Kidney Medicine

Beyond Creatinine: Is Cystatin C the New Global Standard for Estimated Glomerular Filtration Rate Evaluation?

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Accurate assessment of kidney function plays an essential role in routine clinical practice by serving multiple purposes, including diagnosis, prognostication, risk stratification, medication dosing, and guidance surrounding

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therapeutic decisions. Measured glomerular filtration rate (GFR), the gold standard for kidney function assessment,[1] can be determined via clearance of exogenous filtration markers, such as inulin, iothalamate, iohexol, diethylenetriaminepentaacetic acid, or ethylenediaminetetraacetic acid. However, routine measurement of GFR is impractical because it is complex, cumbersome, time-consuming, and expensive. Instead, estimated glomerular filtration rate (eGFR) is generally used because it allows for an efficient and inexpensive method by which to assess kidney function using endogenous filtration markers. Traditionally, creatinine has been the endogenous filtration marker used in eGFR equations; however, cystatin C is an emerging alternative that can be measured in isolation or in combination with creatinine.

Over the past 50 years, a number of eGFR equations focusing primarily on creatinine were developed and implemented to varying degrees into clinical practice.[2-8] The eGFR value most commonly reported by clinical laboratories comes from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation,[4-6] which is recommended by the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines.[1] Notably, the CKD-EPI equations were updated in 2021 to omit a race-based "correction term" from their calculations.[6] Other eGFR equations, such as those from the European Kidney Function Consortium, have similarly followed suit.[8] Although creatinine-based eGFR equations were historically used in routine clinical practice, the powerful recent initiative to eliminate race from eGFR calculations greatly strengthened the motivation to adopt new markers in eGFR equations that are race-independent, such as cystatin C.[9]

Given the evolving landscape of eGFR equations, questions surrounding the accuracy of creatinine- versus cystatin C-based eGFR values naturally emerge along with what (if any) clinical implications these potential inaccuracies may bear. As such, multiple recent population-based observational studies have aimed to address $eGFR_{Cr}$ versus $eGFR_{CysC}$ differences.[10-15] It appears, on average, that $eGFR_{CysC}$ is lower than $eGFR_{Cr}$. Furthermore, approximately 30% of individuals with both $eGFR_{Cr}$ and $eGFR_{CysC}$ measurements demonstrated a discrepancy of 15 mL/min/1.73 m^2 or more. Those individuals with the most substantial decrease in eGFR when transitioning from creatinine-based equations to cystatin C-based equations were older with greater albuminuria and more comorbid conditions. These differences were not trivial because adverse outcomes, including acute kidney injury, end-stage kidney disease, major adverse cardiovascular events, and death were more common in those with a greater discrepancy. Therefore, identifying discordance between $eGFR_{Cr}$ and $eGFR_{CysC}$ appears to be of major clinical relevance.

These common, and often prominent, interindividual differences between $eGFR_{Cr}$ and $eGFR_{CysC}$ suggest that there are likely non-GFR–related variables at play that must be considered. For instance, perhaps the most well-known and reported factor is race because historical observational data reported that Black individuals had higher average serum creatinine levels than non-Black individuals.[16] This was the driving rationale for the inclusion of a race-based "correction term" that, for any given serum creatinine level, results in a higher eGFR value for Black vs non-Black individuals. Ultimately, these race "correction terms" have largely gone by the wayside given that race is a social (rather than biological) construct that ignores the wide genetic diversity within individuals who self-identify as Black.[9] An advantage of cystatin C-based eGFR equations was the apparent limited variation between races, thus supporting their more widespread adoption as a true "global" endogenous filtration marker. Notably, other important factors beyond race may contribute to measurement discrepancies, including muscle mass, obesity, diet, physical activity, smoking, and medications/substances that influence tubular secretion.[17,18] However, an enhanced understanding of the relative importance of each of these factors to eGFR discrepancy would better facilitate interpretation.

