

Larsson et al. in 2011 (Ref.1) presented evidence that the calibration of the Siemens assay for cystatin c (CysC) had drifted during the 2006-2010 period and concluded that there was a 15% decrease in CysC values reported after 2008. These observations were confirmed by Selvin et al. in 2013 (Ref. 2) and using NHANES results, equations were provided to uniform the CysC results by making them traceable to the International Federation of Clinical Chemistry (IFCC) Standard ERM DA 471.

Analyses of CysC in the SEARCH cohort were also performed using Siemens instrument and reagent. For this reason, an approach was established to verify the shift in SEARCH data, create equations to calibrate the CysC results obtained prior and after 2008 to the IFCC Standard ERM DA 471, and to assign a target value to the assay calibrator traceable to the Standard ERM DA 471 to guarantee consistency of the results. Analyses were performed using 100 samples collected prior and 100 samples collected after May 2008.

The goal of these analyses was to be able to estimate the relationship between the previous CysC measures and the updated CysC measures in order to provide a correction to the previous CysC measures. The selection of the number of samples was based on being able to estimate the correlation between the previous and updated CysC measures to a certain level of precision. With a sample size of 100 participants in each calibration sample, a one-sided 95% confidence interval for the correlation coefficient (old CysC with new CysC) had a lower bound within 0.07 of the observed correlation if the correlation is above 0.8. If the correlation between the two methods was higher than 0.8 then the width of the confidence interval would be less than +/- 0.07.

The first step of the analyses was to calibrate the Siemens BNII analyzer using the IFCC reference material and to analyze five times per day for five consecutive days the Siemens calibrator as an unknown sample. The mean of the obtained results was 0.168 ± 0.06 mg/dL while the target as provided by Siemens was 0.148 mg/dL. The second step of the analyses was to analyze the selected 200 samples from the SEARCH cohort using the calibrator with the value traceable to the ERM DA 471 reference material.

Next, the correlation between the old CysC measure and new CysC measure was calculated for both time periods. The observed correlations were 0.88 and 0.85 for samples collected prior to and after May 2008, respectively. Deming regression (Ref 3) models were then fit to derive the correction equations to link the previously measured CysC values with the new CysC values measured with the new methodology. Two separate correction equations were derived, one for each of the two time periods (pre 5/1/2008 and 5/1/2008 – 4/7/2014).

Specifically, for the time period prior to 5/1/2008 (visit date) we applied the formula:

$$\text{Adjusted CysC} = -0.038 + 1.015 \times (\text{raw CysC}).$$

For the time period between 5/1/2008 through 4/7/2014 we applied the formula:

$$\text{Adjusted CysC} = -0.045 + 1.208 \times (\text{raw CysC}).$$

From the period of time after 4/7/2014, CysC was analyzed using the IFCC Standard ERM DA 471 and are correct without any adjustment.

References:

1. Larsson A, Hansson LO, Flodin M, Katz R, Shlipak MG. Calibration of the Siemens cystating c immunoassay has changed over time. Clin Chem 2011; 57(5):777-778.
2. Selvin E, Juraschek SP, Eckfeldt J, Levey AS, Inker LA, Coresh J. Calibration of Cystatin C in the National Health and Nutrition Examination Surveys (NHANES). Am J Kidney Dis 2013; 61(2):353-354.
3. Deming W.E., Statistical adjustment of data. 1943 Wiley, NY (Dover Publications edition , 1985).