Educational Discussion: 2025-B Accuracy-Based Urine

The samples used in the 2025 Accuracy-Based Urine (ABU) Surveys A and B mailings were prepared from pooled human donor urine. The different samples were based on the albumin concentrations for individual donor urine with the other analyte concentrations as found in those donor urines with exception of ABU-06. The ABU-05 and ABU-06 are the same pooled urine with crystalline creatinine added to prepare the ABU-06 sample. The ABU Survey samples were prepared from minimally processed human urine and thus assumed to be commutable with clinical urine samples, and their results can be used to evaluate agreement among measurement procedures.

The Laboratory Working Group of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Standardization of Albumin in Urine (WG-SAU) are collaborating to facilitate developing reference measurement procedures (RMPs) for urine albumin and certified reference materials (CRMs) for use as calibrators in the urine albumin standardization program (Clin Chem 2024;70:382-91). The RMP for urine albumin from the National Institute of Standards and Technology (NIST) was listed by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) in 2025. RMPs from the University of Minnesota and the Chemical Metrology Division of the Health Sciences Authority in Singapore are expected to be listed by JCTLM in 2026. An extent of equivalence study among these urine albumin RMPs supported nearly equivalent results among them (Clin Chem 2024;70:1375-82).

Urine albumin target values for the 2025 ABU samples were assigned by the Chemical Metrology Division of the Health Sciences Authority in Singapore and urine creatinine target values were assigned by the Division of Laboratory Sciences, Centers for Disease Control and Prevention, both RMPs were based on liquid chromatography-isotope dilution-tandem mass spectrometry. Target values for calcium and total protein were assigned as an all method principles/all instruments mean value. The ABU Survey evaluation criteria for each analyte are shown on the previous page. The albumin-to-creatinine ratio (ACR) is not graded but is informative.

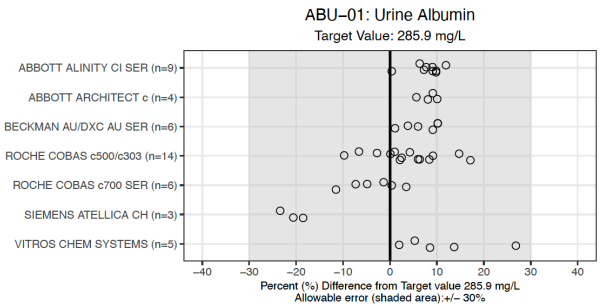
For ABU-A and ABU-B 2025, the overall participant pass rates are shown in the following table. An issue with the creatinine RMP value for ABU-01 prevented evaluating participants' results.

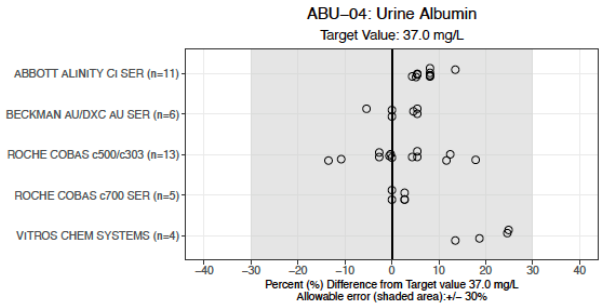
	Albumin target value (mg/L)	Albumin pass rate (%)	Creatinine target value (mg/dL)	Creatinine pass rate (%)	Protein target value (mg/L)	Protein pass rate (%)	Calcium target value (mg/dL)	Calcium pass rate (%)
ABU-01	285.9	98.2			450	100	1.56	96.2
ABU-02	15.01	91.1	80.71	98.3	60	91.3	11.4	100
ABU-03	152.4	94.7	77.13	94.9	260	100	8.51	100
ABU-04	37.0	96.2	121.64	96.4	130	97.4	8.50	100
ABU-05	93.0	98.1	102.24	98.2	180	94.9	10.7	97.1
ABU-06	91.5	98.1	198.94	100.0	180	94.9	10.8	100

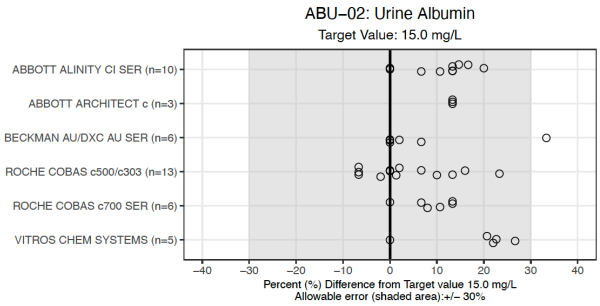
Note that all participant results are included in the calculation of pass rate. For the participant summary report and the analysis that follows, only instrument/reagent groups with 3 or more results are included. A limitation of the data analysis is that the number of participant results in each instrument/reagent group was relatively small, ranging from 3-14.

