Clinical Chemistry 61:10
1226–1229 (2015)

Editorials

Using Glomerular Filtration Rate Estimating Equations: Clinical and Laboratory Considerations

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Glomerular filtration rate (GFR)[3] estimating equations, infrequently used just a decade ago, are now recommended for the evaluation of kidney function for routine clinical care and are routinely reported by the vast majority of clinical laboratories *(1)*. Current clinical guidelines recommend estimated GFR (eGFR) based on serum creatinine ($eGFR_{Cr}$) as the initial diagnostic test, and either a measured clearance or estimated GFR based on serum cystatin C or the combination of serum cystatin C and creatinine ($eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$, respectively) as a confirmatory test *(2, 3)*. These recommendations apply to all adults, irrespective of geographic region or clinical presentation.

According to the guidelines, measurement of serum concentrations of creatinine and cystatin C should use assays traceable to international reference measurement procedures and materials, and estimation of GFR should use equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), specifically the 2009 creatinine equation and the 2012 cystatin C and creatinine–cystatin C equations, unless other equations have been found to be more accurate in the population of interest (Table 1) *(4–6)*. The rationale for these recommendations is as follows.

First, serum creatinine concentration is routinely measured in clinical practice, and most commercial creatinine measurement procedures are now well standardized; thus $eGFR_{Cr}$ is available for use as an initial diagnostic test in most clinical encounters in adults. On the other hand, the international reference standard for cystatin C has been developed only recently, and not all commercial assays are sufficiently well standardized for routine clinical use *(7, 8)*. Second, the CKD-EPI equations can be computed from variables that are generally available in clinical and laboratory information systems (age and sex in addition to serum concentrations of creatinine and cystatin C, with separate values reported for African-American individuals) *(9)*. Third, the CKD-EPI equations were developed using standardized assays, thus avoiding analytical method–related biases in eGFR results. Fourth, the CKD-EPI equations were developed in diverse populations with a wide range of GFR values and clinical characteristics (including subjects with and without CKD and diabetes); thus, they are broadly applicable. However, application to selected populations in which the relationship of the filtration marker to measured GFR (mGFR) differs from the relationship observed in the development population will be associated with systematic bias in eGFR. Fifth, even when unbiased, $eGFR_{Cr}$ and $eGFR_{Cys}$ are limited by imprecision (uncertainty) compared with mGFR, owing to variation in non-GFR determinants of creatinine and cystatin C that are not accounted for by other variables in the equations. However, GFR estimates based on both filtration markers are likely to be more precise than estimates based on either marker alone, by minimizing errors due to non-GFR determinants of the serum concentration of each filtration marker. In particular, serum creatinine and cystatin C concentrations appear to be influenced by different clinical factors (Table 1).

Nonetheless, there are numerous clinical conditions in which GFR estimates are less than accurate, and guidelines recommend understanding factors that lead to inaccuracy (Table 1). Rapidly changing GFR (as in development of and recovery from acute kidney injury) leads to non–steady-state conditions for serum concentrations of creatinine and cystatin C, and GFR estimates are more accurate in the steady state. Systematic differences in non-GFR determinants of the filtration markers or analytical biases for the creatinine or cystatin C measurement procedures used in the study population vs those used for equation development lead to systematic bias in eGFR. Higher GFR magnifies errors under these conditions because of the inverse relationship of GFR with filtration marker concentration. In addition, imprecision or systematic differences in GFR measurement procedures between the study populations used during the development and validation of the GFR estimating equation themselves will lead to the appearance of imprecision or bias in eGFR.

In this issue of *Clinical Chemistry*, Meeusen et al. investigated whether some clinical presentations are associated with differences in performance of the CKD-EPI

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Received July 27, 2015; accepted August 3, 2015.
Previously published online at DOI: 10.1373/clinchem.2015.245282
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[3] Nonstandard abbreviations: GFR, glomerular filtration rate; eGFR, estimated GFR; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; mGFR, measured GFR; KDIGO, Kidney Disease: Improving Global Outcomes.

