LETTERS TO THE EDITOR

Multiple-Biomarker Panel Estimated GFR Is Not Optimal or Cost-Effective

To the Editor:

The race-independent glomerular filtration rate (GFR) estimating equation with creatinine, cystatin C, β-trace protein (BTP), and β_2-microglubulin (B2M) proposed by Inker et al[1] as a replacement for creatinine-based equations is neither optimal nor cost-effective. In a recent study of 2,893 plasma proteins, 680 correlated with measured GFR (mGFR), with cystatin C showing the highest correlation, while B2M was not among the 8 best.[2] The results by Inker et al show that the improvement of $1 - P_{30}$, when using the recommended cystatin C-B2M-BTP equation ($1 - P_{30} = 15.6$), rather than the one based only upon cystatin C ($1 - P_{30} = 17.4$), is not clinically significant and the lack of international calibrators for B2M and BTP will make it very difficult to reproduce this possible advantage in clinical practice. An international calibrator for cystatin C exists and if one wishes to remove the race factors connected with the use of creatinine by using race-independent plasma proteins, it is more convenient and less expensive to use a weighted 2-marker equation, that is, $eGFR = {}^1/_4 \times (eGFR_{cr} + 3 \times eGFR_{cys})$, than to add new proteins without international calibrators and with lower correlations to mGFR. The cystatin C–based CAPA equation (calculator at www.egfr.se/eGFRen.html), validated from 1 year of age and for Asian and European ancestry[3] and African American[4] populations and without a sex term, combined with a creatinine-based equation provides more useful information,[5] at lower cost.

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Comparing Multiple-Biomarker Panels for Estimating GFR With Estimating Equations Without a Coefficient Distinguishing Black Individuals From Persons of Other Groups

To the Editor:

Inker et al[1] propose a new estimated glomerular filtration rate (GFR) equation integrating a panel of biomarkers (creatinine, cystatin C, β-trace protein, and β_2-microglubulin) as an alternative to the creatinine-based CKD-EPI equation ($CKD\text{-}EPI_{cr}$). This equation—the most used GFR-estimating equation—has recently been criticized for applying a discriminative term based on self-reported race.[2] Inker et al convincingly demonstrated that their triple marker–based equation performs better than the CKD-EPI equation based on cystatin C only, a race-independent estimator.[3] While we understand the rationale behind choosing a cystatin C–based comparator, we believe that comparison with the classical $CKD\text{-}EPI_{cr}$ equation with its race factor deleted would be more relevant. Interestingly, the same authors recently reassessed the applicability of the $CKD\text{-}EPI_{cr}$ without its race factor in a population of African Americans and found performance criteria (bias, +4 mL/min/1.73 m^2; RMSE, 0.258)[4] quite similar than those reported in the present study (where the corresponding values were +6.3 mL/min/1.73 m^2 and 0.245, respectively).[1] A direct comparison between the $CKD\text{-}EPI_{cr}$ without use of its race factor and the novel triple-marker equation is thus important to thoroughly evaluate the added value of the latter, especially given the extra cost that would necessarily come with its wider use (which eventually could represent another form of discrimination). Likewise, the added value of the 4-marker equation without race is uncertain in comparison to the CKD-EPI equation combining cystatin C and creatinine,[3] when the race factor (1.08) is omitted. In sum, we question the cost-effectiveness of the multi-panel strategy, particularly in low-income populations.[5]

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In Reply to "Multiple-Biomarker Panel Estimated GFR Is Not Optimal or Cost-Effective" and "Comparing Multiple-Biomarker Panels for Estimating GFR With Estimating Equations Without a Coefficient Distinguishing Black Individuals From Persons of Other Groups"

We appreciate the comments of Drs Grubb, Christensson, and Björk[1] and Drs Delanaye and Mariat,[2] who have made important contributions to estimated glomerular filtration rate (eGFR). Grubb et al agree that eGFR using cystatin C or using the 3-marker panel that includes cystatin C, β_2-microglubulin (B2M), and β-trace protein (BTP), which do not require use of race, is not as accurate as using the combination of cystatin C and creatinine, which requires use of race.[3] We agree that assay standardization for all markers is a prerequisite to widespread clinical use. Grubb et al point out that cystatin C, B2M, and BTP are only 3 of many low-molecular-weight serum proteins that are strongly correlated with measured GFR. In our view, discovery of additional proteins and metabolites and their evaluation as candidate filtration markers for incorporation into a panel could further improve accuracy and further reduce the need to include either creatinine or race for eGFR.[4] Delanaye and Mariat suggest comparing eGFR using the 4-marker panel that includes creatinine, cystatin C, B2M, and BTP without race to eGFR using creatinine without race, as has been implemented in some US medical centers. We have recently reviewed alternative equations for estimating GFR without race with considerations of equity as well as equation performance.[5] We agree that a comprehensive evaluation of "race-free" equations in validation populations is necessary. Race-free GFR estimation can be improved, but will require investment, and may well be worth the cost.

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RESEARCH LETTERS

Estimation of Albumin-Creatinine Ratio From Protein-Creatinine Ratio in Urine of Children and Adolescents With CKD

To the Editor:

Albuminuria and proteinuria are key prognostic indicators of disease progression in chronic kidney disease (CKD).[1-3] Models to predict time to kidney failure