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State of Harmonization of 24 Serum Albumin Measurement Procedures and Implications for Medical Decisions

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BACKGROUND: Measurements of serum and plasma albumin are widely used in medicine, including as indicators of quality of patient care in renal dialysis centers.

METHODS: Pools were prepared from residual patient serum (n = 50) and heparin plasma (n = 48) from patients without renal disease, and serum from patients with kidney failure before hemodialysis (n = 53). Albumin was measured in all samples and in ERM-DA470k/IFCC reference material (RM) by 3 immunochemical, 9 bromcresol green (BCG), and 12 bromcresol purple (BCP) methods.

RESULTS: Two of 3 immunochemical procedures, 5 of 9 BCG, and 10 of 12 BCP methods recovered the RM value within its uncertainty. One immunochemical and 3 BCG methods were biased vs the RM value. Random error components were small for all measurement procedures. The Tina-quant immunochemical method was chosen as the reference measurement procedure based on recovery and results of error analyses. Mean biases for BCG vs Tina-quant were 1.5% to 13.9% and were larger at lower albumin concentrations. BCP methods' mean biases were −5.4% to 1.2% irrespective of albumin concentration. Biases for plasma samples were generally higher than for serum samples for all method types. For most measurement procedures, biases were lower for serum from patients on hemodialysis vs patients without kidney disease.

CONCLUSIONS: Significant differences among immunochemical, BCG, and BCP methods compromise interpretation of serum albumin results. Guidelines and calculations for clinical management of kidney and other diseases must consider the method used for albumin measurement until harmonization can be achieved.

Measurements of serum and plasma albumin concentrations are widely used to indicate fluid balance, nutritional status, nephrotic syndrome, and hepatic function. Albumin binds calcium and many hormones and is incorporated in calculations of "corrected" calcium *(1)* and free hormone concentrations *(2, 3)*. In patients with renal disease, albumin predicts survival and hospitalization *(4–9)*. Albumin is a quality indicator for patient care in renal dialysis centers *(10)*. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative and Renal Network recommend routine measurement of albumin to monitor nutritional status of patients on maintenance renal dialysis *(11, 12)*.

Previous studies have shown differences between results of bromcresol green (BCG)[3] and bromcresol purple (BCP) dye-binding methods for albumin *(13)*. These differences are acknowledged in guidelines and treatment goals for patients on renal dialysis. The goals are defined as the proportion of patients whose albumin concentrations are ≥3.5 (35 g/L) and ≥4.0 g/dL (40 g/L) for BCG results, but are less well defined for BCP *(11)*. In most other applications of albumin, the method of measurement is rarely considered.

Improvement in the agreement of results among different measurement procedures for albumin is needed to enable use of fixed clinical decision thresholds. Previous investigations have mostly been performed with artificial samples *(14)*, or used only 1 off-the-clot serum sample *(15)*. Many studies have compared only 1 procedure from each method type, making it difficult to determine if differences between methods are general method characteristics or if they reflect specific implementation characteristics of a method type in a manufacturer's measurement procedure.

We examined the current state of harmonization and analytical performance of 24 commercially available albumin measurement procedures using freshly collected, nonfrozen serum and plasma from patients with-

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[3] Nonstandard abbreviations: BCG, bromcresol green; BCP, bromcresol purple; RM, reference material; RMP, reference measurement procedure.

out renal disease and serum from patients receiving hemodialysis.

Materials and Methods

PREPARATION OF PATIENT SAMPLES

Residual patient samples were used to prepare (*a*) serum pools from patients without renal disease (n = 50 pools), (*b*) heparin plasma pools from patients without renal disease (n = 48 pools), and (*c*) serum pools from patients with kidney failure collected before hemodialysis (n = 53 pools). Two to 7 individual samples were combined to create individual pools. Non–renal disease samples were selected from clinical locations other than kidney units. Samples with estimated glomerular filtration rates <60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ calculated using the Modification of Diet in Renal Disease study equation (isotope-dilution mass spectrometry–traceable creatinine) or the Chronic Kidney Disease Epidemiology Collaboration equation were excluded from the non–renal disease pools *(16, 17)*.

Samples were submitted for routine testing at Virginia Commonwealth University and the University of Virginia during a 3-week period in 2014. Samples were collected between Sundays at 12 midnight and Wednesdays at 12 noon and were centrifuged at 2500*g* within 5 h from collection and stored at 2–8 °C until pooling. Each pool was mixed by inversion, divided into 24 aliquots of 250 μL and stored in polypropylene cryovials. Aliquots were labeled with a random study number and shipped at 2–8 °C overnight to manufacturers. The maximum time duration from collection to analysis was 5 days. The study protocol was approved by the Institutional Review Boards of each institution.

