Summary
The application of serum creatinine and cystatin C in patients with CKD has been limited to using estimated glomerular filtration rate (eGFR). Criteria for choosing the best GFR estimating equation are 1) accuracy in estimating measured GFR, 2) optimal discrimination of clinical outcomes, and 3) association with CKD risk factors and outcomes similar to that of measured GFR. Notably, these criteria are often not in agreement; and while the last criterion is the most important, it has been widely overlooked. The primary problem with eGFR is that the non-GFR determinants of serum creatinine and cystatin C, as well as their surrogates (age, sex, and race), associate with CKD risk factors and outcomes. This leads to a distorted understanding of CKD, though eGFR based on serum creatinine appears to be less biased than eGFR based on cystatin C. Because of this problem, the use of eGFR should be limited to settings where knowing actual GFR is relevant and eGFR is more informative about GFR than serum creatinine or cystatin C alone. Such settings include staging CKD severity by GFR and dosing medications cleared by glomerular filtration. Alternatively, the diagnosis of CKD, the longitudinal progression of CKD, and prognostic models for CKD are settings where serum creatinine and cystatin C can be better applied and interpreted without eGFR.

The Guidelines
The Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (1) recommend that CKD be diagnosed, classified, and staged by GFR. Throughout the guidelines, specific recommendations for clinical management of CKD are based on the GFR. In most patients, estimated (eGFR) calculated by an equation is recommended for determining the GFR. These new guidelines make specific recommendations for the GFR estimating equation that should be used (until more accurate alternative equations are developed). First, they recommend use of the 2009 CKD-Epidemiology Collaboration (CKD-EPI) equation (2) instead of the Modification of Diet in Renal Disease (MDRD) study equation (3) to estimate GFR from serum creatinine (eGFRcr). Second, they suggest use of the 2012 CKD-EPI equations (4) to estimate GFR (eGFRcys or eGFRcr-cys) whenever cystatin C has been measured. In particular, they suggest using eGFRcys or eGFRcr-cys whenever a confirmatory test is required in patients with an eGFRcr of 45–59 ml/min per 1.73 m² who do not have markers of kidney damage (a common occurrence in elderly adults).

Criteria for Evaluating GFR Estimating Equations
A criterion provided in these guidelines is that the equation most accurately reflecting the value of measured GFR (mGFR) should be used. Another criterion is that CKD classification and staging by eGFR should be influenced primarily by clinical prognosis, as determined by the risk for adverse outcomes (e.g., metabolic complications, kidney failure, cardiovascular events, and death). As such, eGFRcys clearly improves risk stratification over eGFRcr alone (5–7). However, this raises a fundamental question as to the optimal criteria for evaluating GFR estimating equations. Is the goal accuracy in estimating mGFR (criterion 1) or is it optimal discrimination of clinical outcomes (criterion 2)? This commentary argues that these two criteria sometimes disagree and that neither one is the best criterion for staging CKD. A third, widely overlooked, criterion (criterion 3) for identifying the equation closest to the “truth” is similar performance to that of mGFR with respect to association with CKD risk factors and outcomes (Figure 1). To the extent that eGFR differs from mGFR with respect to these associations (causal or not), our understanding of CKD is distorted.

Is the Goal Estimation of GFR or Prediction of Outcomes?
To highlight the tension between criterion 1 and criterion 2, consider two recent meta-analyses comparing eGFRcr by the MDRD study equation with the 2009 CKD-EPI equation. The first meta-analysis compared these two equations with respect to how accurately they estimated mGFR using 13,000 adults from 12 cohorts. They found that neither equation was optimal for all populations, but there was a tradeoff: The MDRD study equation was more accurate in high-risk populations, and the 2009 CKD-EPI equation was more accurate in low-risk populations (8). For example, the largest study in this meta-analysis found less overestimation of mGFR with the MDRD study versus the 2009 CKD-EPI equation in patients...


- Criterion 1. Accuracy in estimating measured GFR.
- Criterion 2. Optimal discrimination of clinical outcomes.
- Criterion 3. Association with CKD risk factors and outcomes similar to that of measured GFR.

Figure 1. Criteria that have been used to determine the best GFR estimating equation.

