GFR Estimation Using β-Trace Protein and β2-Microglobulin in CKD

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Background: β-Trace protein (BTP) and β2-microglobulin (B2M) are novel glomerular filtration markers that have stronger associations with adverse outcomes than creatinine. Comparisons of BTP and B2M to creatinine and cystatin C are limited by the absence of rigorously developed glomerular filtration rate (GFR) estimating equations for the novel markers.

Study Design: Study of diagnostic test accuracy.

Setting & Participants: Pooled database of 3 populations with chronic kidney disease (CKD) with mean measured GFR of 48 mL/min/1.73 m² (N = 3,551; MDRD [Modification of Diet in Renal Disease] Study, AASK [African American Study of Kidney Disease and Hypertension], and CRIC [Chronic Renal Insufficiency Cohort] Study).

Index Tests: GFR estimated using creatinine, cystatin C, BTP, or B2M level.

Reference Test: GFR measured as the urinary clearance of iothalamate.

Results: For BTP and B2M, coefficients for age, sex, and race were smaller than for creatinine and were similar or smaller than for cystatin C. For B2M, coefficients for sex, age, and race were smaller than for creatinine and were similar (age and race) or smaller (sex) than for cystatin C. The final equations with BTP (BTP, age, and sex) or B2M (B2M alone) were less accurate than either the CKD-EPI (CKD Epidemiology Collaboration) creatinine or cystatin C equations. The combined BTP-B2M equation (BTP and B2M alone) had similar accuracy to the CKD-EPI creatinine or cystatin C equation. The average of the BTP-B2M equation and the CKD-EPI creatinine–cystatin C equation was not more accurate than the CKD-EPI creatinine–cystatin C equation.

Limitations: No external validation population, study population was restricted to CKD, few participants older than 65 years, or nonblack nonwhite race.

Conclusions: BTP and B2M are less influenced by age, sex, and race than creatinine and less influenced by race than cystatin C, but provide less accurate GFR estimates than the CKD-EPI creatinine and cystatin C equations. The CKD-EPI BTP and B2M equation provides a methodological advance for their study as filtration markers and in their associations with risk and adverse outcomes, but further study is required before clinical use.

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INDEX WORDS: Beta-trace protein (BTP); beta-2-microglobulin (B2M); filtration marker; chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR); measured GFR; estimating equation; kidney function; diagnostic accuracy.
In adult medical care, clinical assessment of kidney function is routine.1 Clinical laboratories now usually report an estimated glomerular filtration rate (eGFR) when serum creatinine is measured.2 Estimates of GFR are more accurate and more useful than serum concentrations of filtration markers alone because they take into account clinical and demographic factors that are associated with their non-GFR determinants and are expressed on the “GFR scale.” Adding cystatin C to creatinine level improves the accuracy of eGFR for assessment of GFR compared to eGFR using either marker alone.3–5 Use of cystatin C level in combination with creatinine level strengthens the association of decreased eGFR with subsequent risk for cardiovascular disease, death, and other outcomes.6 However, even with the use of both these established markers, the accuracy of eGFR versus measured GFR (mGFR) and its use for clinical decision making such as drug dosing and for prediction of adverse outcomes remain suboptimal. A current area of emphasis is the evaluation of novel filtration markers to improve estimation of mGFR and prognosis.

ß-Trace protein (BTP) and ß2-microglobulin (B2M) are novel endogenous filtration markers. A 168-amino acid glycoprotein enzyme produced in the central nervous system, BTP promotes the conversion of prostaglandin H2 to prostaglandin D2.7,8 B2M is a 100–amino acid protein component of class I major histocompatibility molecules and is found on the surface of nucleated cells.9 Similar to cystatin C, both are low-molecular-weight serum proteins that are filtered by the glomerulus and retained in the blood as GFR declines. Each has been shown to have stronger associations with death, cardiovascular disease, or kidney disease outcomes compared to eGFR from creatinine level.10–18 However, comparisons of the utility of BTP and B2M to serum creatinine and cystatin C levels as measures of kidney function and prognostic factors for adverse outcomes and complications of chronic kidney disease (CKD) are limited by the absence of rigorously developed GFR estimating equations using these novel markers.

