

eGFR: Is It Ready for Early Identification of CKD?

Michal L. Melamed, Carolyn Bauer, and Thomas H. Hostetter

Albert Einstein College of Medicine, Bronx, New York

Reporting estimated glomerular filtration rate (eGFR) with serum creatinine simply provides the information for which the serum creatinine was ordered in the first place. Mass or universal screening is not the purpose of eGFR reporting. Furthermore, such mass screening does not seem justified. Rather, testing of high-risk groups with eGFR and urinary albumin is useful. Population estimates of the prevalence of chronic kidney disease in the United States that use the Kidney Disease Outcomes Quality Initiative staging system lead to disturbingly high estimates. Many of these people are elderly with marginally depressed GFRs and for whom there are no known therapeutic implications. However, an even more disturbing fraction of people with serious and progressive renal disease are not diagnosed, counseled, or treated. Reporting of eGFR is only one tool in attempting to rectify this latter problem. Nephrologists need to educate patients and their primary care colleagues in the use of this tool.

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The only reason to measure serum creatinine is to assess GFR" (1). Unlike other laboratory tests, such as serum sodium or hemoglobin, which have implications of their own, serum creatinine has no clinical utility beyond serving as a marker of kidney function. Of course, there are exogenous markers of glomerular filtration rate (GFR), such as inulin and iothalamate, but they are difficult to use properly and rarely employed outside of research. As with any measurement, even these "gold standards" methods entail error. Timed urinary collections to calculate urinary clearance even for an endogenous marker, such as creatinine, are cumbersome and notoriously inaccurate. For these reasons, estimations of GFR based on the serum creatinine are routinely used. Simply inverting the serum value (in units of mg/dl) gives an approximation of the fraction of normal adult function; but because of the variation of creatinine production, more accurate estimating equations have been developed over the last 30 yr (2). The Modification of Diet in Renal Disease (MDRD) equation seems at present the best available one.

No equation for estimating GFR will be perfect, and the MDRD one seems better than most, having been carefully validated in the largest number of subjects (3). It functions best in the lower ranges of GFR (4), which is not a major limitation, as assessing the differences in GFR in the normal or near-normal range has small clinical value. One could reasonably desire validation in larger numbers of subjects with more varied ethnicity, wider range of GFR, and multiple diseases. Such validation continues, but a goal of a perfect equation is false. Hence, waiting for that perfection would be an error. We acknowledge that the prediction equations will likely improve to

some degree but in our judgment the MDRD in its current form is good enough as a clinical tool. Cystatin C may prove as useful as creatinine as an endogenous index of GFR or perhaps even better (5). However, to estimate GFR from serum cystatin absolutely requires an equation as its urinary clearance is negligible and thus, unlike that of creatinine, it does not approximate GFR. Finally, serum creatinine measurement can now be calibrated to an international standard, making comparison across laboratories more reliable.

Over decades GFR has established itself as the single most useful measure of overall kidney function. Indeed, in ordinary clinical terminology when people ask about the renal function of a patient, they are asking about the GFR. Early renal physiologists speculated that markers of tubular secretion might provide a better gauge of renal injury than GFR, and contemporary investigators pursue new biomarkers with molecular techniques (6,7). However, for the foreseeable future, GFR will for clinical purposes be "renal function" in all but the rather rare cases of tubular disorders. This too seems not so bad because most clinical consequences of chronic kidney disease (CKD) track with the GFR, even those not directly related to glomerular function, such as acidosis or anemia.