PREPARATION OF ALBUMIN REFERENCE MATERIALS

The ERM-DA470k/IFCC Proteins in Human Serum certified reference material (RM) from the Institute for Reference Materials and Measurements was prepared centrally at Virginia Commonwealth University. The material was prepared according to the instructions in the certificate of analysis. Each vial was equilibrated to room temperature for 1 h before gravimetric addition of 1.00 mL of deionized water using a balance with 0.1 mg mass sensitivity. Twelve (week 1) or 13 vials (weeks 2 and 3) of reconstituted RM were pooled to obtain enough material for distribution. A dilution of the materials was prepared by adding 0.9% NaCl gravimetrically to the reconstituted pool for a final concentration of 2.00 g/dL (20.0 g/L). RMs were labeled with a random study number, thus blinded to the participants, and measured in the same runs as patient samples.

Based on the certificate of analysis, the concentration of reconstituted ERM-DA470k/IFCC was 3.72 g/dL (37.2 g/L) with uncertainty (k = 2) 0.12 g/dL (1.2 g/L). The target values for the RM pools were determined by gravimetric reconstitution. Based on mass of water added, the 3 pools (1 prepared each week) of ERM-DA470k/IFCC had concentrations of 3.715, 3.727, and 3.738 g/dL (37.15, 37.27, and 37.38 g/L). The mean value 3.727 g/dL (37.27 g/L) was used as the target to assess recovery. The uncertainty for the mean of RM pools (0.13 g/dL; 1.3 g/L) was the uncertainty value from the certificate of analysis (0.12 g/dL; 1.2 g/L) plus one-half the difference between the lowest and highest mean values for the 3 pool preparations.

QC MATERIALS

Quadruplicate measurements of 2 or 3 QC materials used by each manufacturer were performed at the beginning, middle, and end of each run.

MEASUREMENT OF ALBUMIN BY COMMERCIAL MEASUREMENT PROCEDURES

Sample aliquots were stored at 2–8 °C, allowed to equilibrate at ambient temperature (15–25 °C) for 30 min, mixed by inversion, and measured in quadruplicate by 24 measurement procedures in manufacturers' laboratories using methods based on BCG, BCP, or immunochemistry (see Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol63/issue3). The Advia 1800 BCG method was excluded owing to an apparent calibration difference for 1 run (see online Supplemental Fig. 1K).

STATISTICAL ANALYSES

A power analysis was performed to determine sample size *(18)*. 50 samples per group were needed to achieve a power of >0.8–0.95 to detect an albumin difference of 0.05 g/dL (0.5 g/L) assuming intraassay analytical SDs of 0.1 g/dL (1 g/L) and paired-sample analysis at an α significance level of $P = 0.05$.

We calculated the difference between the mean result for each method and the corresponding mean result for the Roche Tina-quant immunochemical procedure used as the reference measurement procedure (RMP) for each sample. We used the generalized linear model feature of the SAS statistical package (SAS Institute) to perform ANOVA to compare differences in serum vs plasma and in renal disease vs non–renal disease serum. *P* values <0.05 were considered significant.

Components of measurement error were estimated as previously described *(19)*. Briefly, the error model included contributions from intraassay precision and position effects estimated from 4 replicate measurements of patient samples, interassay precision estimated from 4 replicates of QC samples, sample-specific effects estimated as the residual variance not explained by the other random components, and bias vs the Roche Tina-quant method.