We developed GFR estimating equations using BTP and B2M levels, alone and in combination, from participants of 2 clinical trials (the MDRD [Modification of Diet in Renal Disease] Study and AASK [African American Study of Kidney Disease and Hypertension]) and an observational study of CKD (the CRIC [Chronic Renal Insufficiency Cohort] Study).1,19,20 We compared these equations with the CKD-EPI (CKD Epidemiology Collaboration) creatinine- and cystatin C-based equations in these study participants, looking at bias, precision, and accuracy.

METHODS

Data Sources

The CKD-EPI is a research group formed to develop and validate improved estimating equations for GFR by pooling data from research studies and clinical populations. We combined individual-level patient data from the MDRD Study, AASK, and the CRIC Study.4,19,20 GFR was measured in each of these studies using urinary clearance of iothalamate.4,19,20 The institutional review boards of all participating institutions approved the original studies.

Laboratory Methods

All measurements were performed in serum samples thawed after being stored at −80°C. We measured serum cystatin C by the Siemens particle-enhanced immunonephelometric assay (PENIA) and a BN II nephelometer at the Cleveland Clinic Research Laboratory for the MDRD Study and AASK (coefficient of variation [CV], 3.2%)1 and at the University of Pennsylvania for the CRIC Study (CV, 4.9%). Cystatin C values were adjusted so that they could be traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group for the Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements (IRMM) certified reference materials.3,22,23 Creatinine, BTP, and B2M were measured at the University of Minnesota in 2012 to 2013. We measured serum creatinine by the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffman-La Roche, Ltd), traceable to the National Institute of Standards and Technology (NIST) creatinine standard reference material 967 (CV, 1.71%).24 We measured BTP on the Siemens Dade Behring Nephelometer (CV, 5.36%). B2M was measured on the Siemens Dade Behring Nephelometer (CV, 3.09%) for CRIC and on the Roche Modular P (CV, 3.2%) for the MDRD Study and AASK. We performed comparison studies to show the equivalence of the 2 assays and their stability over time.

Metrics for Equation Performance

We assessed bias as the median difference between mGFR and eGFR, and precision as the interquartile range for the differences.4,25 We assessed accuracy as root mean squared error and as the percentage of estimates > 30% from mGFR (1 – P30). Confidence intervals were calculated by bootstrap methods (2,000 bootstraps).26 The significance of the differences among equations was determined using McNemar test for 1 – P30. We also compared the newly developed equations for their ability to predict mGFR thresholds of <60, <45, and <30 mL/min/1.73 m2. The 95% confidence intervals for the area under the receiver operating characteristic curve and comparison between receiver operating characteristic curves were performed using the method of DeLong et al.27

Development and Validation of Equations

We developed estimation equations for GFR based on BTP and B2M levels, alone and in combination with each other. We limited our study variables to age, sex, and race (black vs nonblack) because they are included in the existing CKD-EPI equations. We did not develop new equations using creatinine and cystatin C levels because the existing CKD-EPI equations were developed in these studies and perform well.1,24 If GFR estimates from BTP or B2M levels prove to be useful, they could be averaged with estimates from the existing CKD-EPI equations.3,24 However, for

comparison of the magnitude of coefficients for filtration markers, age, sex, and race across all markers, we included equations with these filtration markers. In preliminary analyses, we verified that the existing CKD-EPI equations performed similarly to equations using the same variables developed in this population (Table S1, available as online supplementary material).

We prespecified a process we previously developed to develop and validate equations to estimate GFR. Briefly, we randomly divided the study population in each study into 2 subpopulations: one for equation development (two-thirds of participants) and the other for internal validation (the remaining one-third of participants) and then pooled the data from each study. We first assessed correlation coefficients of the log of each marker to each other and to the log of mGFR. In the development data set, we used least squares linear regression to relate log-transformed mGFR to log BTP and/or log B2M, age, sex, and race. We tested for nonlinearity of the relationship of log mGFR with log concentrations of markers, and none was seen. Age, sex, or race was included if they were significant at \( P < 0.01 \) in the overall development data set or within each study. We compared the magnitude and direction of correlation coefficients across studies. We evaluated performance in the overall development population and in subgroups defined by age, sex, race, and study and compared models with age, sex, or age with models that included only the filtration markers. We compared the magnitude and direction of correlation coefficients across studies. We evaluated performance in the overall development population and in subgroups defined by age, sex, race, and study and compared models with age, sex, or age with models that included only the filtration markers. We compared the magnitude and direction of correlation coefficients across studies. We evaluated performance in the overall development population and in subgroups defined by age, sex, race, and study and compared models with age, sex, or age with models that included only the filtration markers.

