Performance in Measurement of Serum Cystatin C by Laboratories Participating in the College of American Pathologists 2014 CYS Survey

To the Editor.—We would like to comment on the article "Performance in Measurement of Serum Cystatin C by Laboratories Participating in the College of American Pathologists 2014 CYS Survey" reporting substantial method-specific biases for cystatin C measurements.[1]

We believe the discrepant results reported for the cystatin C assay from Siemens (Siemens Healthcare Diagnostics Inc, Tarrytown, New York) can be attributed to the reporting of the survey results.

Siemens introduced cystatin C assays traceable to the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) reference material ERM-DA471/IFCC in 2012 (for BN Systems) and 2013 (for Dimension Vista Intelligent Lab Systems) outside the United States. However, the transition from the original reagent is still ongoing and was finalized by mid 2014 for most non-US countries only. As of today, there are several countries still using non-IFCC standardized reagents. Therefore, it is almost certain that some non-US participants were using the original assay without IFCC standardization during the study. Moreover, Siemens still offers both product variants in many countries, as some international laboratory groups wish to continue using the reagents approved in the United States. This results in different user groups for each assay variant.

The recalibration of the original Siemens cystatin C assay to ERM-DA471/IFCC resulted in a linear conversion of results by +17.4% over the measuring range. Applying this factor to the observed bias of –20.2% ("wild card" proficiency testing sample CYS-WC1) and –15.6% (CYS-WC2), respectively, for the US-based participant group results in mean values close to the stated target values (Table).

For non-US participants, the bias of –16.7% and –10.5% is lower, as it is expected that, to some extent, laboratories used the IFCC-traceable assay and thereby obtained higher values. A single conversion factor comparable to the US group cannot be determined, as the number of participants using one versus the other assay is not available.

We thank the authors for addressing the need for manufacturers to standardize cystatin C reagents. Furthermore, we wish to highlight that Siemens fully agrees and is working to complete the standardization process, including registration in the United States and the remainder of countries worldwide. Contrary to what is stated in the article, at no time have there been any concerns by Siemens or the US Food and Drug Administration about Siemens' cystatin C measurement procedures. To eliminate confusion in future College of American Pathologists (CAP) CYS Surveys' reporting of Siemens' results, Siemens is working with the CAP to establish 2 separate reporting codes for cystatin C to clearly delineate results of IFCC-standardized versus nonstandardized reagents.

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1. Eckfelt JH, Karger AB, Miller WG, Rynders GP, Inker LA. Performance in measurement of serum cystatin C by laboratories participating in the College of American Pathologists 2014 CYS Survey. *Arch Pathol Lab Med*. 2015;139(5):888–893.

The authors are both employees at Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany. The authors have no other relevant financial interest in the products or companies described in this article.

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In Reply.—We thank the Siemens representatives (Siemens Healthcare Diagnostics Inc, Tarrytown, New York) for clarifying the status of their cystatin C measurement procedures' traceability to the ERM-DA471/IFCC international reference material in the United States and in other countries. What they say is consistent with the US lab to non-US lab bias we reported in the College of American Pathologists (CAP) Survey data. Note that the Siemens recommended correction of +17.4% across the entire measurement range does not agree with the +12% correction that we recommended in 2011 based on the observed calibration bias of a series of serum samples when we used ERM DA471/IFCC to make their results traceable to ERM-DA471/IFCC.[1] We suspect at least a partial explanation for the discrepancy in percentage bias is that the magnitude of the Siemens measurement procedures' bias seems to be slightly concentration dependent, both based on the CAP CYS Survey data we reported in our paper and based on our 2011 report describing a "re-expressed" CKD-EPI cystatin C–based estimated glomerular filtration rate (eGFR) equation. There was an intercept when comparing the original Siemens results to the recalibrated ERM-DA471/IFCC-traceable results for a series of frozen serum pools from healthy individuals and patients who had mild to moderate chronic renal disease (see equation 4 in Box 1 of Inker et al[1]). For simplicity, we opted to recommend a uniform percentage correction across the measurement range because the intercept of the Deming regression was not

Cystatin C Values From College of American Pathologists Survey and Adjusted Values After Restandardization to ERM-DA471/IFCC

US Participant Group	Target Value, mg/L	Siemens-Reported Mean Value, mg/L	Bias of Reported Mean Value, %	Siemens-Recommended Adjusted Mean Value (×1.174), mg/L	Bias of Adjusted Mean Value, %
CYS-WC1	0.96	0.766	–20.2	0.90	–6.6
CYS-WC2	2.37	2.00	–15.6	2.35	–1.3