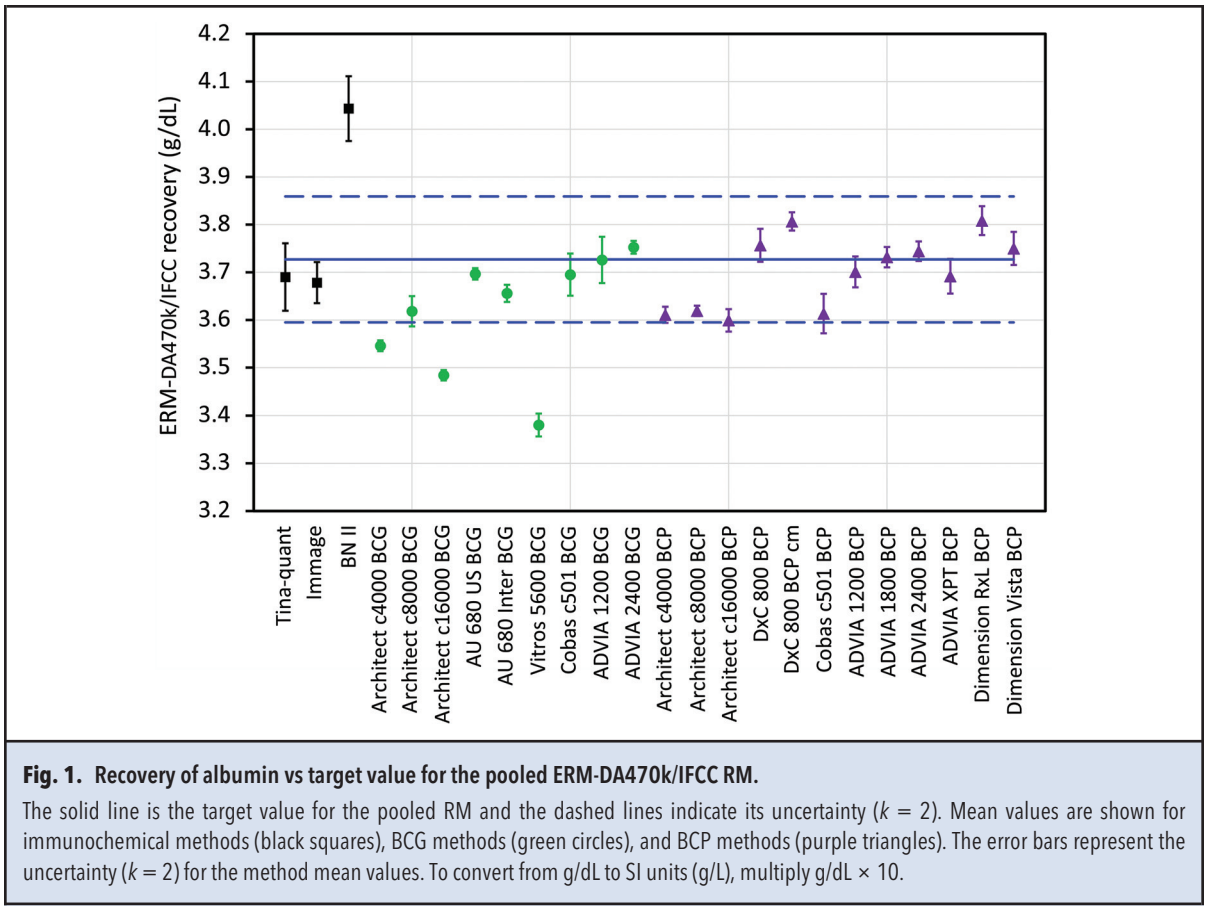

Fig. 1. Recovery of albumin vs target value for the pooled ERM-DA470k/IFCC RM.

The solid line is the target value for the pooled RM and the dashed lines indicate its uncertainty ($k = 2$). Mean values are shown for immunochemical methods (black squares), BCG methods (green circles), and BCP methods (purple triangles). The error bars represent the uncertainty ($k = 2$) for the method mean values. To convert from g/dL to SI units (g/L), multiply g/dL × 10.

Results

Recovery of albumin in the ERM-DA470k/IFCC RM is shown in Fig. 1. The mean value for each method was the combined mean for each of the 3 pools of RM measured in each of 3 weeks. The expanded uncertainty (k = 2) of the mean value for each method was estimated as 2 times the SE using the pooled SD from each of the 3 weekly SD values for the replicate measurements to calculate the SE. The Tina-quant and Immage immunochemical methods had values within the uncertainty of the RM target value. The BNII immunochemical method had a clearly high bias. Five of 9 BCG methods recovered the RM target value within its uncertainty. One BCG method had a mean value within the uncertainty of the RM target value but its uncertainty was outside that of the RM limit. Three BCG methods did not recover the RM target value with low biases from −4.9% to −9.3%. Ten of 12 BCP methods recovered the RM target value within its uncertainty. Two BCP methods had mean values within the uncertainty of the RM target value but their uncertainties were outside that of the RM limits.

The Joint Committee for Traceability in Laboratory Medicine lists measurement of serum albumin by immunoassay with either turbidimetric or nephelometric detection as an RMP *(20)*. Among the 3 immunochemical methods, Tina-quant was selected as the RMP because it had the best recovery [−0.04 g/dL (−0.4 g/L); −1.0%] of the ERM-DA470k/IFCC RM, supporting correct calibration traceability, and it had the lowest combined random error components (Table 1).

Fig. 2 shows box and whisker plots for the difference in results for each measurement procedure vs the RMP for non–renal disease plasma and serum samples. All BCG methods were biased high vs the RMP and had generally higher values than BCP methods. Biases for BCP methods were smaller than for BCG methods and more closely clustered around zero. Mean biases were statistically significantly higher for plasma compared to serum for all but the BNII and Dimension RxL BCP (Fig. 2 and online Supplemental Table 2). For immunochemical methods, results for Immage were similar to those for the Tina-quant with a mean bias of 0.01 g/dL (0.1 g/L) for serum samples, whereas results for the BNII were 0.26 g/dL (2.6 g/L) higher than the other 2 immunochemical methods.

Fig. 3 shows box and whisker plots of the biases of serum samples obtained from patients without disease

Table 1. Estimates of error components.