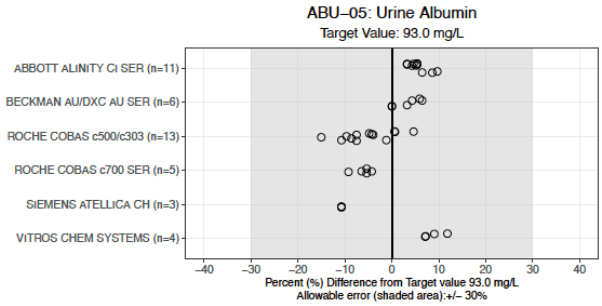
Urine albumin

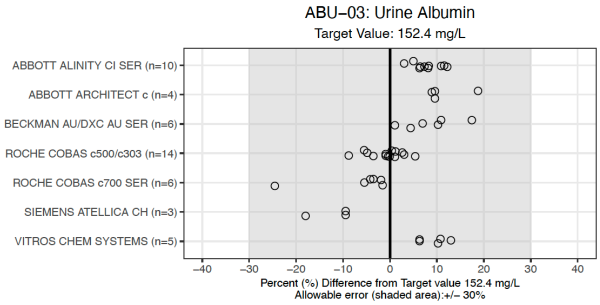
Individual participant results for urine albumin measurement procedure types are shown in the following bias plots. All methods for urine albumin were immunoturbidimetric.

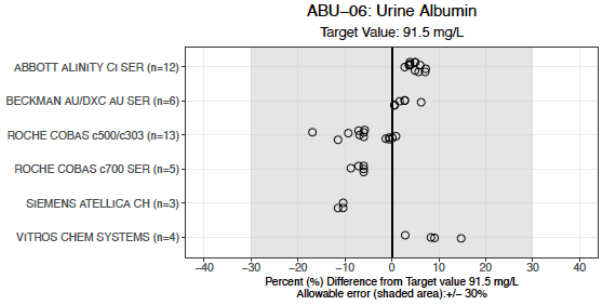












With one exception, the individual participant results fall within the current ABU Survey ±30% acceptable limits for urine albumin. Note that, one exception is not consistent with some of the overall pass rates in the table above because only instrument groups with at least 3 results are shown and outliers were removed before the bias plots were prepared, but outliers are included for the pass rates. The ±30% limits were based on a 2017 report from the NIDDK/IFCC WG. The 2017 recommendation was derived from within individual biological variation for urine albumin which varies widely among studies making identifying a suitable biological variation value somewhat arbitrary but was the only information available at that time. Biological variation is not recommended for deriving analytical performance specifications for urine albumin because urine albumin is normally either absent or present in very low concentrations in healthy people making it unrealistic to estimate biological variation. Soon to be published recommendations based on simulated outcomes for misclassification of kidney disease will propose maximum acceptable uncertainty of ±20% for urine albumin measurement results.

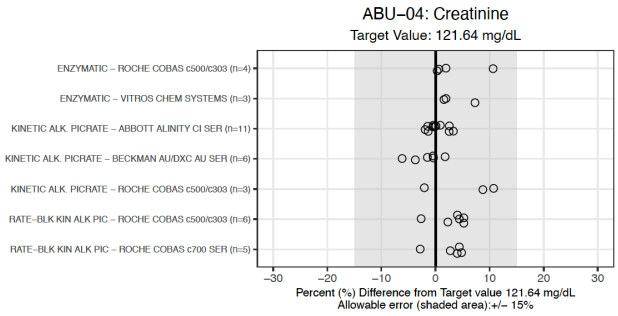
The urine albumin data in the bias plots are encouraging because almost all participant results, which are single measurements, are within the ±30% bias limits. Examination of the bias plots shows some bias

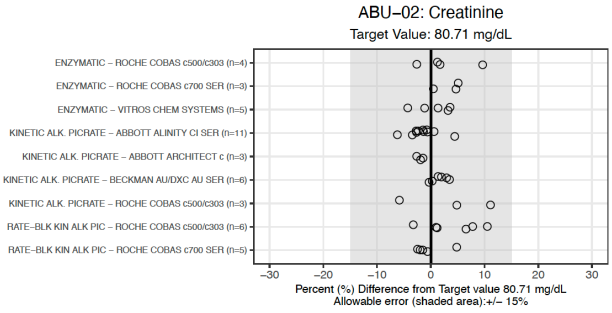
patterns such as all (or most) results on one side of the zero-bias line with some approaching the 30% limits. These observations support the need to improve standardization of calibration of urine albumin measurement procedures by applying the recently developed CRMs and RMPs for the metrological traceability of all urine albumin IVD measurement procedures. Considering the about to be published ±20% analytical performance specification for urine albumin measurement results, removal of the bias patterns seen in the bias plots by applying standardized calibration should enable all results to meet the ±20% goal. At concentrations near 90 mg/L, the results did meet the ±20% performance goal.