We compared the new filtration markers with the existing CKD-EPI equations performed similarly to equations using the same variables developed in this population (Table S1, available as online supplementary material). We compared the new filtration markers with the existing CKD-EPI and cystatin C equations, and the average of the combined BTP-B2M equations with each other, the existing CKD-EPI equations, and the cystatin C equation.

RESULTS

Clinical Characteristics

In the development population, mean ± standard deviation of mGFR was 47.7 ± 21.8 (range, 6-168) mL/min/1.73 m² (Table 1). Mean age was 54.0 ± 11.7 (range, 19-75) years, and 54.5% were black. Clinical characteristics were similar in the development and internal validation data sets (Table 1). Clinical characteristics of participants in each study are shown in Table S2.

Equation Development

All filtration markers were negatively correlated with mGFR, with Pearson correlations (\( \rho \)) ranging from -0.804 to -0.878, and positively correlated with each other, with \( \rho \) ranging from 0.749 to 0.904, with the highest correlation between cystatin C and B2M levels (\( \rho = 0.904 \); Table S3). For the purposes of comparing the magnitude of the age, sex, and race coefficients across markers, we developed

Table 1. Clinical Characteristics of Development and Internal Validation Study Population

<table>
<thead>
<tr>
<th>Participants</th>
<th>Total (N = 3,551)</th>
<th>Development (n = 2,380; 67.0%)</th>
<th>Internal Validation (n = 1,171; 33.0%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD</td>
<td>800 (23)</td>
<td>536 (23)</td>
<td>264 (23)</td>
<td>0.9</td>
</tr>
<tr>
<td>AASK</td>
<td>1,364 (38)</td>
<td>914 (39)</td>
<td>450 (39)</td>
<td></td>
</tr>
<tr>
<td>CRIC</td>
<td>1,387 (39)</td>
<td>930 (39)</td>
<td>457 (39)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Values for categorical variables are given as number (percentage); for continuous variables, as mean ± standard deviation. Conversion factor for creatinine in mg/dL to \( \mu \)mol/L, \( \times 88.4 \).

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; B2M, \( \beta_2 \)-microglobulin; BTP, \( \beta \)-trace protein; CRIC, Chronic Renal Insufficiency Cohort; MDRD, Modification of Diet in Renal Diseases; mGFR, measured glomerular filtration rate.
Box 1. CKD-EPI Equations for GFR Estimation From BTP, B2M, and the Combination

BTP GFR = 55 × BTP^{0.695 × (0.998^{age} × 0.899 if female)}
B2M GFR = 133 × B2M^{0.862}
BTP-B2M GFR = 96 × BTP^{0.278 × B2M^{0.588}}

Note: Coefficients are derived from the combined development and internal validation data sets.
Abbreviations: B2M, β2-microglobulin; BTP, β-trace protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.

equations for each marker and both markers combined and with and without age, sex, and race. In general, coefficients for BTP and B2M in the equations were smaller (closer to zero) than coefficients for creatinine and cystatin C (Table S4). For BTP equations, coefficients for age and sex were all significant, but were smaller than in equations with creatinine level and similar to (age and sex) or smaller (race) than in equations with cystatin C (Table S5). Including race did not improve performance. Thus, the final equation included BTP level, age, and sex. For B2M equations, coefficients for sex, age, and race were significant but were smaller than in equations with creatinine level and were similar to (age and race) or smaller (sex) than in equations with cystatin C level (Box 1). However, B2M equations that included age, sex, or race did not substantially improve performance overall or in subgroups compared with equations that used the marker alone (Table S5), and thus the final equation included just B2M level alone (Box 1). For equations that used both BTP and B2M levels, age and sex coefficients were significant but did not substantially improve performance overall or in subgroups and thus the combined BTP-B2M equation included just the filtration markers (Box 1).