	Intraassay precision (PS[a]), CVe, %[b]	Interassay precision (QC), CV, %[c]	Position effects (QC), CV, %[d]	Sample-specific effects, CV, %[e]	Mean bias, δ, %	Approximate bias at specified concentrations, %[f]		
						2.5 g/dL (25 g/L)	3.5 g/dL (35 g/L)	4.0 g/dL (40 g/L)
Tina-quant	1.9	1.0	1.5	fixed at 0	NA	NA	NA	NA
Immage	1.7	0.8	3.7	NA[g]	1.3	−2.0	2.0	2.5[h]
BN II	2.0	1.2	2.3	NA[g]	7.2[h]	8.5[h]	7.4[h]	5.4[h]
Architect c4000 BCG	0.4	0.6	0.0	3.5	3.7[h]	7.8[h]	1.9	0.8
Architect c8000 BCG	0.9	0.4	0.0	3.6	5.7[h]	4.9[h]	0.1	−0.7
Architect c16000 BCG	0.3	0.7	0.2	3.8	1.5	4.9[h]	0.1	−0.7
AU 680 US BCG	0.7	0.7	1.1	2.9	5.6[h]	8.8[h]	4.0[h]	3.2[h]
AU 680 Intr BCG	0.7	0.2	0.9	2.9	5.1[h]	8.3[h]	3.4[h]	2.6[h]
Vitros 5600 BCG	0.8	0.8	0.0	4.7	5.3[h]	8.2[h]	3.9[h]	3.3[h]
Cobas c501 BCG	1.4	1.3	1.8	0.0	7.7[h]	11.2[h]	6.7[h]	4.4[h]
Advia 1200 BCG	1.1	2.1	0.8	0.0	13.0[h]	23.0[h]	10.2[h]	7.0[h]
Advia 2400 BCG	0.6	2.0	0.3	4.3	13.9[h]	23.5[h]	11.0[h]	8.2[h]
Architect c4000 BCP	0.4	0.3	0.1	2.7	−4.8[h]	−5.2[h]	−4.3[h]	−3.9[h]
Architect c8000 BCP	0.6	0.4	0.0	2.6	−4.6[h]	−5.2[h]	−4.2[h]	−3.7[h]
Architect c16000 BCP	0.9	0.6	0.0	3.0	−5.4[h]	−5.8[h]	−4.7[h]	−4.1[h]
DxC 800 BCP	1.0	0.3	0.0	3.5	1.0	0.8	1.0	1.6
DxC 800 BCP cm	0.6	0.3	1.4	2.0	1.2	0.0	1.8	2.0
Cobas c501 BCP	0.9	1.4	1.0	2.7	−3.5[h]	−3.3[h]	−2.8[h]	−2.8[h]
Advia 1200 BCP	1.1	2.0	0.0	4.7	−1.3	−2.1	−0.5	0.6
Advia 1800 BCP	1.1	2.0	1.3	4.6	−1.3	−1.4	−0.6	−0.1
Advia 2400 BCP	0.6	2.1	0.0	4.8	−0.3	−0.7	−0.6	0.8
Advia XPT BCP	0.9	2.8[h]	0.0	3.6	−2.1	−2.7[h]	−1.7	−1.2
Dimension RxL BCP	0.9	0.4	0.0	2.2	0.3	−1.5	1.5	1.9
Dimension Vista BCP	0.7	0.5	0.0	1.8	0.4	−0.1	1.3	0.6

[a] PS, patient samples.
[b] Between replicates, intraassay; based on 4 replicates of PS.
[c] Interassay; based on 4 replicates of QC samples performed at the beginning, middle, and end of each run.
[d] Position effects; based on QC samples.
[e] Sample-specific effects; based on PS.
[f] Bias was estimated by the moving average of 21 consecutive differences centered on the indicated value.
[g] Sample-specific effects could not be estimated because position effects dominated random error components.
[h] Indicates a parameter that exceeds the minimum performance specification based on biological variability criteria; 2.4% for intra- or interassay CV and 2.1% for bias.

and patients on renal dialysis. With exception of Immage, BN II, Vitros 5600 BCG, Dimension RxL BCP, and Dimension Vista BCP, all measurement procedures had statistically significantly lower biases for serum from patients on renal dialysis compared to patients without renal disease (Fig. 3 and online Supplemental Table 3). The previous observation that BCP methods had lower values than BCG methods for serum and plasma from patients without renal disease (Fig. 2) was also seen with serum samples from patients on renal dialysis (Fig. 3).

Table 1 presents error components analysis for each procedure using results from the Tina-quant as the RMP. Performance specifications for albumin measurement can be estimated using model 2 based on biological variation described in the Milan 2014 conference *(21)*. For albumin biological variation, the intraindividual CV of 3.2% and interindividual CV of 4.75% has been published, resulting in desirable and minimum, respectively, analytical specifications for CV of 1.6% and 2.4%, and for bias of 1.4% and 2.1% *(22, 23)*. Intraassay and interassay estimates of preci-