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Table 1. Endogenous filtration markers and CKD-EPI GFR estimation equations recommended by 2012 KDIGO guidelines for use in adults.

Marker	eGFR notation	Reference	Other variables	Clinical conditions that affect non-GFR determinants of serum concentrations of marker[a]	Interference with serum assays for marker[a]	Recommended use	Comment
Creatinine	$eGFR_{Cr}$	Levey et al. 2009 (*4*)	Age, sex, race (African-American vs other)	Alteration in generation due to extremes of body weight (obesity, anorexia), extremes of diet (meat intake or creatine supplements, vegetarian diets), neuromuscular diseases, limb amputation Drug-induced inhibition of tubular secretion (cimetidine, ranitidine, fenofibrate) Decreased extrarenal elimination by inhibition of gut creatininase by antibiotics Increased extrarenal elimination by dialysis, large losses of extracellular fluid (drainage of pleural fluid or ascites)	Spectral interferences (bilirubin, some drugs) Chemical interferences (glucose, ketones, bilirubin, some drugs)	Initial diagnostic test	
Cystatin C	$eGFR_{Cys}$	Inker et al. 2012 (*5*)	Age, sex	Hypo- and hyperthyroidism, glucocorticosteroids, increased extra-renal elimination by dialysis, large losses of extracellular fluid (drainage of pleural fluid or ascites)	Not reported	Confirmatory diagnostic test	As accurate as $eGFR_{Cr}$ without requiring specification of race and may be more accurate if muscle mass is decreased
Creatinine and cystatin C	$eGFR_{Cr\text{-}Cys}$	Inker et al. 2012 (*5*)	Age, sex, race (African-American vs other)	All of the above	All of the above	Confirmatory diagnostic test	More precise than $eGFR_{Cr}$ or $eGFR_{Cr\text{-}Cys}$[b]

[a] Larger errors at higher eGFR.
[b] Less uncertainty compared with mGFR.

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equations *(10)*. The authors compared performance of $eGFR_{Cr}$, $eGFR_{Cys}$, and $eGFR_{Cr\text{-}Cys}$ in a study population of 1612 patients who underwent GFR measurements at the Mayo Clinic, including potential kidney donors, patients with chronic kidney disease, and patients with a history of a kidney or other solid organ transplant. They observed generally good performance of the estimating equations across all clinical presentations: the mean percent biases of $eGFR_{Cr}$, $eGFR_{Cys}$, and $eGFR_{Cr\text{-}Cys}$ were −11.6%, 4.8%, and −2.7%, respectively, in potential donors; −0.8%, 0.1%, and −1.9% in CKD patients; 0.5%, −5.4%, and −4.8% in kidney transplant recipients; and 1.3%, −7.7%, and −5.6% in other organ transplant recipients. Concordance of eGFR vs mGFR categories was best for $eGFR_{Cr\text{-}Cys}$ in all presentations.

Differences in equation performance were significant in some subgroups based on clinical presentation or level of GFR. $eGFR_{Cr}$ had significantly larger bias (negative) than $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ among potential donors. $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ had significantly larger bias (negative) than $eGFR_{Cr}$ among transplant recipients with eGFR <45 mL · min^{-1} · (1.73 m^2)$^{-1}$. The authors speculated that underestimation of mGFR by $eGFR_{Cr}$ in potential donors is consistent with the higher creatinine generation in healthy donors, and that underestimation of mGFR by $eGFR_{Cys}$ in transplant recipients may be related to effects of inflammation or immunosuppression on non-GFR determinants of cystatin C. They concluded that their findings support a "conceptual shift" in which "the exact method used to assess GFR is chosen on the basis of the type of patient being treated and the indication for testing." They advised further that $eGFR_{Cr}$ not be used in kidney donor evaluations and $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$ not be used in transplant recipients.