In this issue of *Kidney Medicine*, Chen et al[19] conducted a large observational study using the UK Biobank to assess the prevalence and predictors of discordance between creatinine- and cystatin C-based eGFR equations. The UK Biobank comprehensively collects data on a wide range of sociodemographic, lifestyle, comorbid condition, medication, physical, and laboratory non-GFR factors that facilitated multivariable modeling methods to examine differences between $eGFR_{Cr}$ and $eGFR_{CysC}$. The study included ~500,000 adults aged 40-69 years with a mean eGFR of ~90 mL/min/1.73 m^2 at the time of enrollment (2006-2010) who underwent standardized health and

lifestyle assessments along with same day measurements of serum creatinine and cystatin C. $eGFR_{Cr}$ was calculated using the 2021 CKD-EPI_{Cr} equation[6] whereas $eGFR_{CysC}$ was calculated using the 2012 CKD-EPI_{CysC} equation.[5]

The mean $eGFR_{CysC}$ (88 mL/min/1.73 m^2) was lower on average than $eGFR_{Cr}$ (95 mL/min/1.73 m^2), consistent with prior studies.[19] Similarly, 30% of individuals had an $eGFR_{Cr}$ and $eGFR_{CysC}$ difference of 15 mL/min/1.73 m^2 or greater, comprised of 25% with $eGFR_{CysC}$ lower than $eGFR_{Cr}$ by 15 mL/min/1.73 m^2 or more and 5% with $eGFR_{Cr}$ lower than $eGFR_{CysC}$ by 15 mL/min/1.73 m^2 or more. In multivariable analysis, prominent predictors of $eGFR_{CysC}$ being lower than $eGFR_{Cr}$ included older age, male sex, South Asian ethnicity, smoking, lower socioeconomic status, comorbid conditions (eg, diabetes, hypertension, cancer, and thyroid disease), glucocorticoid use, waist circumference, body fat percent, and greater albuminuria. Prominent predictors of $eGFR_{Cr}$ being lower than $eGFR_{CysC}$ included Black race (odds ratio, 7.32; 95% confidence interval, 6.80-7.89), dietary meat consumption, and use of trimethoprim-containing medications. The investigators also developed and tested the following 3 prediction models for identifying likely $eGFR_{Cr}$ vs $eGFR_{CysC}$ discordance: (1) an all-encompassing model, (2) excluding race/ethnicity, and (3) a simplified clinical model restricted to only variables collected as part of routine practice. All models demonstrated fair-to-good discrimination (C-statistic in the 0.70-0.75 range) along with good calibration.

Several limitations of this study should be taken into consideration. Most notably, the lack of measured GFR does not allow for the determination of whether serum creatinine or cystatin C was the primary source of bias in cases of wide eGFR discordance. Moreover, the reliance on single-day serum creatinine and cystatin C values does not account for the day-to-day variability in these measurements that can impact eGFR calculation and potentially the discordance between creatinine- and cystatin C-based results.[20] Nevertheless, this study provides a nice addition to the literature in assessing the non-GFR factors that may explain differences between creatinine- and cystatin C-based eGFR values. Encountering eGFR differences will become increasingly frequent with more widespread adoption of cystatin C measurements. As opposed to simply looking at single factors in isolation, the present study used expansive multivariable models to comprehensively identify independent associations between a host of variables and $eGFR_{Cr}$ versus $eGFR_{CysC}$ discordance.

Does this study suggest that cystatin C is ready for widespread adoption and to be crowned the new king of eGFR? It is not that clear-cut. First, it hints at a broader spectrum of race/ethnicity contributions to eGFR discordance, which historically focused solely on Black versus non-Black comparisons. Not only did the study find that Black individuals had more than 7-fold higher odds for having lower $eGFR_{Cr}$, but it also found that South Asians had 60% higher odds for having lower $eGFR_{CysC}$. This illustrates and complicates the optimal filtration marker in racially and ethnically diverse populations. Second, cystatin C is significantly more expensive than serum creatinine thereby limiting its use in resource-limited settings. Certainly, the costs of widespread measurements of cystatin C may not be feasible in all locations. Therefore, there may be instances in which the need for cystatin C should be determined on a case-by-case basis rather than for the entire population. Identifying specific subpopulations in which a wide discrepancy between creatinine- and cystatin C-based eGFR measures would be expected because of non-GFR factors may help to better prioritize these finite testing resources. Finally, because nephrologists will increasingly need to compare creatinine- and cystatin C-based eGFR results, standardized creatinine values traceable to isotope dilution mass spectrometry and standardized cystatin C values traceable to the International Federation of Clinical Chemistry and Laboratory Medicine should exclusively be employed. This will allow for a more reliable, standardized approach in both clinical practice and future research studies by which to compare eGFR results.

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