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Point/Counterpoint

Automatic Reporting of Estimated Glomerular Filtration Rate—Just What the Doctor Ordered

Andrew S. Levey,[1] Lesley A. Stevens,[1*] and Thomas Hostetter[2]

Chronic kidney disease (CKD) is a recently recognized public health problem. CKD is defined as the presence of markers of kidney damage or of glomerular filtration rate (GFR) <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ [<1 mL · s^{-1} · (1.73 m^2)$^{-1}$] for 3 months or more *(1–3)*. According to these definitions, the prevalence of CKD in noninstitutionalized US adults is estimated as ~11%, or ~20 million people *(4)*. CKD is associated with poor outcomes and high cost, disproportionately affecting the elderly and racial and ethnic minorities. Thus, new public health campaigns focus on early detection of CKD, especially in patients at increased risk, including those with hypertension, diabetes, cardiovascular disease, or a family history of CKD *(5)*.

To facilitate early detection of CKD, many national and international organizations now recommend automatic reporting of estimated glomerular filtration rate (eGFR) whenever serum creatinine is measured *(1–3, 5–12)*. Approximately 20% of participants in the College of American Pathologists' chemistry survey were reporting eGFR calculations in 2005 *(13)*. In this issue of *Clinical Chemistry*, Dr. Rainey offers a dissenting view, likening automatic eGFR reporting to "jumping the gun". A careful examination of the arguments reveals, in our view, that reporting eGFR whenever a serum creatinine is requested is "just what the doctor ordered".

The only reason to measure serum creatinine is to assess GFR

Dr. Rainey asserts that "Most creatinine measurements are not made to assess renal function in persons who have CKD or are at high risk for CKD. The great majority of creatinine measurements are ordered as part of a Basic Metabolic Panel".

The serum creatinine level holds no clinically useful meaning other than to serve as an index of kidney function. Creatinine itself has no notable toxicity. It has simply proven to be a useful measure of GFR, and GFR has been accepted as the best single measure of kidney function in health and disease. Surely, many creatinine measurements are performed specifically to assess kidney function, particularly in patients with CKD or CKD risk factors. In what other conditions do clinicians order measurement of serum creatinine, and for what purpose?

Creatinine is measured routinely in patients with acute illnesses requiring surgery or other procedures and who are receiving intravenous fluids or drugs with potential toxicity to the kidney. Many of these patients have CKD or risk factors for CKD and all are at risk for acute kidney injury. Acute kidney injury, like CKD, is defined by a fall in GFR, and therefore the decline in eGFR offers information similar to that gained from an increase in serum creatinine. Creatinine is measured for accurate interpretation of the metabolic panel. For example, hyperkalemia has quite a different differential diagnosis in a patient with kidney failure [defined as a GFR of <15 mL · min^{-1} · (1.73 m^2)$^{-1}$] than in a patient with normal GFR. Clinicians also measure serum creatinine to estimate creatinine clearance for drug dosing. The principal equation that has been available for estimating creatinine clearance, the Cockcroft and Gault formula, is less accurate in estimating GFR than the MDRD Study equation in many populations *(14, 15)*.

Thus, although the estimation of GFR has important implications beyond that of identifying CKD, the measurement of serum creatinine has only one purpose—to estimate GFR. If clinicians do not want an estimate of the GFR when ordering a metabolic panel, why then is creatinine included in the panel? We believe that an eGFR is the information that the clinician desires when requesting a serum creatinine either alone or as part of a metabolic panel.

[1] Division of Nephrology, Department of Medicine, Tufts-New England Medical Center, Boston, MA.
[2] Renal Division, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY.
* Address correspondence to this author at: Lesley A Stevens, Division of Nephrology, Tufts-New England Medical Center, 750 Washington St, Box 391, Boston, MA 02111. Fax 617-636-5740; e-mail Lstevens1@Tufts-nemc.org.
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GFR estimating equations provide more accurate estimates of GFR than does serum creatinine alone

Dr. Rainey agrees that "mathematical estimates of GFR that incorporate creatinine concentration, as well as factors affecting creatinine production rates, such as size, gender, age and ethnic background, are more sensitive to changes in renal function than serum creatinine". The MDRD Study equation has now been evaluated in numerous populations. It is reasonably accurate in nonhospitalized patients known to have CKD (including blacks, whites, and Asians), in people with diabetic and nondiabetic kidney disease and in kidney transplant recipients *(15, 16)*. For example, in the MDRD Study population, 90% of GFR estimates were within 30% of the measured value, which we believe is sufficient for clinical use. Preliminary data *(17)* suggest similar accuracy in other populations if creatinine assays are calibrated to yield results that agree with the assay used in the MDRD Study.