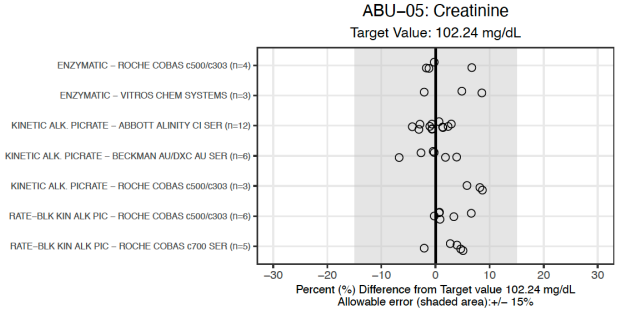
Urine creatinine

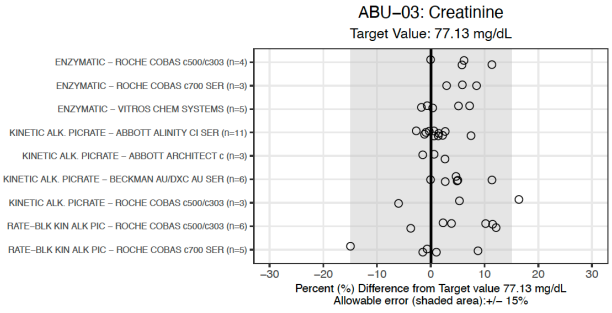
Individual participant results for each of the urine creatinine measurement procedure types are shown in the following bias plots. Creatinine methods are grouped by enzymatic and type of Jaffe procedure used. An issue with the creatinine RMP value for ABU-01 prevented analysis.

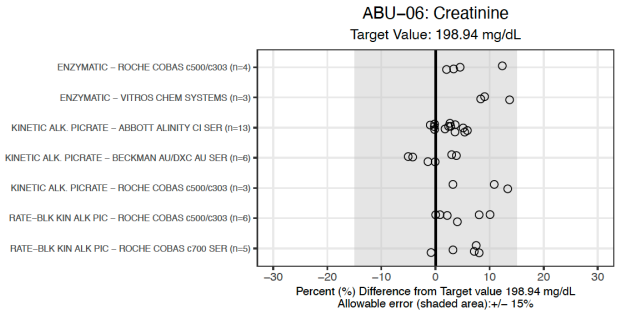
With one exception, the individual participant results for urine creatinine fall within the current ABU Survey ±15% acceptable limits for urine creatinine. Note that, one exception is not consistent with some of the overall pass rates in the table above because only instrument groups with at least 3 results are shown and outliers were removed before the bias plots were prepared, but outliers are included for the pass rates. The individual results are evenly distributed among positive and negative values vs the targets supporting that there is minimal calibration bias for the IVD measurement procedures for urine creatinine. The observed scatter represents imprecision in the measurement procedures among the participating laboratories.











Urine albumin to creatinine ratio (UACR)

UACR results are not reported by instrument groups. The overall observations are summarized in the following table organized from low to high UACR values. ABU-01 is excluded because an issue occurred with the creatinine RMP value.

	UACR (mg albumin / g creatinine)				
	ABU-02	ABU-04	ABU-06	ABU-05	ABU-03
Expected value (from RMPs)	18.6	30.4	46.0	91.0	198
All results minimum	11.0	21.7	38.1	75.9	161
All results median	20.8	31.4	44.8	91.9	200
All results maximum	24.9	39.0	51.0	107	730
Interval (Max-Min)	13.9	17.3	12.9	31.1	569

UACR is the recommended way to report urine albumin because the ratio to creatinine normalizes for hydration and correlates better with the clinically useful urine albumin excretion rate. The Kidney Disease Improving Global Outcomes (KDIGO) 2024 *Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* and other clinical practice guideline decision thresholds are based on UACR (normal to mildly increased <30 mg/g, moderately increased 30-300 mg/g, and severely

increased >300 mg/g). Examination of the data shows that UACR values have relatively large intervals that will lead to ambiguity and misclassification of severity of disease for values near decision thresholds. For example, ABU-04 had UACR values from 21.7-39.0 mg/g, and ABU-03 had UACR values from 161-730 mg/g. The large intervals for UACR will be reduced when the urine albumin standardization program is implemented by the IVD manufacturers to reduce the calibration biases. However, the imprecision of measurements will remain such that there will always be some ambiguity in results near the clinical decision thresholds. All clinical practice recommendations are to measure UACR at least twice over three months to improve the confidence in a clinical decision.

