When clinicians speak of kidney function, they almost always are talking about the glomerular filtration rate (GFR).\(^1\) The kidney has many other functions, however. Most excretory functions are related in some way to glomerular filtration, at least as it is modified by the variable reabsorption of water and some solutes and the addition of yet other solutes via secretion. The kidney also has important endocrine functions (such as the production of erythropoietin and active vitamin D) and metabolic functions (such as the metabolism of insulin and other low molecular weight proteins) that are not related to excretory function; however, as the GFR declines because of chronic kidney disease (CKD), all of these functions also tend to decline, roughly in parallel. Thus, taking the overall kidney function as equivalent to the GFR is a generally useful approximation.

Clinicians’ equating of the GFR with kidney function has an additional practical utility. Estimating GFR relies on simple tests, which are based mainly on serum creatinine, whereas many other kidney functions are more difficult to measure. For example, the extensive machinery for secreting organic solutes has become increasingly well described in molecular detail, but the major natural or xenobiotic solutes that are secreted are still largely unidentified. Hence, estimating the residual secretory function by measuring the serum concentrations of such solutes is not feasible, regardless of how important to health this excretory mode might be.

Creatinine was found to be a good marker of the kidney’s creatinine excretion. They thus obviate urine collections. The best iteration of these equations is the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (1). It was developed by relating the GFR, as measured by iothalamate clearance, to the serum creatinine concentration, coupled with the individual’s age, sex, and race—all normalized to a standard body surface area. This equation has been validated in nearly 4000 individuals. Most laboratories in the US and many laboratories around the world use the serum creatinine concentration along with the CKD-EPI equation or its forerunner, the Modification of Diet in Renal Disease (MDRD) Study equation, to report the estimated GFR (eGFR).

Although such automatic reporting of the eGFR provides a useful estimate of kidney function, does such reporting influence clinical practice? Researchers in Canada have begun to address this question (2). They used a laboratory registry in Alberta to track nephrology consultations before and after the implementation of eGFR reporting and found reporting to be associated with an increase in nephrology referrals. The increase was particularly notable in people with advanced CKD (eGFR < 30 mL min\(^{-1}\) 1.73 m\(^2\)) in women, and in the elderly (in whom a reduced GFR is often not detected via an increased serum creatinine concentration alone because of low creatinine production). Although most laboratories have different serum creatinine reference intervals for men and women and although the decrease in creatinine production with age is known, clinicians tend to disregard these points and base CKD diagnoses solely on the serum creatinine concentration without consideration of the differences in production rates among the various subgroups. This tendency underscores the value of applying the equations for estimating GFR, as opposed to simply reporting the creatinine concentration. The Canadian study also noted an increase in referrals for patients with diabetes and hypertension, conditions known to be associated with CKD and with a high risk for adverse out-
comes associated with CKD, including kidney failure, cardiovascular disease, and death. The study was too brief to ascertain whether there would be other clinical outcomes, such as delay in the need for dialysis or transplantation. One can expect follow-up studies from this and other groups that will pursue the effects of eGFR reporting on clinical outcomes.

The impetus of clinical laboratories to report the eGFR derives largely from the desire to apply more generally the advances in CKD care that were discovered in the 1990s. Most importantly, clinical trials showed that the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers slowed the decline in the GFR in many types of CKD. Early recognition of CKD, which is usually asymptomatic in the early stages, requires laboratory testing. Given the variation in creatinine production, however, simply measuring the serum concentration can be misleading, especially in those with low creatinine production. Perhaps surprisingly, the Canadian study did not find an increased use of ACE inhibitors and angiotensin receptor blockers. The authors speculated that this finding might have been because the prevalence of the appropriate use of these medications was already rather high (60%–80%) before reporting. Such widespread use before eGFR reporting might not apply to a more fragmented healthcare system, such as in the US, and a greater effect of reporting on the use of such drugs might be hypothesized in these populations. Currently under testing are a number of additional promising therapies, including further targeted interruption of the renin–angiotensin–aldosterone system, anticytokine therapies, and maneuvers as simple as treatment of acidosis.