Internal Validation

Figure 1 compares the median difference of mGFR versus eGFR by level of eGFR for the 3 new equations in the internal validation data set. For BTP and B2M equations, there is a small underestimation of mGFR at the higher eGFR range; this underestimation is less with the use of both BTP and B2M levels. Among the 3 equations, there is minimal variation in the median difference between mGFR and eGFR across subgroups of age, sex, race, body mass index, and diabetes (Fig 2).

Table 1 compares the performance of new to existing equations in the internal validation data set. Improved precision was noted using 2 versus 1 filtration marker regardless of whether BTP was combined with B2M or creatinine was combined with cystatin level. The BTP and B2M equations are less accurate than the CKD-EPI creatinine or CKD-EPI cystatin C equations, whereas the combined BTP-B2M equation has similar accuracy to the CKD-EPI creatinine and CKD-EPI cystatin C equations. The combined CKD-EPI creatinine–cystatin C equation is more accurate than the CKD-EPI creatinine and CKD-EPI cystatin C equations, as has been previously shown,3 and is also more accurate than the combined BTP-B2M equation. The average of the combined BTP-B2M equation with the CKD-EPI creatinine–cystatin C equation had similar accuracy as the CKD-EPI creatinine–cystatin C equation. Of the newly developed equations, the combined BTP-B2M equation was better able to predict mGFR < 30, <45, and <60 mL/min/1.73 m² than equations with either marker alone (Fig S1).

DISCUSSION

It is crucial that assessment of GFR is performed accurately for interpretation of symptoms, signs, and laboratory abnormalities associated with CKD, as well as for drug dosing and staging, management, and prognostication of these diseases. Currently used filtration markers, creatinine and cystatin C, are recommended for general use; however, greater accuracy of GFR estimates could facilitate better clinical decision making.29 Blood levels of BTP and B2M were first mentioned as possible endogenous filtration markers at least 2 decades ago.7-9,30-32 They have been used in GFR estimating equations in selected populations, including children or transplant recipients,30-32 and investigated as prognostic markers in CKD studies and in the general population.10-18 As such, the availability of rigorously developed GFR estimating equations using BTP and B2M would enable expression of these markers on the GFR scale for comparison with established makers in the evaluation of kidney function and risk associations. In this report, we present new CKD-EPI equations using BTP and B2M alone and in combination with each other and compare their performance with existing CKD-EPI equations based on creatinine and cystatin C levels in a large population of adults with CKD. Our main findings are that BTP and B2M levels, like cystatin C level, are less influenced by age, sex, and race than creatinine level and less influenced by race than cystatin C level and do not vary across subgroups of body mass index and diabetes, but BTP and B2M levels do not improve GFR estimation beyond currently available equations including creatinine and cystatin C levels. These findings provide valuable lessons for the development of GFR estimation equations and may have important applications in research, as we describe. Steady-state serum levels of endogenous filtration markers are used to estimate GFR. However, all endogenous filtration markers are affected by
physiologic processes other than GFR (ie, non-GFR determinants), including generation, tubular reabsorption and secretion, and extrarenal elimination. The GFR estimating equations use easily measured demographic or clinical variables, such as age, sex, and race, as surrogates for non-GFR determinants. Imprecision in the relationship of observed surrogates to the unmeasured physiologic processes contribute significantly to imprecision of GFR estimates compared to mGFR. We hypothesize that a combination of multiple markers could lead to more precise GFR estimating equations that require fewer surrogates if the markers are not highly correlated with each other and the non-GFR determinants of the markers are independent of each other. For creatinine, muscle mass is a major determinant of variation in generation; age, sex, and race are included as surrogates, but do not account sufficiently for individual variation, leading to a search for alternative markers. Like cystatin C, BTP and B2M levels appear to be less dependent upon muscle mass than creatinine.\textsuperscript{32,33} Like cystatin C, BTP equation performance improves with inclusion of age and sex, but not race, but coefficients are weaker than that of creatinine-based equations. The B2M equation and the combined BTP-B2M equation do not require age, sex, or race. The lack of improvement in precision of GFR estimation by BTP and B2M levels beyond that of creatinine and cystatin C levels suggests that factors other than age, sex, and race affect BTP and B2M more than they affect creatinine and cystatin C levels; these factors are not well understood. It has been shown that BTP level is increased with steroids and potentially in certain inflammatory states and B2M level is increased in malignancy and inflammation.\textsuperscript{7-9,31,32,34,35} If these factors could be captured by easily measured surrogates, the precision of GFR estimation using BTP and B2M levels alone and in combination with creatinine or cystatin C levels could be improved. Failure to account for them could limit the use of these filtration markers for GFR estimation in patients with cancer or inflammatory states. Alternatively, lack of improvement in the precision of GFR estimation by BTP and B2M compared to creatinine and cystatin C levels may reflect larger measurement error in the filtration markers. Prior studies have shown that BTP level has greater within-person variability (CV, 11.6%) compared to creatinine, cystatin C, or B2M levels (CVs of 7.6%, 6.8%,