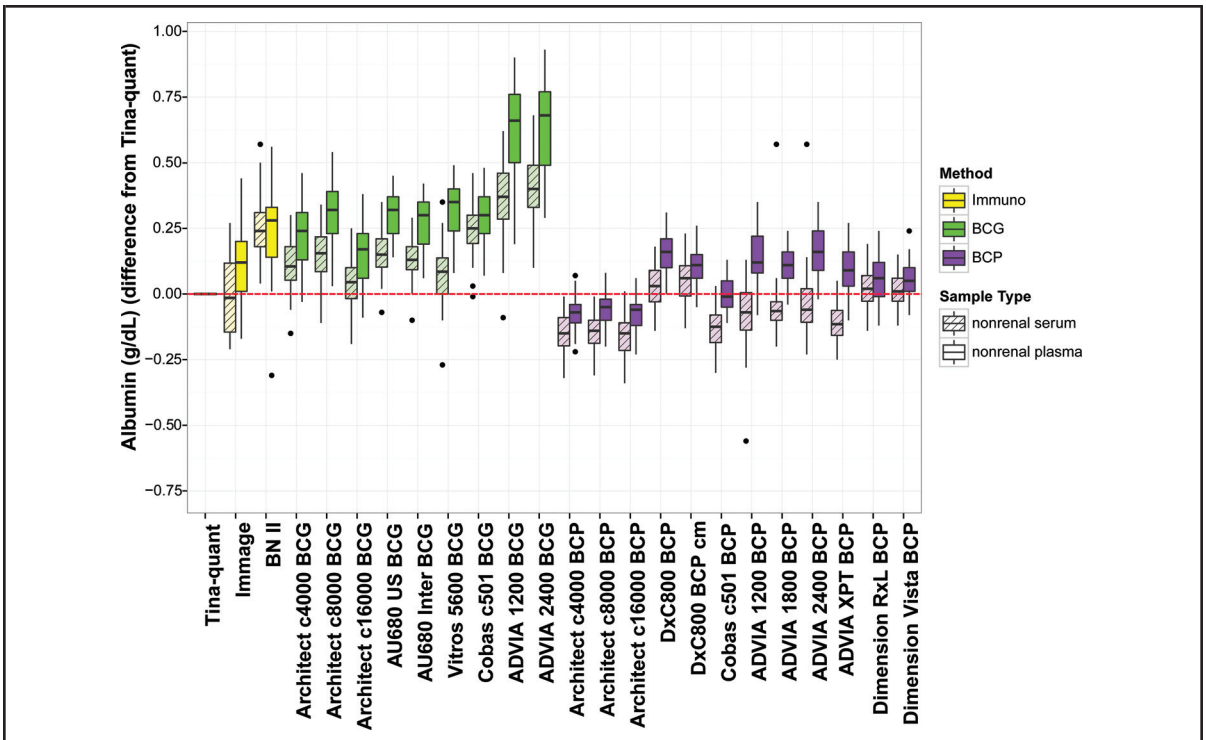

Fig. 2. Difference in albumin results for each method vs the Tina-quant RMP for non–renal disease plasma (darker shade) and non–renal disease serum (lighter shade with stripes) samples.

The boxes show the median, 25th, and 75th percentile values, and whiskers represent the 10th and 90th percentile values. Black circles indicate values that exceed the 10th and 90th percentiles. Median values for Tina-quant were 3.28 g/dL (32.8 g/L) and 2.95 g/dL (29.5 g/L) for serum and plasma, respectively. To convert from g/dL to SI units (g/L), multiply g/dL × 10.

sion were 2.0% and 2.8% or less, respectively, for all measurement procedures. Only the Advia XPT had an interassay CV that exceeded the minimum performance requirement and 16 of 22 methods had CVs within the desirable specification. Position effects were <2% for all BCG and BCP methods. The Immage and BN II had position effects large enough that sample-specific effects could not be estimated. Sample-specific effects were <5% for all other measurement procedures. With few exceptions, random error components were small and within minimum performance specifications for precision for all measurement procedures.

The dominating error component was bias for most measurement procedures (Table 1). Mean biases for BCG methods ranged from 1.5% to 13.9% with bias for all BCG methods exceeding the minimum performance specification at 1 or more concentrations. BCG methods generally exhibited larger biases than BCP methods whose mean biases ranged from −5.4% to 1.2%. Seven of 12 BCP methods met minimum performance specification for bias at all concentrations. BCP methods had generally lower biases than BCG methods for samples from patients on renal dialysis (Fig. 3). Bias for renal dialysis samples ranged from −2.2% to 9.1% for BCG methods and from −7.9% to −0.7% for BCP methods (see online Supplemental Table 4). Analogous error components were observed when examined separately for each of the 3 sample types. The BN II immunochemical measurement procedure had an approximate 7% bias compared to either of the other 2 immunochemical procedures for all sample types.

Fig. 4 shows difference plots for the least and most biased BCG and BCP methods vs the RMP. Difference plots for all measurement procedures are shown in online Supplemental Fig. 1. Also shown in the Figs. are differences in results for the undiluted and diluted ERM-DA470k/IFCC RM for BCG and BCP methods compared to the RMP. In general, the diluted ERM-DA470k/IFCC material exhibited a different relationship compared to patient samples for BCG but a similar relationship for BCP and immunochemical methods.

