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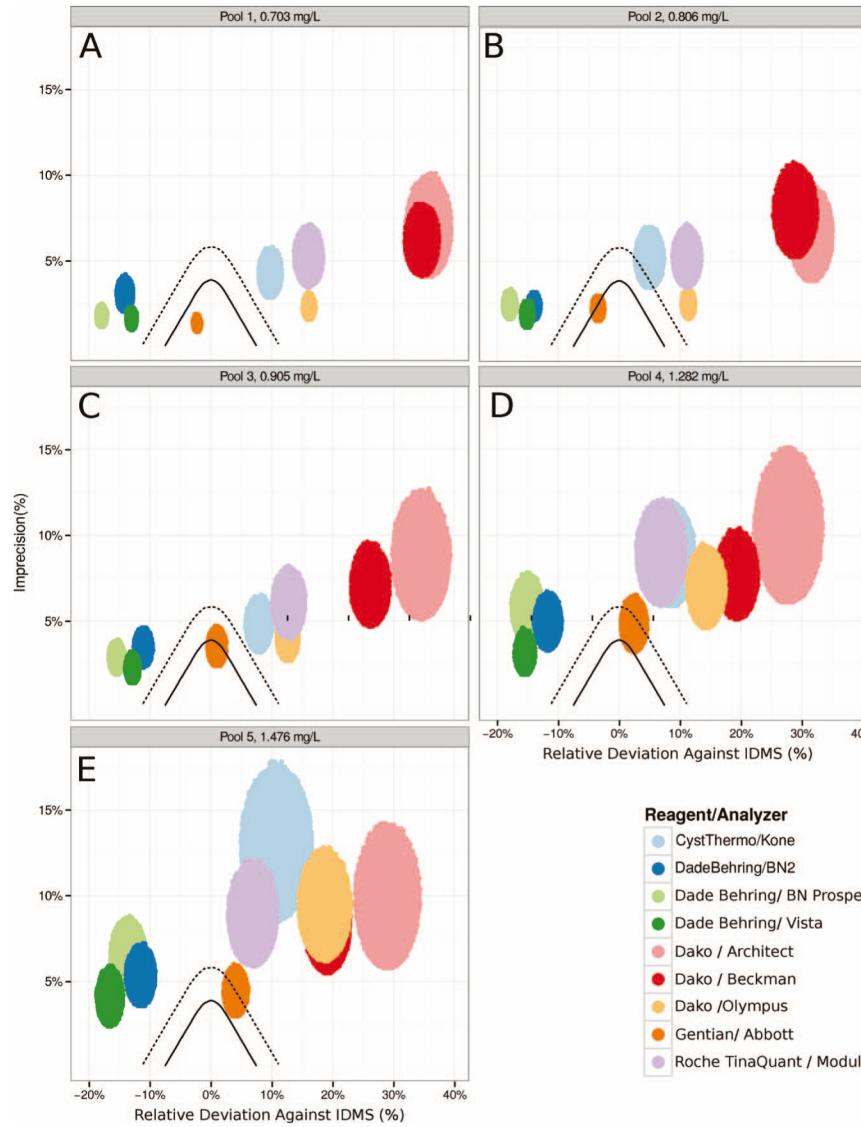
Reference Method and Reference Material Are Necessary Tools to Reveal the Variability of Cystatin C Assays

To the Editor.—We read with great interest the article by Eckfeldt et al[1] regarding the accuracy of cystatin C (cystC) measurements in the College of American Pathologists 2014 survey. In 2008, The French Society of Clinical Biology (SFBC) conducted a multicentric evaluation of isotope dilution mass spectrometry (IDMS)-traceable creatinine enzymatic and nonstandardized cystC assays[2] using a panel of 5 off-the-clot, fresh-frozen serum pools prepared to cover concentrations critically important at initial stages of renal disease. Nine automated methods were evaluated: 4 particle-enhanced nephelemetry immunoassay: Siemens on BN II, ProSpec, and Vista (Siemens Healthcare Diagnostics, Marburg, Germany), and Dako reagents (DakoCytomation, Glostrup, Denmark) on Beckman Immage (Beckman Coulter, Fullerton, California); and 5 particle-enhanced turbidimetry immunoassays: Thermo Fisher on KoneLab (Thermo Fisher Scientific, Passau, Germany), Dako reagents on ARCHITECT (Abbott Laboratories, Abbott Park, Illinois), Dako reagents on Olympus AU2700 (Olympus, Rungis, France), Gentian (Gentian, Moss, Norway) reagents on ARCHITECT, and Roche Tina-quant on the Modular analyzer (Roche Diagnostics, Mannheim, Germany). Each method (reagent/analyzer) was assessed independently by 3 different laboratories. The pools were assayed on 3 separate runs per day for 3 consecutive days.[2] At that time, there was no reference method, and no certified reference material was available,[3] making it difficult to assign reference values to our samples. To overcome that issue, an IDMS-based candidate-reference method from the University of Oviedo (Oviedo, Spain) had its accuracy successfully validated with the recently released certified reference material ERM-DA471/IFCC (International Federation of Clinical Chemistry and Laboratory).[4] The IDMS cystC mean (SD) levels, measured in pools stored at –80°C, were 0.703 (0.056), 0.806 (0.073), 0.905 (0.046), 1.282 (0.057), and 1.476 (0.063) mg/L for pools 1, 2, 3, 4, and 5, respectively. Because the design of the College of American Pathologists study and our study were similar, we decided to compare our findings to those subsequently obtained by Eckfeldt et al[1] using ERM-DA471/IFCC traceable target values.