The importance of measuring kidney function in the ambulatory clinic derives from several facts. First, the incidence of end-stage renal disease (ESRD) climbed at staggering rates for nearly 25 yr in the United States and has perhaps only recently leveled off, albeit at a very high number of 100,000 cases per year. Second, the value of angiotensin-converting enzyme inhibitors and angiotensin II receptor blocker to slow the progression of most CKDs and glycemic control to attenuate diabetic nephropathy were solidly established in the 1990s (8–11). Third, these therapies were nevertheless inadequately applied to the pool of people with CKD (12). Treatment requires diagnosis. Because renal disease is symptomless in its early phases, laboratory diagnosis, an estimation of GFR, is essential. Unfortunately, additional therapies have not continued to appear,

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Correspondence: Dr. Thomas H. Hostetter, Renal Division, Abraham Levitt Professor of Medicine, Albert Einstein College of Medicine, Room 615, Ullmann Building, 1300 Morris Park Avenue, Bronx, NY 10461. Phone: 718-430-3158; Fax: 718-430-8963; E-mail: thostett@aecom.yu.edu

but applying the available ones at the earliest phase of the disease should provide the greatest benefit, reemphasizing the need for early detection.

Multiple lines of evidence indicate that clinicians infer GFR from serum creatinine rather poorly (13,14). This is not surprising because the relation is not linear and the rates of creatinine production vary widely. Thus, women and the elderly often have substantial reduction in renal function before their impairment is recognized. Even the oldest and perhaps simplest estimating equation, the Cockcroft-Gault one for creatinine clearance, is still complex. To expect a busy practitioner to use it regularly is unrealistic. Reporting an estimation of GFR with the serum creatinine delivers what the practitioner is really requesting. Many laboratories have begun to do so routinely, and we applaud this practice.

As with any test, interpretation of the estimated GFR (eGFR) requires judgment and knowledge. Non—steady-state conditions make it less useful. In addition, extreme body habitus, such as cachexia or obesity, renders the estimation suspect. Finally, values more than 60 ml/min per 1.73 m² are not reliable, and reporting in that range is discouraged.

A particular concern is the large number of elderly patients whose GFR may be less than 60 ml/min per 1.73 m². That many elderly do indeed have GFRs in this range is not doubted. This may be of little consequence, especially if their estimated GFR is only slightly less than 60 and they have neither proteinuria nor risk factors for progressive renal disease, especially diabetes or hypertension. The vast majority of such patients will not progress to ESRD either because the renal process is indolent or their life expectancy is less than that required to reach ESRD (15). However, even such patients should profit from avoidance of nephrotoxins and some degree of monitoring. Furthermore, some conditions that accumulate with age, such as hypertension and osteoporosis, have on careful study proven worthy of treatment even when they become almost the norm in older age (16). Hopefully, its prognosis and perhaps therapy will become clearer, but acting as although aging does not reduce GFR will hardly be a spur to better understanding. For now interpretation of depressed GFR with aging is an area in which nephrologists should act as guides to both patients and the primary care providers. In clinical reporting, we see no easy way of discounting the GFR for age as the potential benefits might thereby be lost.

Drs Glasscock and Winearls refer to “mandatory” reporting of eGFR. Presumably, this means government regulation. Neither we nor the National Kidney Disease Education Program has called for mandatory reporting. While some groups have advocated such an approach in the past, no major kidney organization in the United States is currently doing so to our knowledge. Nevertheless, many clinical laboratories do report the estimate voluntarily, presumably because of the additional value to the clinician. Furthermore, in countries that have mandated such reports, we know of no serious problems (1). Although no systematic studies of such country-wide effects are available to our knowledge, we find it difficult to envision a rigorous trial designed to detect efficacy, risk, and cost.

We largely agree with Drs Glasscock and Winearls on several

points. Stages 1 and 2 of the Kidney Disease Outcomes Quality Initiative (KDOQI) classification seem to us of little use as we have previously stated. The term “disease” is psychologically freighted, and we would prefer some simple designations, such as moderate kidney impairment, severe kidney impairment, and kidney failure or ESRD for stages 3, 4, and 5, respectively. The relation of renal insufficiency to cardiovascular disease seems quite clear (17). Indeed, the American Heart Association recognizes CKD as a risk factor for the development of cardiovascular disease (18). However, there are no current specific therapeutic implications to this link other than optimizing treatment of other cardiovascular risk factors. More research is needed to understand this connection. In the meantime, this recently recognized nonrenal outcome of renal impairment should not distract nephrologists from the fact that 100,000 people are developing kidney failure each year, and we can do something about that but are doing too little at present.