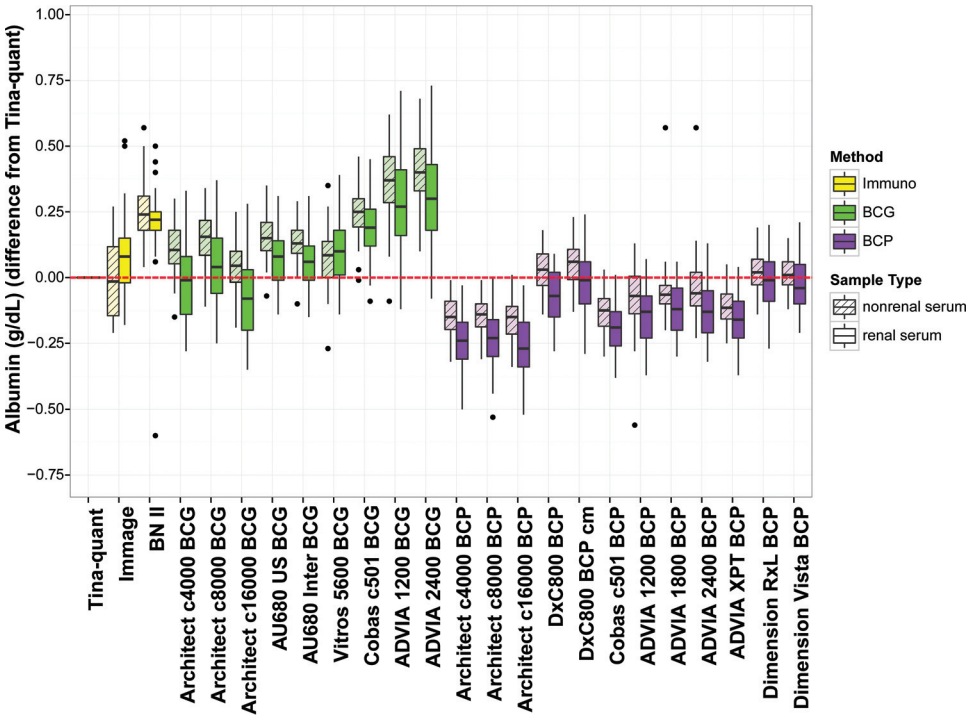

Fig. 3. Difference in albumin results for each method vs the Tina-quant RMP for serum samples from patients on hemodialysis (darker shade) and non–renal disease serum samples (lighter shade with stripes).

The box shows the median, 25th, and 75th percentile values, and whiskers represent the 10th and 90th percentile values. Black circles indicate values that exceed the 10th and 90th percentiles. The median values for Tina-quant were 3.41 g/dL (34.1 g/L) and 3.28 g/dL (32.8 g/L) for renal and non–renal samples, respectively. To convert from g/dL to SI units (g/L), multiply g/dL × 10.

Discussion

The Joint Committee for Traceability in Laboratory Medicine lists measurement principles based on immunoassay with either turbidimetric or nephelometric detection of the immune complex as an RMP for albumin in serum *(20)*. ERM-DA470k/IFCC is listed as a certified RM for calibration of immunoassays. We used the Tina-quant turbidimetric immunochemical measurement procedure as the RMP to determine relative biases among measurement procedures and sample types because it had excellent recovery of albumin in the RM, supporting correct calibration traceability to the RM, and small random error components. Between the other 2 immunochemical methods, the Immage nephelometric procedure had similar performance characteristics as the Tina-quant while the BN II had significant positive bias vs the RM value and the Tina-quant procedure for all sample types. These observations imply that the calibration of the BN II was incorrect and use of an immunochemical measurement principle does not assure accurate results for albumin unless calibration traceability is verified.

In general, BCG methods were biased high compared to BCP methods. Mean biases for BCP methods vs the RMP were smaller and the magnitude of proportional error did not change with concentration. In contrast, mean biases for BCG methods vs the RPM were larger and proportional error varied with the concentration of albumin, with larger positive biases at lower concentrations. In addition, there was a larger range of differences among the BCG methods compared to BCP methods, suggesting that BCG methods are influenced to a greater extent by other proteins or substances in the samples than are BCP methods.

None of the BCG methods met the minimum performance specifications for bias based on biological variability criteria over a physiologically reasonable range of concentrations. Eight of 12 BCP methods met the minimum performance for bias and those that did not had generally smaller biases than were observed for BCG methods. Our data show that BCP methods had better selectivity for albumin and had proportional biases; thus, it is likely that harmonization of results can be achieved. The variable bias with concentration and nonselectivity of BCG methods implies that methods using BCG tech-