**Figure 1.** Comparison of performance of β-trace protein (BTP), β2-microglobulin (B2M), and BTP-B2M equations in the internal validation data set. Difference between measured and estimated versus estimated glomerular filtration rate (GFR). Shown are smoothed regression line and 95% confidence intervals (CIs; computed using the Lowess smoothing function in R), using quantile regression, excluding lowest and highest 2.5% of estimated GFR values. Abbreviations: IQR, interquartile range; $1 - P_{30}$, percentage of estimates > 30% different from measured GFR.
and 8.4%, respectively). Possibly BTP and B2M levels may improve GFR estimation in populations with a higher range of GFR compared to what is seen here because the CKD-EPI creatinine and cystatin C equations are known to be more accurate in populations with CKD and a lower range of GFR.

Although performance of these new CKD-EPI BTP and B2M equations was not shown to be better than that
of the existing CKD-EPI equations based on creatinine and cystatin C levels, they may have potential utility. First, in conditions in which creatinine generation is altered, there would be a use for estimating GFR without creatinine level. For example, in amputees, patients with disorders of muscle, or those with extremes of diet, GFR estimates from cystatin C, BTP, and B2M levels may be more accurate than estimates from creatinine level.\(^3\) Cystatin C level is thought to be affected by fat mass, and therefore BTP and B2M levels may be more accurate than creatinine or cystatin C levels in obese patients. These applications would require explicit evaluation in other populations. Second, the combination of BTP and B2M levels without demographics provides equivalent results to the use of creatinine-based eGFR. In some circumstances, there may be advantages of being able to compute eGFR without the use of demographics, especially race. Third, many studies have compared the associations of cystatin C, BTP, or B2M level with adverse outcome to associations with creatinine level. Because the markers have different scales, it has been challenging to directly compare risk associations across markers alone or in combination. Expressing BTP and B2M on the GFR scale would facilitate these comparisons between markers. In addition, our finding of less accurate estimation of mGFR using BTP and B2M than creatinine suggests that prior findings of stronger risk associations of BTP and B2M than creatinine-based eGFR may be due to factors affecting levels of BTP and B2M other than GFR.\(^1\)\(^-\)\(^14\)\(^,\)\(^18\) Nevertheless, these and other uses of eGFR based on BTP and B2M levels must be weighed against the complexity and additional cost for their measurement. We would anticipate that use of these or other novel markers would be as a confirmatory test of creatinine-based eGFR. Of note, B2M assays are widely available and relatively inexpensive. At present, there is no commercially available assay in the United States for BTP.

A key strength of this study is our use of 3 large CKD cohorts for development and internal validation of the new equations. In addition, we used a prespecified rigorous analytical plan for testing of all variables. All 3 studies used similar methods for estimation of GFR. Moreover, pooling across studies allows for a more generalizable result than would be obtained from a single study. Fourth, use of the average of the CKD-EPI creatinine–cystatin C equation with the BTP-B2M equation does not optimize the coefficients for all 4 markers. Development of new equations with BTP and B2M levels in combination with creatinine and cystatin C levels in a diverse pooled data set is ongoing. Fifth, these populations were not selected for marked alterations in non-GFR determinants of the filtration markers, in which accuracy in equation performance would be lower. Sixth, error in the filtration markers or mGFR may account for some of the noted imprecision. Error in mGFR is especially important in evaluating improvements in precision of GFR estimates using multiple markers.