We agree with Dr. Rainey that the MDRD Study equation has been reported to be less accurate in populations without CKD, such as young patients with type 1 diabetes without microalbuminuria and in potential kidney donors *(15, 16)*; as discussed later, some of the studies are flawed by use of assays to measure serum creatinine that provide results different from the serum creatinine assay used in the development of the MDRD Study equation. However, on average, even after calibration of the serum creatinine assay, GFR estimates of <90 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ in these populations are lower than measured GFR *(17)* Hence, it is recommended that eGFR be reported as a numeric value only when it is <60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$; higher values should be reported as "eGFR ≥ 60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$". As the expected values for measured GFR in healthy young men and women are ~ 130 and 120 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$, respectively, this practice would avoid reporting incorrect values in individuals with GFRs that are within the reference interval, but may lead to misclassification of some healthy individuals with reduced GFR as having CKD. This practice will not compromise detection of CKD because the diagnosis of CKD in patients with eGFR >60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ requires a marker of kidney damage, such as an increased albumin excretion rate.

Limitations of GFR estimates primarily reflect limitations of serum creatinine as an endogenous filtration marker

Despite their utility, all GFR estimating equations have limitations; thus Dr. Rainey suggests not reporting eGFR until these limitations are resolved. However, these limitations primarily reflect limitations of serum creatinine as an endogenous filtration marker rather than limitations of GFR estimating equations, per se. Reporting serum creatinine without estimating GFR does not overcome these limitations.

Variation in creatinine assays. Variation in serum creatinine assays among laboratories introduces error in GFR estimation, especially in the lower range of serum creatinine, corresponding to the higher range of GFR *(18, 19)*. This same variation also makes it difficult to compare creatinine concentrations and eGFR among laboratories. Indeed, in the table compiled by Dr. Rainey, the studies with the largest reported errors *(20–22)* did not calibrate their creatinine assay to agree with the assay used during the MDRD Study. The plan developed by the National Kidney Disease Education Program (NKDEP) to calibrate clinical laboratory assays by use of a standardized serum creatinine assay is intended to reduce method-dependent variation in serum creatinine assays *(23)*. The MDRD Study equation has now been reexpressed for use with such standardized serum creatinine assays *(14)*. Dr. Rainey rightly points out that "varying interindividual nonspecificity" cannot be eliminated by calibration. Increased use of enzymatic methods may reduce the extent of these nonspecificities. In addition, creatinine standardization may make these individual nonspecificities easier to detect.

Determinants of serum creatinine other than GFR. Variation in muscle mass or diet can affect serum creatinine independent of GFR (Table 1), leading to inaccurate interpretation of the concentration of creatinine in serum, and consequently of eGFR, even at rates <60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ *(15)*. Muscle wasting is common in the elderly, chronically ill, and hospitalized patients, leading to low concentrations of serum creatinine for the same GFR compared with healthy individuals and subsequently an

Table 1. Factors affecting creatinine generation.[a]

Factor	Effect on serum creatinine
Older age	Decrease
Female sex	Decrease
Race[b]	
African American	Increase
Hispanics	Decrease
Asian	Decrease
Body habitus	
Muscular	Increase
Amputation	Decrease
Obesity	No change
Chronic illness	
Malnutrition, inflammation, deconditioning (e.g., cancer, severe cardiovascular disease, hospitalized patients)	Decrease
Neuromuscular diseases	Decrease
Diet	
Vegetarian diet	Decrease
Ingestion of cooked meat	Increase

[a] Variation in muscle mass accounts for the predominant proportion of variation in creatinine generation.

[b] White race served as the reference group.

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overestimation of true GFR by eGFR. In addition, the serum creatinine concentration can be increased by drugs that inhibit tubular creatinine secretion (e.g., trimethoprim and cimetidine) or inhibit gastrointestinal degradation of creatinine (e.g., broad spectrum antibiotics). As expected, these medications will also affect eGFR, although measured GFR may not change.