Strengths of the study include the use of rigorous statistical techniques and large sample size, allowing valid detection of small differences in bias between groups. The laboratory methods are similar to those used in development of the CKD-EPI equations, including GFR measurement using urinary clearance of iothalamate and measurement procedures for creatinine and cystatin C that have been shown to have very good traceability to international reference systems, allowing inferences that systematic differences in equation performance between patient groups likely reflect biases due to patient clinical characteristics rather than measurement procedure. There are important limitations of the study. The clinical presentations were defined by the level of kidney function, and the recommendations appear more directed to nephrology and transplantation specialists than general clinicians. By contrast, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are directed to all clinicians, including those in general practice and other specialists, and are relevant to clinical presentations in which the level of kidney function is not already known. Further, the methods used to select patients in the study by Meeusen et al. may have contributed to some of the findings: for example, underestimation of mGFR by $eGFR_{Cr}$ in potential donors was greater at lower eGFR (<90 mL · min^{-1} · (1.73 m^2)$^{-1}$) than at higher eGFR, as would be expected if donors were selected by mGFR in addition to $eGFR_{Cr}$. The sample sizes for comparison of some subgroups based on both clinical presentation and eGFR level are small, which may have led to some chance findings. Inferences about equation performance are based primarily on bias, with less consideration of precision compared with mGFR (for example, their emphasis on the modeled bias shown in Fig. 2 rather than the imprecision of eGFR shown in Fig. 1). Other studies *(11)*, including a prior report from the Mayo Clinic group *(12)*, generally show better precision for $eGFR_{Cr\text{-}Cys}$ than either $eGFR_{Cr}$ or $eGFR_{Cys}$. Both bias and imprecision contribute to the overall accuracy of individual GFR estimates *(13)*. Inferences about bias are expressed on a percentage scale, rather than a raw scale, which can exaggerate the clinical importance of differences in bias at lower GFR. For example, a 10% bias at an eGFR of 30 mL · min^{-1} · (1.73 m^2)$^{-1}$ is a difference of only 3 mL · min^{-1} · (1.73 m^2)$^{-1}$.

In our opinion, the authors may have somewhat overstated the clinical importance of their findings. Although we do not dispute that there are systematic differences in bias between $eGFR_{Cr}$ and $eGFR_{Cys}$, we do not agree with some of their conclusions. For example, we do not agree that $eGFR_{Cr}$ is not useful for evaluation of potential kidney donors; indeed, $eGFR_{Cr}$ is a reasonable initial diagnostic test for evaluation of kidney donors. Furthermore, current regulations for donor evaluation in the US require performance of clearance measurements for confirmation of the level of GFR *(14)*. Indeed, the data from the study by Meeusen et al. suggest that $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ should be evaluated as an alternative confirmatory test. We do not agree that $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ are not useful in evaluation of organ transplant recipients; indeed, Meeusen et al. showed that the concordance of eGFR and mGFR categories was highest for $eGFR_{Cr\text{-}Cys}$ among transplant recipients. The improvement in precision of $eGFR_{Cr\text{-}Cys}$ compared with $eGFR_{Cr}$ may outweigh the small improvement in bias of $eGFR_{Cr}$ compared with $eGFR_{Cys}$. Our overall interpretation is that the study by Meeusen et al. provides important confirmation of the relatively good performance of all 3 estimating equations across a variety of presentations particularly important to nephrology and transplantation specialists, including generally better performance of $eGFR_{Cr\text{-}Cys}$ than either $eGFR_{Cr}$ or $eGFR_{Cys}$. We agree with Meeusen et al. that the finding of systematic differences in bias across clinical presentations is likely a result of systematic differences in non-GFR determinants of

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filtration marker concentrations. Further investigation of the cause for these systematic differences in non-GFR determinants is likely worthwhile. However, we do not agree that their findings suggest the need for a "conceptual shift" from the strategy recommended by the KDIGO guidelines for the use of eGFR in general clinical practice.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: J.H. Eckfeldt, Gentian.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: The Division of Nephrology at Tufts Medical Center receives funding from NIH. J.H. Eckfeldt, NIH.
Expert Testimony: None declared.
Patents: A.S. Levey, patent pending (PCT/US2015/044567): Precise estimation of glomerular filtration rate from multiple biomarkers.

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