We disagree when Drs Glasscock and Winearls equate an eGFR with “universal screening.” Provision of the estimated GFR along with serum creatinine simply supplies the information that the ordering physician has requested, namely, the renal function (1). We do not advocate mass or universal screening for kidney disease, and neither has the National Kidney Disease Education Program. The use of eGFR is not the same as screening for cancers or metabolic screening in neonates, wherein testing is recommended for everyone of a certain age. The topic of screening for CKD has been recently reviewed by Jaar *et al.* (19), and we concur with them. Screening should be routine only for those at high risk. By screening we mean serum creatinine for eGFR and urine albumin quantification, the latter at least in diabetes. The population at risk would surely include patients with diabetes and those with hypertension. Reasonable cases could be made for testing the elderly, first-degree relatives of ESRD patients, and people with cardiovascular disease. While this would not be universal screening, it might encompass a substantial fraction of the adult population in the United States. However, we think that the best screening strategies are yet to be developed but will include some estimate of GFR and urinary albumin. Although we agree that universal screening is not warranted, we do not think that reporting eGFR constitutes such screening.

Finally, the epidemiologic use of the KDOQI does lead to very large estimates of kidney disease. The notion that one in eight Americans has kidney disease beggars belief. We do not doubt the epidemiology but rather have reservations about using the staging system at least in its current expansive form as a template for such estimates (20). Here too the term “disease” loads the finding with more than we really know. In this instance, epidemiologic surveys, while not discounting aging, should make clear its large effect on population estimates of kidney impairment and that the estimate depends on an equation with age as a member. Drs Glasscock and Winearls seem to be conflating use of the KDOQI staging for epidemiologic estimates with the clinical utility of automatic reporting of eGFR. We too have doubts about the value of using the staging to estimate population prevalence but think the equation is useful for clinical practice.

Using the staging system, kidney disease may be overestimated at least with respect to solid prognostic and therapeutic implications. However, in practice, renal insufficiency is still underdiagnosed and inadequately treated. Less than one half of people with an eGFR less than 30 ml/min per 1.73 m² could recall being told they had weak or failing kidneys (21). Physicians diagnose less than 40% patients with CKD even when their eGFRs are in this very low range (22). Nephrology referral late in the course of CKD is associated with a higher mortality on dialysis (23,24) and more early hospitalizations (24). In addition, because not all patients with CKD will progress to dialysis, there are also reports showing that nephrologic care is associated with better kidney and overall survival in patients with earlier-stage CKD (25,26). However, only 28% of patients with severe kidney impairment (CKD stage 4) had at least one visit to a nephrologist in the Veterans Health Administration system from 1997 to 2000 (26).

Reporting eGFR seems to provide what the clinician actually is requesting, but we cannot be sure that it will reduce the incidence of ESRD or even push its median age of onset later. However, we can think of few laboratory reports that can be clearly shown to reduce disease. Demanding that reporting of eGFR be shown to have that benefit seems an unattainably high standard. However, to apply the therapies that we do have at an early stage of CKD and even to plan for ESRD therapy, a depression in GFR must be recognized. The cost of actually delivering the estimate is small but, as noted above, if mild impairments are labeled as disease, we see that as an error. Substantial data do indicate that early detection is cost-effective and even cost saving (19). Of course, primary care providers may in some cases need guidance in avoiding unnecessarily detailed workups. However, the bulk of the care for people with depressed GFR will necessarily be delivered by primary care providers. Although nephrology consultation may often be needed, we do not see it as mandatory or even desirable in every case. Publications reviewing experiences with eGFR suggest that reporting it increases awareness of CKD but emphasize the need for education as an adjunct (27–30). The American Society of Nephrology in collaboration with the National Kidney Disease Education Program provides a free slide set at its web site. Nephrologists can use those slides to educate their primary colleagues about kidney disease (31). The National Kidney Disease Education Program provides free material for patients and their providers that explains kidney disease and eGFR in simple terms (32). Routine reporting of GFR supplies a needed tool in early diagnosis. Nephrologists should counsel their patients and educate their primary care colleagues in using this tool.

Disclosures

None.

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