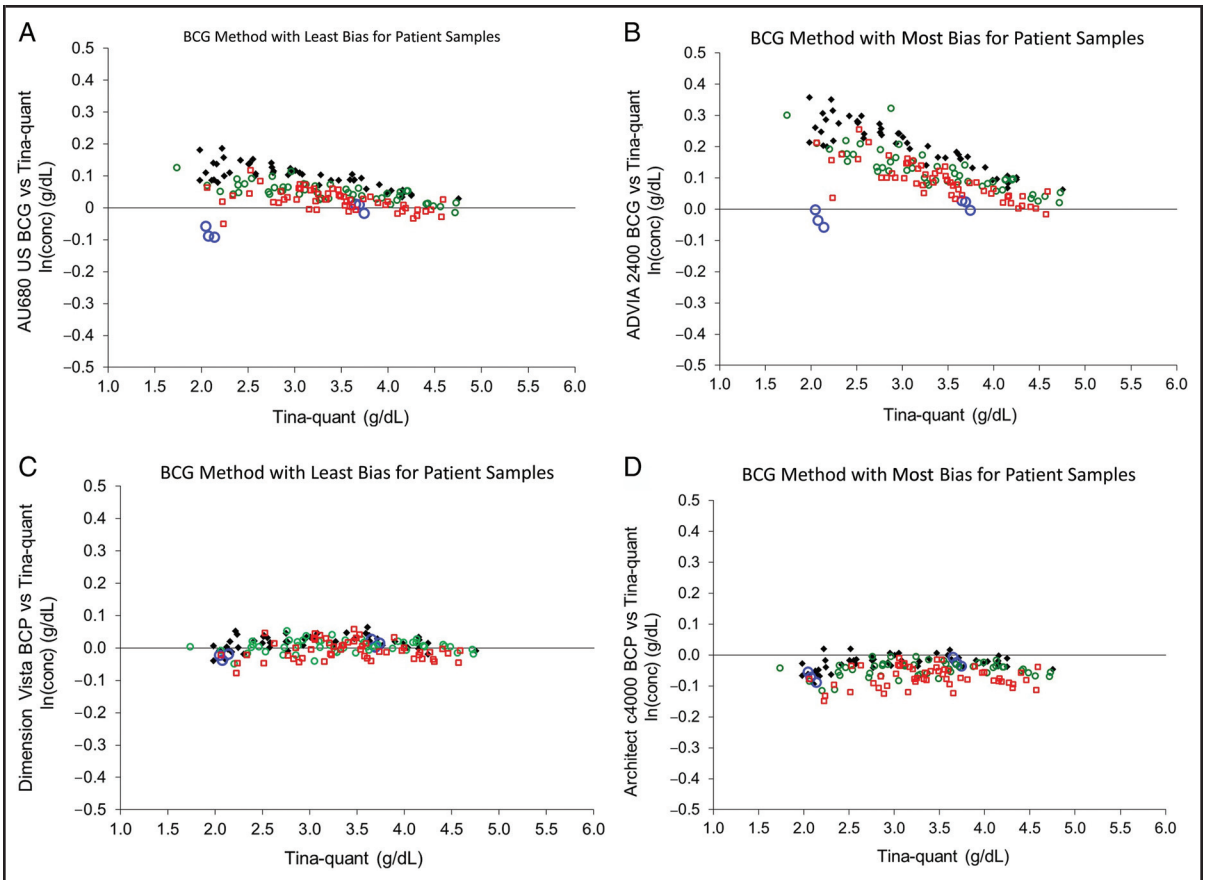

Fig. 4. Representative albumin difference plots for BCG and BCP methods vs the Tina-quant RMs.

Differences are shown as ln concentration [ln(conc)]. The ln concentration multiplied by 100% represents approximate % CV [100·SD(ln *x*)≅ CV(*x*)] *(17)*. (A), BCG method with the smallest overall bias for patient samples; (B), BCG method with the largest overall bias; (C), BCP method with the smallest overall bias; and (D), BCP method with the largest overall bias. The diamonds show results for non–renal disease plasma samples, the small circles show results for non–renal disease serum samples, the squares show results for renal disease serum samples, and the larger circles show results for the undiluted and diluted ERM-DA470k/IFCC RMs. These figures are also shown with separate colored symbols for non–renal disease plasma, non–renal disease serum, renal disease serum, and the RMs in the online Data Supplement. To convert Tina-quant results from g/dL to SI units (g/L), multiply g/dL × 10.

nology cannot be harmonized and should therefore be eliminated from use in clinical laboratories.

An observation that measurements using heparinized samples caused erroneous results in BCG methods has been reported previously *(24, 25)*. All measurement procedures in this study, with the exception of the Image nephelometric procedure, are approved by the US Food and Drug Administration–for both serum and heparin plasma samples. Our observations suggest that specificity issues associated with heparinized samples continue to be problematic for current-generation BCG methods.

Nineteen of 24 measurement procedures claimed to have calibration traceability to ERM-DA470k/IFCC or its predecessor ERM-DA470 serum RM. Differences in implementation of calibration traceability strategies likely contributed to the biases. However, the observed differences in results for serum vs plasma and for samples from patients with renal disease compared to patients without renal disease also supports albumin methods as suffering from selectivity limitations that differ among sample types.

Achieving harmonized results for serum and plasma albumin using dye-binding technology will require specifying a single reagent type. Our data support BCP as the preferred approach because the relative biases were smaller than for BCG methods and were consistent over the concentration interval examined, whereas BCG methods had nonproportional biases over the concentration interval that make standardization impossible.