In addition to the identification of CKD and attempts to slow its progression, other benefits might accrue from eGFR reporting. For patients with a severe reduction in the eGFR (15–29 mL·min⁻¹·(1.73 m²)⁻¹, which is classified as CKD stage 4) and who might achieve a modest delay in progression, the recognition of CKD should permit better and more cost-effective arrangements for dialysis or preemptive transplantation. For patients with a moderate reduction in the eGFR (30–59 mL·min⁻¹·(1.73 m²)⁻¹, which is classified as CKD stage 3), recognition of CKD would allow an improved dosing of drugs excreted by the kidney and the avoidance of nephrotoxic agents. These potential outcomes remain speculative.

Use of estimating approaches for the GFR has a few limitations. The estimating equations were developed for a steady state of creatinine balance; consequently, the estimates are not as accurate in patients with a rapidly changing GFR, such as those with acute kidney injury. Furthermore, the equations were developed with individuals with a muscle mass relatively typical for a given age, sex, and race; therefore, the equations overestimate the GFR in people with major muscle loss, such as that due to amputations, paralysis, or cachexia. As with other laboratory results, including the simple measurement of serum creatinine itself, the eGFR must be interpreted within the larger clinical setting.

A single eGFR calculation is not sufficient to predict whether or how fast a patient will progress to kidney failure. Most data suggest that concomitant albuminuria offers some predictive value, with higher albuminuria suggesting a greater likelihood of rapid progression (3). At present, we have few other markers that will help with this prognostication. Considerable effort is now being expended with a range of approaches, from proteomic screening to the screening of candidate injury molecules, in the search for better biomarkers. Other efforts are under way to develop practical risk-prediction scores, similar to the Framingham risk equations used to predict clinical cardiovascular disease. At present, however, the best predictions are based on serial measurements of kidney function made over a period of years.

This prognostic dilemma often arises with elderly patients, who quite frequently have eGFR values between 60 and 45 mL·min⁻¹·(1.73 m²)⁻¹. The elderly are a rapidly growing segment of the kidney failure population, so the finding of a low eGFR in this group is not necessarily a benign result. That the GFR tends to decline with age, even without other major risk factors for CKD, is a well-documented phenomenon (4). Even in the elderly, early application of measures to retard the progression of CKD (ACE inhibitors, for example) should forestall or prevent kidney failure. Avoidance of common nephrotoxins such as nonsteroidal antiinflammatory drugs and contrast agents may also be particularly germane for individuals in an age group with high use of over-the-counter analgesics for musculoskeletal complaints and who are subject to increased radiographic testing. Furthermore, a low eGFR is associated with an increased risk of cardiovascular disease at all ages, including the elderly, but whether this risk is predictable or modifiable is not as clear (3). Thus, in our view, the reporting of eGFR values adjusted somehow for age would be misleading and could reduce the beneficial actions noted above. Whether CKD should be defined or formally staged in an elderly person with a very modest reduction in the eGFR and no other risk factors has been a matter of debate (5, 6). Even small reductions in the eGFR to <60 mL·min⁻¹·(1.73 m²)⁻¹ require some discussion between patient and clinician and usually some follow-up. A decreased kidney function may be relatively stable and of little clinical consequence, or it may presage a serious
course. Educational materials are available to aid these discussions.

Routine reporting of the eGFR appears to be having salutary clinical effects. Some potential benefits are unproved, and some will be difficult to assess. One can hope that as additional biomarkers are discovered, as risk predictions become more accurate, and as the therapeutic options expand, we will look back on this step in laboratory practice as a key element in stemming the decades-long increase in the incidence of kidney failure and other adverse outcomes of earlier stages of kidney disease.

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**References**


