerns of litigation, to perform extensive and expensive

workups to more accurately assess renal function. Some of these patients have been stigmatized with a "preexisting condition" and have been denied insurance coverage upon reemployment.<sup>6</sup> However, the diagnosis of stage 3 CKD for many patients cannot be substantiated other than with an estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup> according to the MDRD equation.

Nephrologists have not adequately addressed the clinical and public health consequences of using the MDRD equation as a criterion for the detection and classification of CKD and have failed to acknowledge the many implications of the flaws in this approach. For instance, it is counterintuitive that more patients are classified as having stage 3 of a chronic disease than earlier stages, ie, stage 1 and 2 combined, in sharp contradistinction to other chronic disease states such as heart failure.<sup>7</sup> The result has been that the nephrology community appears to have undermined its own important work in public health by overdiagnosing a non-existent disease in millions of elderly persons as well as in women in whom the MDRD equation calculates a 25% worse kidney function by default,<sup>3</sup> or in adults with larger muscle mass or other nutritional states associated with higher serum creatinine independent of kidney function.<sup>8</sup> Use of the epidemiological classification of such an imperfect surrogate as estimated GFR does not square with the clinical reality of patient diagnosis and treatment. Many patients with so-called CKD stage 3 do not die of renal causes, and do not develop end-stage kidney disease over time, so there is a disconnect between classification based on estimated GFR equations and patients' clinical course.

At the same time, the diagnosis of true kidney disease may be missed in some persons with lower serum creatinine levels due to smaller skeletal muscle mass, low or no protein intake, or significant glomerular, tubular, or vascular kidney disease but with higher estimated GFR. As a result, and despite the overwhelming data on the association of kidney disease with cardiovascular events and death, the cardiology community has generally not considered CKD based on estimated GFR alone as a credible cardiovascular risk fac-

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tor.<sup>9</sup> A better CKD detection tool with a more accurate estimate of GFR might help overcome these problems.

In this issue of the *JAMA*, in a pooled analysis of more than 1 million adults from 45 contemporary cohorts, Matsushita et al<sup>10</sup> compared the CKD detection, classification, and risk stratification of the conventional MDRD equation with the more recently developed, and mathematically more sophisticated, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that uses the same 4 components: serum creatinine concentration, age, sex, and race. The investigators report the superiority of the CKD-EPI equation across several dimensions in that it reclassified 24% of patients to a less severe CKD stage, whereas less than 1% were reclassified as having a more severe CKD stage, when compared with staging according to the MDRD equation. In particular, use of the CKD-EPI equation led to a 28% reduction in classifying individuals with CKD stages 3 to 5 (estimated GFR <60 mL/min/1.73 m<sup>2</sup>). Given the problem that the MDRD equation categorizes many otherwise healthy adults with CKD stage 3a (estimated GFR 45-60 mL/min/1.73 m<sup>2</sup>) as having kidney disease including elderly persons, women, and less muscular persons, more than one-third of these patients were reclassified with estimated GFR above 60 mL/min/1.73 m<sup>2</sup>. While no GFR criterion standard was used to examine the validity of this substantial correction of the misclassification by the MDRD equation of CKD stages, persons who were reclassified to a less severe stage of kidney function (estimated GFR >60 mL/min/1.73 m<sup>2</sup>) had substantially lower incidence rates of unfavorable outcomes compared with those who remained in the stage 3a range: 71%, 79%, and 38% lower crude rates of all-cause mortality, cardiovascular mortality, and progression to end-stage kidney disease, respectively.<sup>10</sup>

Even though CKD staging using the more conservative CKD-EPI equation seems valid because it produces more meaningful risk profiles,<sup>10</sup> it is premature to conclude that the ultimate tool for estimated GFR accuracy has been found. An even more conservative and accurate equation may be developed eventually, perhaps by these same investigators who first developed and advocated the MDRD equation (that is still in use in many estimated GFR laboratory reports) and who have now advanced the CKD-EPI equation to replace its MDRD predecessor. Some inherent limitations of the MDRD equation remain essentially unchanged in the CKD-EPI equation, in particular the reliance on creatinine as a single suboptimal filtration marker that not only is a close correlate of skeletal muscle mass but also probably varies with the magnitude of ingested meat and nutritional status.<sup>11</sup> To date no single circulating biomarker meets the desired criteria of the ideal renal filtration marker. It is possible that a panel of several filtration markers,<sup>12</sup> including cystatin C, for instance, combined with some surrogate markers of nutritional status and body composition, will provide a more accurate and clinically meaningful estimate of GFR.

The introduction and pragmatic classification of CKD in 2002 based on estimated GFR calculated with the MDRD equation has led to improvements in education and awareness about kidney disease. At the same time, there has been

an unchallenged reliance on a mathematical equation to estimate GFR that has resulted in overdiagnosis and misclassification of CKD stages among many patients who may not have any renal disease threatening their health or future. Compared with the MDRD equation, the CKD-EPI equation appears to provide a more accurate estimation of GFR and the implied risks of subsequent disease,<sup>10</sup> although inherent limitations of its core component filtration marker, creatinine, make it less than perfect.

Estimating GFR based on filtration markers such as serum creatinine or cystatin C concentration should serve as a screening tool and should be interpreted conservatively to avoid labeling healthy individuals with the diagnosis of CKD stage 3 before timed-urine collection or other tests are assessed carefully. Although use of the CKD-EPI equation may mitigate this problem, and this equation should now replace the MDRD equation, the search for better filtration markers and estimated GFR equations continues. In the interim, a wiser cutoff level at which patients should be warned about possible kidney disease, such as an estimated GFR lower than 45 mL/min/1.73 m<sup>2</sup> measured by the CKD-EPI equation, would be prudent.

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