Generalizing an estimating equation developed in a population with CKD to populations without CKD. It is likely that the determinants of serum creatinine other than GFR differ between populations with and without kidney disease. Hence, the MDRD Study equation, developed from a study of patients with CKD, does not perform as well in people without CKD. As described elsewhere *(15)*, the reasons for this likely reflect differences in the relationship between serum creatinine and GFR in patients with and without CKD. Thus, this limitation is also inherent in the use of serum creatinine as a filtration marker.

Rapidly changing kidney function. Changes in serum creatinine, and therefore changes in eGFR, lag behind changes in GFR. GFR can be estimated from the rate and magnitude of change in the eGFR, analogous to the interpretation of changes in serum creatinine.

in some circumstances, creatinine clearance measurements can be used as confirmatory tests

Dr. Rainey states there is no confirmatory test for possibly erroneous eGFR estimates other than measurements of clearance of exogenous filtration markers, which are available in only some medical centers. Routine measurements of creatinine clearance are no longer recommended because of errors in urine collection. They may be helpful, however, in selected circumstances, such as in patients with extremes of muscle mass or dietary intake (Table 1), or in apparently healthy individuals without risk factors for CKD or markers of kidney damage. In principle, repeated 24 h urine collections may overcome part of the limitations related to collection errors. Recently, cystatin C has been proposed as an alternative to creatinine as an endogenous marker of glomerular filtration because it is not as dependent as creatinine on muscle mass and diet. If cystatin C is shown to be a better marker of GFR, estimation of GFR from cystatin C might also be helpful in these circumstances.

early detection and appropriate evaluation and management of ckd can improve outcomes

CKD is not, as Dr. Rainey states, "a life sentence . . . irreversible and incurable except by kidney transplant". There are now proven therapies for the 3 main complications of CKD: progressive loss of kidney function, complications of decreased GFR (hypertension, anemia, malnutrition, and bone and mineral disorders), and increased risk for cardiovascular disease *(1, 2)*. Some authorities believe that CKD may even be reversed if discovered and treated early *(24)*. However, if patients are not identified until terminal symptoms arise or until serum creatinine is conspicuously abnormal, these new approaches are less valuable.

reporting eGFR simplifies the evaluation and management of CKD

The reciprocal, nonlinear relationship between GFR and serum creatinine makes it difficult for clinicians to determine the GFR and to appreciate the rate of change in GFR by simply monitoring serum creatinine. Recent guidelines define "action plans" for CKD according to the GFR, including referral to nephrologists at GFRs <30 mL $\cdot$ min^{-1} $\cdot$ (1.73 m^2)$^{-1}$ *(1, 2)*. Late referral to nephrologists before initiation of dialysis is associated with increased rates of morbidity and mortality *(25)*. For adjustment in doses of medication excreted by the kidney, use of GFR estimating equations is recommended *(26)*. Measures to reduce kidney toxicity associated with radiographic contrast procedures are now based on eGFR *(27)*. Thus, eGFR has become a powerful decision tool in CKD. Reluctance by clinical laboratories to compute and report eGFR when serum creatinine is measured requires clinicians to perform these calculations for routine evaluation and management. In practice, such calculation is likely to be infrequently performed by busy clinicians other than kidney specialists. Medical errors could possibly be avoided by providing greater access to eGFR.

the benefit of reporting eGFR likely outweighs the harm

Dr. Rainey has characterized the current recommendations for eGFR reporting "for anyone who has a creatinine measurement . . . as making that person a subject in a medical experiment, a medical experiment for which there is no informed consent and no right of refusal". With all due respect, this assertion seems exaggerated. There are trade-offs in all public health campaigns. Underestimation of measured GFR in healthy populations may lead to a false-positive diagnosis of CKD. Although it has not been studied rigorously, we believe that the benefit of early detection of CKD outweighs the harm from falsely labeling persons without CKD.