<table>
<thead>
<tr>
<th>Population</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Measured GFR</td>
<td>ESRD or mortality</td>
</tr>
<tr>
<td>2009 CKD-EPI Equation</td>
<td>2009 CKD-EPI Equation</td>
<td></td>
</tr>
<tr>
<td>2009 CKD-EPI Equation</td>
<td>MDRD Study Equation</td>
<td></td>
</tr>
</tbody>
</table>

The Non-GFR Determinants of eGFR Are a Problem

The non-GFR determinants of an endogenous filtration marker can themselves contribute to the prediction of CKD outcomes because age, sex, and race only partially model the non-GFR determinants. A good example of this is the superior performance of cystatin C or eGFRCys compared with eGFRCr in predicting CKD outcomes (criterion 2) (5–7,16,17), despite the similar performance between eGFRCys and eGFRCr in estimating mGFR (criterion 1) (4,18,19). The 2012 KDIGO guidelines suggest that eGFRCys be used as a confirmatory test in patients with an eGFRCr of 45–59 ml/min per 1.73 m² when the diagnosis of CKD is less certain. This is supported by data showing that the increased risk of treated ESRD, mortality, and CVD outcomes is mostly limited to the subset of patients with an eGFRCys <60 ml/min per 1.73 m² (5–7). But this is very likely due to the non-GFR determinants of cystatin C being predictive of morbidity and mortality rather than just improved estimation of GFR by cystatin C. First, an elevated cystatin C level is just as predictive of mortality in persons without CKD (in whom GFR variation is physiologic) as it is in persons with CKD (in whom GFR variation is pathologic) (6). Second, hyperfiltration by mGFR or urinary creatinine clearance is associated with CKD risk factors and complications (obesity, diabetes, hypertension, left ventricular hypertrophy) (20–24), with developing albuminuria (25–28), with structural abnormalities in the kidney (cysts, enlarged kidneys, and decreased glomerular density) (29–33), and with subsequent GFR decline and ESRD (29,34,35). Although eGFRCr also identifies hyperfiltration as an increased-risk state (16,24,28,35,36), eGFRCys identifies hyperfiltration as a low-risk state (Figure 3) (16,23,24,35).

Surrogates for Non-GFR Determinants of eGFR Are a Problem

Some might find it surprising that more accurate estimation of mGFR by eGFR (criterion 1) does not always translate into better discrimination of clinical outcomes (criterion 2). One reason for this is that the surrogates (age, sex, and race) for the non-GFR determinants of endogenous filtration markers (generation, metabolism, and nonglomerular excretion rate) are themselves predictive of outcomes such as mortality and ESRD. For example, creatinine-based equations use age, sex, and race as surrogates for muscle mass, the dominant source of endogenous creatinine generation. An equation for estimating urinary creatinine clearance has similar accuracy whether based on age and sex or based on a direct measurement of muscle mass. But for predicting mortality, the equation based on age and sex outperforms the equation based on muscle mass because age is a more potent predictor of mortality than is muscle mass (15). Likewise, the better performance of the 2009 CKD-EPI equation compared with the MDRD study equation in predicting mortality can be partially attributed to the increased contribution of age to the GFR estimate, particularly in the higher eGFR range with the 2009 CKD-EPI equation (serum creatinine contributes less to the estimate when ≤0.9 mg/dl in men and ≤0.7 mg/dl in women). The logical, but often overlooked, conclusion is that the more emphasis an eGFR equation gives age in the calculation, the better the equation will perform in predicting age-related outcomes. eGFR does not distinguish age, sex, and race as surrogates for non-GFR determinants of markers from age, sex, and race as predictors of clinical outcomes.

with CKD (3% versus 6%) and transplant recipients (1% versus 8%), but less estimation of mGFR with the 2009 CKD-EPI versus the MDRD study equation in predonation kidney donors (−8% versus −18%) and postdonation kidney donors (−7% versus −15%) (9). Because not one eGFRCr equation is optimal across the spectrum of health (high creatinine generation) and CKD (low creatinine generation) (10,11), this finding is expected. The second meta-analysis of these two equations compared prediction of mortality and ESRD using 1.1 million adults from 45 cohorts. They found the 2009 CKD-EPI equation was better than the MDRD study equation in discriminating mortality and ESRD in both high-risk and low-risk populations (12). As shown in Figure 2, these two meta-analyses disagree about which equation is better in high-risk populations, depending on the criterion used. Although we may care most about prediction of clinical morbidity and mortality (13), we should keep in mind that these equations were specifically designed to estimate mGFR, not predict prognosis (14).
A Simple Test for Non-GFR Biology with Any Endogenous Filtration Marker

