The health and economic burdens of end-stage renal disease are staggering. Earlier stages of reduced renal function, termed chronic kidney disease (CKD), are no less so. As a matter of fact, it is estimated that CKD, as defined by a reduced glomerular filtration rate of <90 mL/min in conjunction with urinary or structural abnormalities, may affect 11% of the adult population in the United States. Early CKD may not be detected by serum creatinine. Its diurnal variation, heavy dependence on muscle mass, change in production with aging, and possibly some inherent genetic differences in handling creatinine make it less than a perfect marker for early dysfunction. The definitive method to diagnose depression in GFR is by actually measuring the disappearance of a filterable, nonabsorbed, and nonsecreted marker such as inulin. The cumbersome and time-consuming nature of such tests has limited their widespread use. The National Kidney Foundation strongly and rightfully recommends using the Modification of Diet in Renal Disease (MDRD) formula to estimate GFR. Although this prediction model has proved generally useful in patients with established kidney disease, its ability as a screening tool has not been well established.

In this issue of the Journal, Rule et al tested the ability to detect CKD by using three separate methods: namely, extreme elevations of serum creatinine, depressed estimated GFR (<60 mL/min), and elevated urinary albumin/creatinine ratio (ACR) in a cohort that was mostly female, older, 56% African American, and, most importantly, 77% hypertensive. Almost all subjects with an elevated serum creatinine had a reduced GFR. The overlap between elevated serum creatinine and elevated urinary ACR was, however, greater. In fact the agreement between elevation in serum creatinine and elevated ACR was 0.19 ± 0.02 as measured by the $\kappa$ statistic, as opposed to a $\kappa$ statistic of 0.07 ± 0.02 for the agreement between reduced GFR and elevated serum creatinine. The $\kappa$ statistic is a measure that quantifies agreement between observers or measurements and corrects for the expected agreement from chance alone. A value of 0 to 0.2 indicates a strength of agreement that is slight, and a value of 0.8 to 1.0 indicates almost perfect agreement. The most important finding of this work, however, is the demonstration that the adjusted odds ratio for kidney disease for men was not higher than that in women by reduced GFR. In addition, African Americans seemed actually to be protected from kidney disease when estimated GFR was used as the method of definition of CKD. This was not true when the two other methods of defining CKD were applied. Of interest, when the coefficients were derived from a healthy population and entered into the MDRD equation, the more acceptable conclusion was achieved: namely, the risk of CKD was significantly higher in men and was also higher in African Americans of both sexes, as has generally been known and demonstrated in other observational studies.

There are four sources of variability that can affect the reproducibility of results of a screening test. The first relates to the biological variation inherent in the actual manifestation being measured, in this case serum creatinine. The second is variation caused by the test method or measurement leading to the reliability of the instrument itself; in this case creatinine was calibrated against a standard. The third is interobserver variability, which refers to differences in repeated measurements by the same screener; this was not an issue here. The fourth source is interobserver variation, which refers to the inconsistencies attributable to differences in the way that different screeners apply or interpret test results; this, again, was not an issue here. This leads to the conclusion that it was actually the method of measurement that was at fault: namely the estimated GFR—not a surprise, considering that MDRD was developed in subjects with CKD. Therefore the lack of measurement of GFR using inulin or iothalamate constitutes a major limitation of the study by Rule et al.

In summary, CKD is common and needs to be detected...
earlier. The commonly recommended MDRD formula falls short of being an ideal screening tool in every individual. Therefore the clinician is encouraged to use the knowledge obtained from the serum creatinine–based formula and the demonstration of proteinuria. When the suspicion is high for early reduction in GFR, one should consider isotope measurement of GFR, which is commonly available at many large hospitals.

References