First, several studies now show lack of awareness of CKD among nonnephrologists that is related, at least in part, to difficulty in interpreting serum creatinine concentrations. Coresh et al. *(4)* demonstrated awareness of kidney disease in only 24.3% of participants with eGFR between 15–59 mL $\cdot$ min^{-1} $\cdot$ (1.73 m^2)$^{-1}$. Stevens et al. *(28)* found the frequency of ordering serum creatinine measurement to be only 20%–30% in patients with CKD risk factors of diabetes, hypertension, cardiovascular disease, or age >65 years. Among patients with orders for serum creatinine measurement, only 10% and 39% of those with eGFR of <60 and <30 mL $\cdot$ min^{-1} $\cdot$ (1.73 m^2)$^{-1}$, respectively, had diagnostic codes for CKD. Bouleware et al. *(29)* showed that only 56% of general internists and 71%

of family physicians, compared with 96% of nephrologists, correctly recognized CKD in a sample case of a woman with two measurements of serum creatinine a few weeks apart of 186 μmol/L and 203 μmol/L (2.1 and 2.3 mg/dL), corresponding to eGFR of 32 and 29 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ [0.54 and 0.48 $mL \cdot s^{-1} \cdot (1.73\ m^2)^{-1}$]. This accords well with a separate survey of 600 primary care providers by NKDEP who were provided another vignette and asked at what concentration of serum creatinine a 65-year-old white woman with diabetes and hypertension would have CKD. Seventy seven percent chose a concentration of 90 μmol/L (1.6 mg/dL) or higher, corresponding to an eGFR of 34 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ [0.58 $mL \cdot s^{-1} \cdot (1.73\ m^2)^{-1}$] or lower. Akbari et al. *(30)* reported a small clinical trial of automatic eGFR reporting, showing an increase in recognition of CKD from 22% to 85% of physicians participating in the study.

Second, patients with eGFR $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ likely do have reduction in measured GFR. A young person with a GFR estimate of $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ may indeed have a measured GFR as high as $70–80\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$, but this likely reflects a large decline in GFR from the normal value. GFR declines with age, and the reference interval for measured GFR in the elderly is not well defined. However, even if low measured GFR in the elderly is common, it may reflect an important reduction in kidney function. Patients over 65 years of age constitute the fastest growing subpopulation of patients developing kidney failure. Possibly, evaluation for CKD in patients with eGFRs that are thought to be falsely low may disclose important abnormalities.

Third, despite the bias in current GFR estimating equations, there is strong evidence that eGFR $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ is associated with adverse outcomes, especially in cardiovascular disease (Fig. 1) *(12, 31)*. This association is particularly strong in the elderly, and recent data suggest that this increase in risk may begin at eGFR of $>60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ in the elderly *(32, 33)*. It is now recommended to intensify management of cardiovascular disease risk factors in patients with reduced eGFR *(1, 2)*.

Fourth, clinicians can use the clinical context to assist in the interpretation of eGFR to reduce the risk of misclassification *(15)*. Patients with markers of kidney damage such as albuminuria, or abnormalities on imaging studies or kidney biopsies have CKD, even if eGFR is above $60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. Patients without markers of kidney damage with eGFR $>60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ are unlikely to have CKD. There is some uncertainty with respect to patients without markers of kidney damage with eGFR just $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. Clinical decision making in these cases will depend on other characteristics of the patients, such as the presence or absence of risk factors for CKD or complications of CKD. Clinicians may decide to defer further evaluation in some patients, but it may be prudent to monitor eGFR more frequently, adjust the dose of medications that are excreted by the kidney, and avoid nephrotoxic medications and procedures with increased risk in patients with CKD.