Urine total protein

The median of participant results for each of the urine total protein measurement procedure types are shown in the following table grouped by reagent type.

		Difference between instrument group median and all methods mean (%)					
		ABU-01	ABU-02	ABU-03	ABU-04	ABU-05	ABU-06
All methods mean		452 mg/L	61.4 mg/L	264 mg/L	142 mg/L	186 mg/L	184 mg/L
Abbott Alinity	Benzethonium Chloride	-2.4	10.8	-4.2	-5.6	-3.2	-5.4
Roche cobas c500/c300	Benzethonium Chloride	0	6.5	2.3	-1.4	6.4	3.3
Roche cobas OUS[1] c500/c300	Benzethonium Chloride	-16.6	-12.0	-13.6	-17.6	-12.9	-17.4
Roche cobas OUS c700	Benzethonium Chloride	-12.0	-10.4	-12.1	-16.9	-8.1	-10.9
Abbott Alinity	Biuret	-0.2	10.8	-2.6	-14.1	-4.8	-6.5
Siemens Atellica	Biuret	12.4	33.6	17.0	40.1	36.6	43.5
Beckman AU/DxC	Pyrogallol Red	23.4	21.5	16.3	15.5	14.0	15.8
Interval between maximum and minimum difference (%)		40.0	45.6	30.7	57.8	49.5	60.9

[1] Abbreviation OUS is marketed out of the United States.

There is no RMP for urine total protein. Consequently, an all method principles/all instruments mean value is used as the target value. However, this target value may not be a reliable estimate of a true value because the different types of proteins found in urine are each expected to have different instrument responses for a given type of reagent. The pass rates for urine total protein in an earlier table are good because the acceptance criterion (±3 SD) accommodates the influence of differences in protein responses in reagent systems. To assess total protein agreement among the different instrument groups, the biases between instrument/method types are compared as the intervals between them as shown in the last row in the table above. The intervals among median value differences range from 30.7% to 60.9% for the ABU samples with concentrations between 61.4 mg/L and 452 mg/L. A limitation of the ABU samples for assessing urine total protein methods is they were prepared based on urine albumin

concentrations in donor urine and not likely to include all of the types of protein found in patients with kidney disease who may have much higher total protein concentrations. However, within these limitations, the data supports that agreement is poor among different urine total protein measurement procedures. Given the technical issues associated with different responses of the reagent systems to different types of proteins found in urine, it is unlikely that calibration standardization can be improved and there is not a current activity to attempt such an effort. Laboratories should be aware that interpretation of urine total protein results is method dependent and advise users of laboratory results accordingly.

Urine calcium

The median of participant results for each of the urine calcium measurement procedure types are shown in the following table grouped by reagent type. The ABU-01 sample is not included because its low calcium value compared to other samples suggests a potential issue with that sample's results.

		Difference between instrument group median and all methods mean (%)				
		ABU-02	ABU-03	ABU-04	ABU-05	ABU-06
All methods mean		11.3 mg/dL	8.51 mg/dL	8.45 mg/dL	10.7 mg/dL	10.8 mg/dL
Abbott Alinity	Arsenazo	-3.2	-2.5	-3.2	-4.7	-5.6
Abbott Architect	Arsenazo	-5.3	-6.0			
Beckman AU/DxC	Arsenazo	4.2	3.4	4.1	0.9	1.8
Siemens Atellica	Arsenazo	1.8	5.8	1.8	2.8	2.8
Roche cobas c500/c300	NM-BAPTA[1]	3.1	2.2	2.5	2.8	3.2
Roche cobas c700	NM-BAPTA	2.9	2.2	3.0	1.9	0.9
Interval between maximum and minimum difference (%)		9.6	11.8	7.3	7.5	8.8

[1] NM-BAPTA is an abbreviation for 5-nitro-5'-methyl-(1,2-bis(o-aminophenoxy)ethan-N,N,N',N'-tetraacetic acid.

ABU samples do not currently have values assigned for urine calcium using an RMP although there is one RMP listed by the JCTLM. Consequently, an all method principles/all instruments mean value is used as the target value. The median values for each sample from different measurement procedures are similar, suggesting similar responses of the different instrument/reagent systems to calcium and supporting that the all methods mean is a reasonable target value. The intervals among median value differences in the last row of the table above range from 7.3-11.8% over calcium concentrations from 8.45-11.3 mg/dL with no trends. These results support that calibration of urine calcium measurement procedures is suitable for use.

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