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Educational Discussion: 2026-A Accuracy-Based Glucose, Insulin and C-peptide

To promote standardization and harmonization of clinical laboratory results, the CAP has integrated the former ING Survey (which assessed insulin, C-peptide, and gastrin) into the Accuracy-Based Glucose, Insulin, and C-peptide (ABGIC) Survey overseen by the Accuracy-Based Programs Committee. Specimens used in accuracy-based programs are created from pooled, freshly frozen serum samples using procedures that minimize matrix effects that can be observed with traditional synthetic PT materials. Therefore, accuracy-based PT samples are highly representative of true patient specimens, and their presumed commutability allows for a more accurate assessment of the current state of assay harmonization across laboratory peer groups and methods. For the ABGIC Survey, serum is collected from donors before and after administration of Glucola (a formulated glucose drink used in glucose-tolerance testing), to provide samples with normal range and elevated endogenous concentrations of insulin, C-peptide, and glucose for comparative assessment of methods.

Target values for glucose and C-peptide are established using reference methods certified by the Joint Committee on Clinical Laboratory Medicine (JCTLM), which allows for the assessment of both harmonization and standardization of these biomarker measurements. This approach can contrast biomarkers that have assays that are well-calibrated to the reference method and those that are not. Specifically, the accuracy and harmonization of glucose methods is excellent for all three samples in this Survey. As shown in the included bias plots, where the dashed line represents the reference method target value, all methods have means within approximately 2 mg/dL (0.1 mmol/L) of the target value, and within and between-method CVs generally < 3%. In contrast, for C-peptide, bias plots demonstrate that most methods are notably higher than the target set by the reference method for all three samples, indicating inaccurate calibration for the majority of C-peptide assays. Additionally, the between-method CV's for the three samples were 11-12% for C-peptide indicating significant disagreement across methods. These data confirm the results of a prior study comparing 13 commercial C-peptide assays, which also found systematic overestimation (11-53%) of C-peptide concentrations across the entire measurement range.[1] When the authors recalibrated the overestimated results to the reference method for C-peptide, the methods showed significant improvements in between-method agreement and accuracy.[1]

While there is not a JCTLM-certified reference method for insulin to assess accuracy of methods for this Survey, harmonization of methods can be assessed due to the use of presumably commutable PT materials. It is notable that the between-method CVs for the three samples are approximately 16% for insulin, demonstrating a need to improve harmonization across the measurement range. Our data confirm the findings of a recent study assessing nine commercial insulin assays, which found substantial inter-assay discordance.[2] Additionally, the investigators compared the insulin assay results to a candidate reference measurement procedure (isotope-dilution mass spectrometry) and found that the majority of insulin assays underestimated insulin concentration.[2]

In conclusion, the results of this 2026 ABGIC-A Survey demonstrate the need for manufacturers to improve the harmonization and standardization of C-peptide and insulin methods. The CAP Accuracy-Based Programs Committee will continue to advocate for manufacturers to improve their calibration traceability to certified reference measurement procedures (when available) or certified reference materials, to enhance the utility of assay results when standardized clinical cut-offs or decision points are in use.

1. Rohlfing C, Petroski G, Connolly SM, Hanson S, Little RR, Kabytaev K. A comparative analysis of current C-peptide assays compared to a reference method: can we overcome inertia to standardization? *Clin Chem Lab Med*. 2025;63(6):1124-1131.

2. Rohlfing C, Petroski G, Hatten-Beck M et al. The current status of serum insulin measurements and the need for standardization. *Clin Chem Lab Med*. 2025;63(12):2442-2446.

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