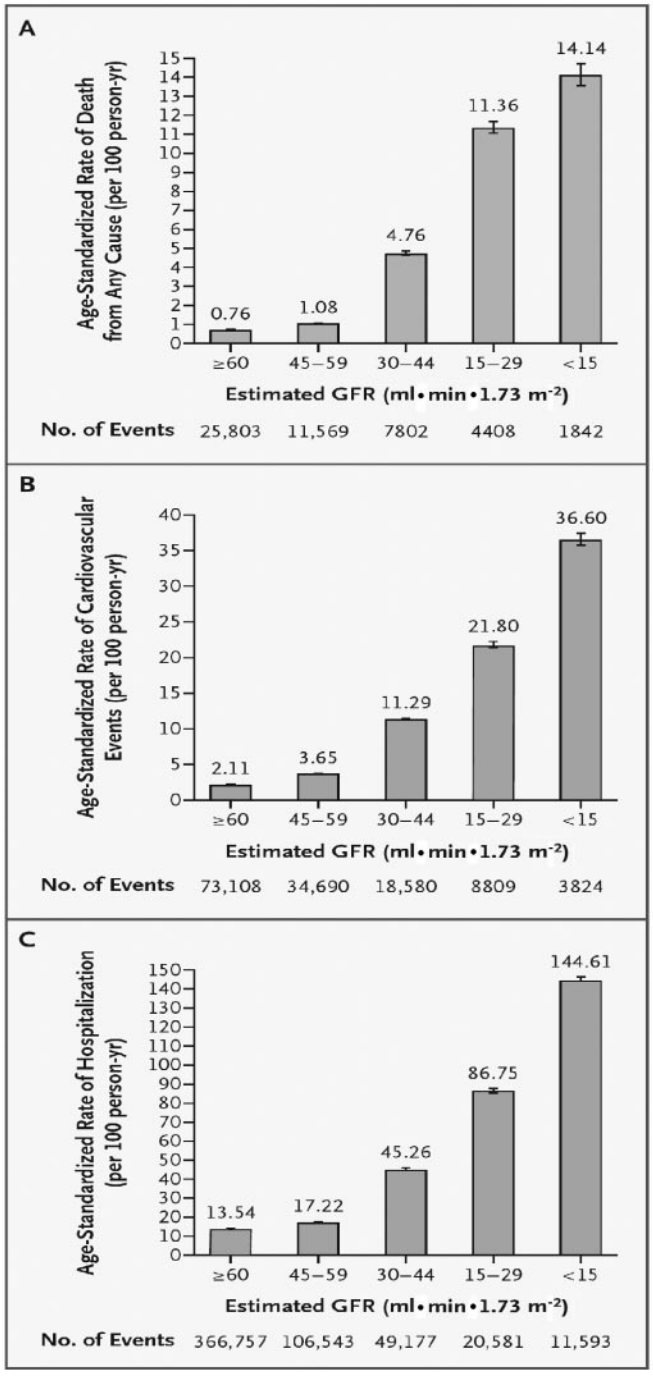

Fig. 1. Relationship between eGFR and clinical outcomes.

Age-standardized rates of death from any cause (*A*), cardiovascular events (*B*), and hospitalization (*C*), according to the eGFR among 1 120 295 ambulatory adults. Reprinted with permission from the *New England Journal of Medicine (32)*.

EDUCATION VS LEGISLATION

There is no single best means to introduce reporting of eGFR. Providing a GFR estimate only on physician re-

quest, as Dr Rainey suggests, seems a poor approach to us. Because serum creatinine is used only to estimate GFR, it seems redundant to ask an ordering physician to request not only the serum creatinine but also the eGFR. Understandably some individuals and groups have been opposed to legislative initiatives that would require mandatory reporting. Recognizing the greater palatability for some of a voluntary system, it is still worth noting that the entire country of France mandates routine creatinine clearance based on the Cockcroft and Gault equation without notable reported problems (personal communication, Jerome Rossert, September 27, 2006). Because, as we have argued, the reporting of eGFR delivers so much more information to the clinician at little incremental cost, routine reporting would seem desirable even without mandates, as is already occurring.

Routine reporting requires education of clinicians, especially the nonnephrologist, about CKD, GFR and GFR estimation. Anecdotally, this has been accomplished rather smoothly in some systems in the US that have undertaken routine reporting. Educational efforts are probably best initiated by laboratorians and nephrologists. It takes time to become accustomed to any new report. Useful educational materials to guide this process are already available for clinicians and patients at NKDEP and National Kidney Foundation websites *(5, 34)*. While GFR estimation will improve with creatinine standardization and better estimating equations, we believe it is reasonably accurate and useful now. Coupled with an appropriate educational program, routine reporting of eGFR will provide clinicians requesting serum creatinine measurements just what they ordered.

L.A.S. is Co-Principal Investigator, Chronic Kidney Disease Epidemiology Collaboration (NIDDK UO1 053869). A.S.L. is Chair, NKF/K-DOQI Workgroup on Clinical Practice Guideline for Chronic Kidney Disease: Classification, Evaluation, and Stratification and Principal Investigator, Chronic Kidney Disease Epidemiology Collaboration (NIDDK UO1 053869). T.H. is a previous Director, National Kidney Disease Education Program, National Institute of Diabetes, Digestive and Kidney Disease. L.A.S. reports receiving lecture fees from Quest Diagnostics and consulting for Medtronics.

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