Ample evidence suggests that both serum creatinine and cystatin C reflect non-GFR biology. mGFR is based on ideal exogenous markers that are metabolically inert and exclusively cleared by glomerular filtration, such as inulin, iohexol, or iothalamate. eGFR is a statistical model that estimates mGFR from endogenous filtration markers. Endogenous filtration markers are generated at varying rates, can be metabolically active (cystatin C is a protease inhibitor), and are cleared by mechanisms other than solely by glomerular filtration. Importantly, the non-GFR determinants of endogenous filtration markers vary across the spectrum of health and CKD. A simple plot can demonstrate the imperfect association between an endogenous filtration marker and mGFR (Figure 4). An ideal endogenous filtration marker would have an exponential coefficient of $-1$ with mGFR consistent with clearance physiology (GFR should be proportional to 1 divided by the ideal marker level because GFR = UV/P, where U is the urine level, V is the timed volume of urine, and P is the plasma level). So far, no endogenous filtration marker has been shown to have an exponential coefficient of $-1$ with mGFR. Serum creatinine has an exponential coefficient of about $-1.2$ with mGFR (2,3,37), consistent with decreased creatinine generation and increased tubular secretion of creatinine as GFR declines (10,38). Cystatin C has an exponential coefficient of about $-1.3$ with mGFR (4,18,39), but the reasons for this are not clear. Evidence suggests that the non-GFR determinants (possibly endogenous generation rate) for increased cystatin C levels are associated with obesity, inflammation, and atherosclerosis (10,24,40–43), findings common among patients with CKD. However, if CKD leads to increased cystatin C generation, then an exponential coefficient $>1$ with mGFR would be expected, not the $-1.3$ with mGFR that has been detected. Clearly, more work is needed to understand the biology of cystatin C in order to interpret serum levels correctly.

The eGFR$_{Cr-Cys}$ Paradox

It is worth considering whether combining serum creatinine and cystatin C into one equation to estimate GFR (eGFR$_{Cr-Cys}$) will compensate for the limitations of each of these markers alone. It has been shown that eGFR$_{Cr-Cys}$ does indeed improve the accuracy of mGFR estimation over eGFR$_{Cr}$ or eGFR$_{Cys}$ in a variety of populations (criterion 1) (4,18,19,44,45). However, eGFR$_{Cr-Cys}$ is inferior to eGFR$_{Cr}$ by another criterion (criterion 3). As shown in Figure 5, the association between most CKD risk factors and GFR was more consistent between eGFR$_{Cr}$ and mGFR than between eGFR$_{Cr-Cys}$ and mGFR (10). The small improvement in
estimation of mGFR with the addition of cystatin C to serum creatinine comes at the cost of less accurate representation of the true association between GFR and common CKD risk factors. This leads to the eGFRCr-Cys paradox: eGFRCr-Cys is superior for the estimation of mGFR (criterion 1) and superior for the prediction of outcomes because it contains cystatin C (criterion 2), but eGFRCr is superior for associating with most CKD risk factors in a manner that is similar to mGFR (criterion 3). For eGFR to be used for diagnosing and staging CKD, we would argue that criterion 3 is the most relevant.

Imprecision with mGFR Is a Problem That Can Be Adequately Addressed

It has been argued that imprecision (within-individual error) with mGFR is responsible for suboptimal performance of mGFR compared with eGFR (criterion 2). mGFR error does have a small effect on evaluating the performance of eGFR by criterion 1 (46). However, all laboratory tests have error, including both eGFR and mGFR. The difference is that averaging repeated measures of mGFR to reduce error will always approach true GFR, whereas averaging repeated measures of eGFR to reduce error will remained biased by non-GFR determinants. For example, patients with muscle mass that is higher than average for their age, sex, and race will have an average eGFRCr that is lower than true GFR, and patients with muscle mass that is lower than average for their age, sex, and race will have an average eGFRCr that is higher than true GFR. Error is best determined by the test-retest reliability, which does not appear to differ much between eGFR and mGFR (10,47). To the extent that eGFR error is similar in magnitude to mGFR error, differences in method precision do not explain stronger associations with eGFR compared with mGFR.

The effect of mGFR error on associations with CKD risk factors or outcomes can also be addressed with appropriate study design and statistical methods. In fact, most GFR estimating equations are derived in a manner that minimizes the effect of mGFR error by making mGFR the dependent variable in a standard regression model. A similar approach can be used to minimize the effect of error on associations with eGFR and mGFR. eGFR and mGFR can be simultaneously modeled as dependent variables to minimize their error using generalized estimating equations (10). Alternatively, “error-in-variables” statistical models can be used to account for mGFR error (24). Finally, studies that obtain repeated measures of mGFR and eGFR can use various averaging techniques to minimize error. For criterion 3, use of thoughtful study design and statistical methods can help ensure that differences in associations with eGFR versus mGFR are not explained by differences in error.

