Measured and Estimated Glomerular Filtration Rate

TO THE EDITOR: The article by Stevens et al. (June 8 issue)[1] on the assessment of kidney function is both helpful and comprehensive. Chronic kidney disease, which poses a public health threat of epidemic proportions, is largely underdiagnosed and often inadequately treated. The authors correctly note that timely referral of patients to nephrologists for comanagement may decrease morbidity

and mortality. We were disappointed that after making their case, the authors recommended that patients be referred to nephrologists when their estimated glomerular filtration rate (GFR) is less than 30 ml per minute per 1.73 m^2 of body-surface area. This recommendation is akin to closing the barn door after the horses have escaped. As health care researchers and providers, we too believe in the importance of early referral, but we recommend that patients be referred to nephrologists when their estimated GFR is 60 ml per minute per 1.73 m^2 or less. Although most of the catastrophic complications of chronic kidney disease occur in persons with stage 4 or 5 of the disease, the course is set, so to speak, in stage 3. The likelihood of good management and prevention of serious sequelae is much greater when these complications are addressed sooner rather than later.

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TO THE EDITOR: With respect to the review by Stevens et al., we add a caveat. The Modification of Diet in Renal Disease (MDRD) study equation underestimates the GFR in patients with chronic kidney disease and above-average creatinine production.[1,2] For example, Patients 1 and 2 are 40-year-old white men, each with a serum creatinine level of 5 mg per deciliter. Patient 1 is 1.83 m tall, weighs 100 kg, and is muscular and omnivorous (24-hour urinary creatinine excretion, 3000 mg). Patient 2 is 1.68 m tall, weighs 60 kg, is not muscular, and is a vegetarian (24-hour urinary creatinine excretion, 900 mg). The MDRD study equation results in the same GFR for both men (13.7 ml per minute per 1.73 m^2, indicating stage 5 chronic kidney disease, with recommendations for renal-replacement therapy if uremia is present). However, when the two rates of creatinine clearance are compared, a different picture emerges. Patient 1 has a creatinine clearance of 33.4 ml per minute per 1.73 m^2. Patient 2 has a creatinine clearance of 12.8 ml per minute per 1.73 m^2. The creatinine clearance overestimates the GFR; thus, Patient 2 may need renal-replacement therapy soon. Patient 1 will not, even if the creatinine clearance overestimates his GFR by as much as 50%. The application of the GFR derived from the MDRD study equation GFR to individual patients requires confirmation by actual measurement of creatinine clearance to avoid referral bias for renal-replacement therapy, especially for patients with above-average creatinine production because of their large body size, muscularity, or diet.

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TO THE EDITOR: In addition to the various circumstances noted by Stevens and colleagues, we suggest that GFR estimates should also be used with great caution for kidney-transplant recipients. Indeed, several recent reports have strongly challenged the accuracy of these equations when applied to these patients.[1,2]

Although kidney-graft function itself has emerged as a meaningful surrogate marker, an accurate evaluation of GFR is becoming particularly critical for clinical research on transplantation. In this context, we and others have shown that several predictive equations, including the Cockcroft–Gault formula and the MDRD study equation, are not safe substitutions for a direct measurement of GFR and may lead to flawed interpretations.[3,4]

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TO THE EDITOR: Stevens et al. argue that equations to estimate the GFR "should result in improved patient care and better clinical outcomes." We are not convinced. There are key questions regarding renal function. For instance, is the GFR reduced? If so, by how much? Is the GFR changing? If so, at what rate? An astute clinician who has seen the patient can usually deduce the answers to these questions from the concentration of serum creatinine alone.

One of the strongest arguments for equations is that they help identify people with reduced renal function but "normal" creatinine concentrations. However, in the setting of normal creatinine concentrations, the use of equations to estimate the GFR is not very accurate[1] and, as Stevens and colleagues note, "may lead to a false positive diagnosis of chronic kidney disease." The other recommended indications are even less compelling. It has never been proved that a precise knowledge of GFR is more helpful than grouping patients into broad categories of renal function.[2] With rare exceptions, acute changes in the serum creatinine concentration indicate inverse changes in the GFR.[2] Most nonrenal factors that alter the serum creatinine concentration[3] also affect the results of the equations to estimate the GFR.

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THE AUTHORS REPLY: Current clinical practice guidelines recommend referral of all patients with a GFR of less than 30 ml per minute per 1.73 m^2 to kidney disease specialists for comanagement with primary care or other specialty physicians. We agree with Fein and colleagues that there are many other reasons for referral. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative included a more complete list in its clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease.[1]

Hebert and colleagues and Mariat and colleagues comment on the inherent limitation of serum creatinine as a filtration marker. Equations to estimate the GFR can overcome some of these limitations with regard to average differences within the population for creatinine generation according to age, sex, race, and body size. However, these equations may not provide accurate estimates of the GFR for people with creatinine generation that differs substantially from that of the average person. These people include those with very high levels of creatinine generation, such as bodybuilders (as pointed out by Hebert and colleagues) and people with very low levels of creatinine generation, such as some kidney-transplant recipients (as pointed out by Mariat and colleagues). Clinicians should be cognizant of these limitations of equations to estimate the GFR on the basis of serum creatinine, and they should order clearance measurements if more accurate estimates of the level of the GFR are required.

We agree with Spital and Abuelo that astute clinicians may be able to interpret changes on the basis of the serum level alone. However, we expect that routine use of GFR estimates will facilitate interpretation of kidney function for all clinicians. We disagree with their statement, "in the setting of normal creatinine concentrations, the use of equations to estimate the GFR is not very accurate." For example, a 70-year-old white woman with a serum creatinine concentration of 1.2 mg per deciliter, which would fall within the normal range in most laboratories, would have an estimated GFR of 47 ml per minute per 1.73 m^2. GFR estimates in this range are relatively accurate in most studies with the use of calibrated serum creatinine concentrations. They represent a substantial reduction in kidney function that is associated with an increased risk of complica-

tions and the need for adjustment in the dose of many commonly prescribed medications.

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