All BCP and 6 of 9 BCG methods recovered the ERM-DA470k/IFCC RM target value similarly. Results for patient samples and undiluted and diluted RM for immunochemical and BCP methods vs the RMP had similar relationships, and the RM is likely suitable for use with these methods. However, results for the diluted RM had noticeably different relationships for BCG methods, and therefore diluted RMs may be noncommutable with patient samples for BCG methods. We do not know if the RM is diluted in calibration traceability approaches used by manufacturers, and there may be commutability issues with BCG methods if diluted materials are used. The certificate of analysis states the primary intended use of the RM is for calibration of immunoassay procedures, includes minimal information regarding suitability for dye-binding methods, and recommends that commutability should be verified for use with a particular measurement procedure. Further studies are needed to determine the commutability characteristics of RMs for the dye-binding albumin measurement procedures.

The differences in bias of albumin measurement procedures have implications for patient care. The National Kidney Foundation's guidelines on nutrition in chronic renal failure recommend routine measurement of albumin in patients on maintenance renal dialysis *(11, 26)*. In the US, the Centers for Medicare and Medicaid Services sets standards for care of dialysis patients *(27)*. Consistent with the National Kidney Foundation's guidelines *(11)*, the goal *(28)* is for albumin concentrations to be ≥4.0 g/dL (40 g/L) when measured by a BCG method (or "laboratory normal" for a BCP method).

For 2016, dialysis centers are expected to achieve albumin above 4.0 g/dL (40 g/L) in 38% of treated patients *(29)*. For patients whose serum albumin is <3.5 g/dL (<35 g/L), centers must show evidence of a plan to improve nutrition. For patients whose albumin is below the guideline values, aggressive protein supplementation is used *(30)*. Supplements may adversely affect phosphorous, potassium, and other electrolyte concentrations, the costs of supplements and personnel time are usually nonreimbursable, and a definitive mortality benefit has not been shown *(31, 32)*. The lack of standardization in albumin assays thus risks subjecting a large number of dialysis patients to unproven and costly therapy.

The choice of albumin measurement procedure produced large differences in the percentages of renal disease samples that met the goals in this study. Among BCG methods, the goal of albumin ≥4.0 g/dL (≥40 g/L) was met for 32% of samples as measured by the Advia 2400 but for only 13% of samples as measured by the Architect c16000. Similarly, 70% and 36% of the results from these measurement procedures, respectively, were at or above the goal of 3.5 g/dL (35 g/L). Clearly, the use of quality goals at fixed concentrations is not tenable with the current state of harmonization of albumin methods.

Another example of the effects of the differences among results of measurement procedures is apparent when using serum albumin to calculate "corrected" serum calcium concentrations *(33)*. The calculation attempts to account for differences in the amount of calcium that albumin binds, thus lowering the biologically active unbound calcium. Such calculations are frequently used in patients with low albumin, including patients with liver and kidney disease and cancer. As shown by Labriola et al. *(33)*, the corrected calcium results produced discordant classifications of calcemic status when a Roche Modular P BCG measurement procedure was compared with a Beckman Unicel DxC 800 BCP measurement procedure. Our results are consistent with these findings and suggest that "corrected" calcium will be substantially influenced not only by the choice of BCG or BCP methods but also by the specific implementation of a given measurement procedure. Sample type will also influence "corrected" calcium. Until harmonization of albumin assays is achieved, the analytical variability of measurements of albumin support moving away from use of "corrected" calcium. Consistent with this view, the 2016 update of the Centers for Medicare and Medicaid Services guidelines for dialysis centers *(29)* has replaced reporting of "corrected calcium" with "uncorrected calcium."

Serum albumin is also used in the clinical decision-aid for patients with end-stage renal disease who must choose between kidney transplantation and dialysis *(34)*. The decision aid uses a single albumin cutpoint of 3.5 g/dL (35 g/L). For a patient with albumin below the cutpoint, the predicted 1-year survival on renal dialysis is decreased by up to 10%, but the predicted survival after renal transplantation is affected little. The Emory University Department of Surgery website *(35)* provides further information on this topic. The choice of albumin measurement procedure may affect many renal dialysis patients since, for example, 70% of results for renal disease samples in the present study were ≥3.5 g/dL (35 g/L) by the Advia 2400 BCG measurement procedure, but only 36% of results for those samples were ≥3.5 g/dL (35 g/L) by Architect c16000 BCG measurement procedure.

Limitations of this study include the use of pools rather than individual-patient samples due to sample volume limitations. Pools may not be ideal representatives of individual samples. When samples with high concentrations of albumin are mixed with lower-concentration samples, the molecular form of albumin present in the high sample predominates and interfering substances present in either sample are diluted. Another limitation is that a single measurement procedure (Tina-quant) was used as the RMP. It is possible that sample-specific influences on the Tina-quant measurement procedure could have confounded our observations. In addition, interas-

say precision estimates were obtained on a limited number of runs.

In summary, BCG methods have larger biases than BCP methods when compared to the RMP. Furthermore, the bias of BCG methods, but not BCP methods, varies with the concentration of albumin. Due to the general differences between measurements obtained using BCG and BCP methods, as well as differences between specific manufacturer's implementations of each method type, single decision thresholds for albumin concentration are likely inappropriate for patient-care decisions. Standardization of albumin results using dye-binding methods will require adoption of BCP as the preferred reagent.

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