Using Endogenous Filtration Markers without Using eGFR

We disagree that the better discrimination of outcomes by eGFR than by mGFR (criterion 2) implies that mGFR is not the “gold standard” (48) because eGFR is predicated on mGFR being the “gold standard.” Nonetheless, the optimal discrimination of CKD outcomes (criterion 2) is arguably what matters most with the application of endogenous filtration markers to patient care. The problem is that some markers, such as cystatin C, are superior to mGFR in discriminating prognosis (24,35,48,49). In such cases, the answer may not be with the eGFR construct. As shown in Figure 6, the current approach takes a statistical model (eGFR) for predicting mGFR and relates this statistical model to outcomes, risk factors, and renal pathology. An alternative approach is to limit the use of eGFR to settings where the actual filtration rate is relevant, such as dosing of drugs cleared by glomerular filtration or staging the severity of CKD. In other settings, endogenous filtration markers could be reported and interpreted in relation to outcomes, risk factors, comorbidity, and renal pathology.
pathology without resorting to the use of eGFR. A better understanding of the non-GFR biology of endogenous filtration markers would improve their clinical interpretation. Developing models that optimally use endogenous filtration markers to determine clinical outcomes would also be helpful. By doing so, CKD would be refocused on using endogenous filtration markers to characterize clinically relevant aspects of disease, instead of estimating another test (mGFR) for disease.

**Practical Implications**

In our opinion, the application of endogenous filtration markers in CKD needs radical change in order to advance the field. The main principles should be to limit the use of eGFR to settings where (1) actual GFR is relevant and (2) eGFR is clearly more informative about GFR than simply using the serum level of the filtration marker. The problem with defining CKD by abnormal levels of GFR is that the GFR threshold varies by method. For example, the fifth percentile for eGFR Cr is about 10 to 15 ml/min per 1.73 m² lower than the fifth percentile for mGFR (50). We would define CKD by an elevated serum creatinine level relative to a health-associated reference ranges (e.g., 0.6–1.1 mg/dl in women and 0.8–1.3 mg/dl in men). Health-associated reference ranges (typically 2.5th to 97.5th percentiles) are used for most clinical laboratory tests (51). These ranges should be age-, sex-, and race-specific as needed. In particular, we see no value in telling older persons with normal serum creatinine levels that they have CKD based on eGFR Cr < 60 ml/min per 1.73 m² alone (52–54). Confirmatory testing in selected patients should be done using abnormal levels of mGFR or urinary creatinine clearance, also based on health-associated reference ranges. The role of abnormal serum levels of cystatin C as a confirmatory test for CKD requires further work. In particular, to what extent are abnormal cystatin C levels among patients with normal serum creatinine levels due to non-GFR pathology?

We agree with staging the severity of CKD by GFR, but we would use the GFR estimating equation that most closely reflects mGFR based on criterion 3. eGFR Cr appears to be superior to eGFR Cr,Cys or eGFR Cys,α but whether the MDRD study equation or the 2009 CKD-EPI equation best reflects criterion 3 requires further work. Knowing the actual GFR is particularly relevant for dosing medications that are predominantly cleared by glomerular filtration, and this may be a setting where eGFR equation selection by criterion 1 is more important than selection by criterion 3. Prognostic models that estimate kidney failure risk are clearly needed (55), but instead of eGFR by criterion 2, the optimal combination of serum creatinine, serum cystatin C, age, sex, race, and other clinical factors should be used when the goal is to estimate risk of kidney failure, not GFR. Finally, we would define CKD progression by changes in endogenous filtration marker levels (e.g., doubling of serum creatinine level) as opposed to changes in eGFR (e.g., 50% decrease in eGFR Cr). Our rationale is that change in eGFR is not more informative than the change in serum level of the filtration marker. The sex and race components of eGFR do not change, and changes in the age component of eGFR are universal and do not discriminate progression.

**Conclusions**

GFR estimating equations are not moving us closer to the truth because eGFR is not being judged by the most important criterion (criterion 3). Criterion 3 is important because eGFR should have the same association with CKD risk factors and outcomes as mGFR. To the extent that criterion 3 is not met, our understanding of kidney disease is based on biologic processes other than kidney function. Some endogenous filtration markers, such as cystatin C, outperform mGFR in predicting outcomes. Such markers will perform well by criterion 2, but at the expense of the more relevant criterion 3. We should not estimate an inferior test (mGFR) from such markers in order to apply them within prediction tools for clinical practice. BUN, a well known endogenous filtration marker, is widely used to identify and manage prerenal states, such as heart failure (56), without being reported as eGFR BUN. Likewise, avoiding the flawed eGFR construct with cystatin C and similar markers would prevent their misinterpretation as GFR and potentially improve their utility in patient care.

**Acknowledgments**

A.D.R. was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (Mayo Clinic O’Brien Urology Research Center DK83007) from the National Institutes of Health, U.S. Public Health Service. The authors thank Pierre Delanaye for his thoughtful feedback.

**Disclosures**

The authors reported no disclosures related to the content of the manuscript. Please see the Supplemental Material to view unrelated disclosures.

**References**


42. Staun-Ram E, Miller A: Cathepsins (S and B) and their inhibitor Cystatin C in immune cells: Modulation by interferon-β and role played in cell migration. J Neuroimmunol 232: 200–206, 2011

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01240213/-/DCSupplemental.