Monte-Carlo simulations representing 95% confidence regions of performances (relative deviation against isotope dilution mass spectrometry [IDMS] and imprecision value couples) for pool 1 (A), pool 2 (B), pool 3 (C), pool 4 (D), and pool 5 (E) sorted by cystatin C (cystC) reagent-analyzer combinations. Nine automated CystC reagent-analyzer combinations were evaluated: Thermo Fisher on KoneLab (Thermo Fisher Scientific); Siemens on BN II, ProSpec, Vista (Siemens Healthcare Diagnostics); Dako reagents (DakoCytomation) on ARCHITECT (Abbott Laboratories), Beckman Immage (Beckman Coulter), and Olympus AU2700 (Olympus), Gentian (Gentian) reagents on ARCHITECT and Roche Tina-quant on Modular (Roche Diagnostics). Continuous curve, region defined by a total error less than 7.6%. Dashed curve, region defined by a total error less than 11.4%.

The performance of the assays (total error includes the contribution of bias and imprecision) were computed using Monte-Carlo simulations and compared against Ricos criteria based on both intraindividual (5%) and the interindividual (13%) biologic variation of cystC. The combination of bias and precision (standard deviation) delimiting the desirable (total error = 7.6%) and minimum (total error = 11.4%) performances were obtained and plotted as parabolic curves (Figure, A through E). We observed a high dispersion in cystC values with interlaboratory coefficients of variation ranging from 2% (pool 1, Gentian; mean [SD], 0.69 [0.01] mg/L) (Figure,

A) to 7% (pool 5, Thermo; mean [SD], 1.64 [0.11] mg/L) (Figure, E). In total agreement with the College of American Pathologists reports, the Siemens methods exhibited a negative bias ranging from –11% (pool 3, BNII; bias, –0.10 mg/L) (Figure, C) to –18% (pool 1, BN ProSpec; bias, –0.13 mg/L) (Figure, A) compared with the IDMS target value. The Gentian method exhibited the best accuracy with both the lowest bias (<4.1%, pool 5; bias, 0.06 mg/L) (Figure, E) and precision among laboratories (<3.5%, pool 3; mean [SD], 0.91 [0.03] mg/L) (Figure, C). By contrast, the Roche method displayed a positive bias, ranging from 7% (pool 5; bias, 0.10 mg/L) (Figure, E) to 16% (pool 1; bias, 0.11 mg/L) (Figure, A) in our study. In addition, we observed a positive bias, ranging from 11% (pool 2, Olympus; bias, 0.09 mg/L) (Figure, B) to 36% (pool 1, ARCHITECT; bias, 0.25 mg/L) (Figure, A) for the Dako reagents and from 5% (pool 2; bias, 0.04 mg/L) (Figure, B) to 11% (pool 5; bias, 0.16 mg/L) (Figure, E) for cystC Thermo/KoneLab.

The comparison between the two studies demonstrated that despite standardization of cystC assays, the variability of cystC measurements was similar when compared with ERM-DA471/IFCC traceable target values or IDMS reference methods. It is difficult to speculate on the causes of the between-method differences versus the IDMS method, which could be attributed to analytic factors, such as antibody selectivity, method adaptation with different instruments, incorrect assignment of calibrator values, or noncommutability of manufacturer's calibrators. For example, the Roche method showed an improvement between the two periods. The manufacturer claimed that the method had been standardized against ERM-DA471/IFCC reference material in 2014, whereas the first generation of Tina-quant CystC was standardized against an in-house gravimetric (dry mass) reference preparation of pure recombinant human cystC. More studies need to be performed to reliably use cystC in assessing kidney function alone or in combination with creatinine.[5] To check the effect of standardization of cystC methods, the SFBC group initiated a new study based on a similar experimental design as that in 2008. The primary available, standardized cystC methods are currently being compared versus IDMS-based candidate reference method using 5 commutable serum pools ranging from 0.9 to 2.2 mg/L.

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