### Table 2. Performance of GFR Estimating Equations in Internal Validation Data Set

<table>
<thead>
<tr>
<th>Description</th>
<th>IQR (95% CI)</th>
<th>(1 - P_{30}), % (95% CI)</th>
<th>(1 - P_{50}), % (95% CI)</th>
<th>RMSE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTP(^a)</td>
<td>15.0 (14.1-15.9)</td>
<td>23.6 (21.3-26.1)</td>
<td>43.6 (40.8-46.5)</td>
<td>0.274 (0.255-0.299)</td>
</tr>
<tr>
<td>B2M(^a)</td>
<td>12.9 (12.2-13.8)</td>
<td>18.4 (16.2-20.8)</td>
<td>37.2 (34.6-40.1)</td>
<td>0.243 (0.231-0.257)</td>
</tr>
<tr>
<td>BTP-B2M(^a)</td>
<td>12.1 (11.4-13.0)</td>
<td>15.5 (13.3-17.7)</td>
<td>35.4 (32.5-38.1)</td>
<td>0.224 (0.213-0.235)</td>
</tr>
<tr>
<td>CKD-EPI creatinine(^a)</td>
<td>11.6 (10.9-12.4)</td>
<td>16.4 (14.2-18.6)</td>
<td>34.5 (31.7-37.3)</td>
<td>0.224 (0.213-0.236)</td>
</tr>
<tr>
<td>CKD-EPI cystatin C(^a)</td>
<td>11.4 (10.6-12.4)</td>
<td>16.9 (14.9-18.6)</td>
<td>34.8 (32.1-37.6)</td>
<td>0.228 (0.217-0.239)</td>
</tr>
<tr>
<td>CKD-EPI creatinine–cystatin C</td>
<td>9.3 (8.7-10.1)</td>
<td>11.3 (9.5-13.2)</td>
<td>25.5 (23.1-28.0)</td>
<td>0.189 (0.180-0.199)</td>
</tr>
<tr>
<td>Average of CKD-EPI creatinine–cystatin C and BTP-B2M</td>
<td>10.2 (9.5-11.0)</td>
<td>9.6 (8.0-11.4)</td>
<td>25.0 (22.6-27.8)</td>
<td>0.186 (0.177-0.195)</td>
</tr>
</tbody>
</table>

*Note: Shown is the performance of equations developed in the development data set (two-thirds) and tested in the internal validation data set (one-third). Bias is not shown because it is expected to be near zero since both the development and the internal validation data set are random samples of the total data set.*

Abbreviations and definitions: B2M, \(\beta_2\)-microglobulin; BTP, \(\beta\)-trace protein; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range of difference between measured GFR and estimated GFR; \(1 - P_{30}\) (1 – \(P_{50}\)), percentage of estimates > 30% (>20%) different from measured GFR; RMSE, root mean squared error calculated on log scale.

\(^a\)\(^1\) \(P_{30}\) significantly different (\(P < 0.001\)) from CKD-EPI creatinine–cystatin C equations.
In conclusion, the CKD-EPI BTP and B2M equations are less accurate than the CKD-EPI creatinine and cystatin C equations in populations with CKD, but do not require the use of demographic variables. Further evaluation is necessary to determine whether these equations have utility in more diverse populations with and without CKD. Nevertheless, they provide a methodological advance for the study of these markers in ongoing and future research studies.

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Contributions: Research idea and study design: LAI, HT, JC, MCF, AHA, GJB, GC, TG, ABK, JWK, JLash, JLewis, JRS, SDN, JS, TS, ASL; data acquisition: LAI, HT, JC, MCF, AHA, GJB, GC, TG, ABK, JWK, JLash, JLewis, JRS, SDN, JS, TS, ASL; data analysis/interpretation: LAI, HT, JC, MCF, AHA, GJB, GC, TG, ABK, JWK, JLash, JLewis, JRS, SDN, JS, TS, ASL; statistical analysis: LAI, HT, JC, MCF, TG; supervision or mentorship: LAI, JC, TG, ASL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LAI takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Performance in internal validation data set of Cr and CysC equations developed in development data set, compared to existing CKD-EPI equations.

Table S2: Clinical characteristics of study population.

Table S3: Pearson correlation coefficients among log-transformed filtration markers and mGFR.

Table S4: Regression coefficients for GFR estimating equations developed in development data set.

Table S5: Performance of GFR estimating equations including vs not including age, sex and race in development data set.

Figure S1: ROC curves for prediction of mGFR < 30, <45 and <60 for BTP, B2M, and BTP-B2M equations.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.07.025) is available at www.ajkd.org.

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