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Setting Analytical Quality Goals with Biological Variation Data

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DOI: 10.15428/CCTC.2019.310276

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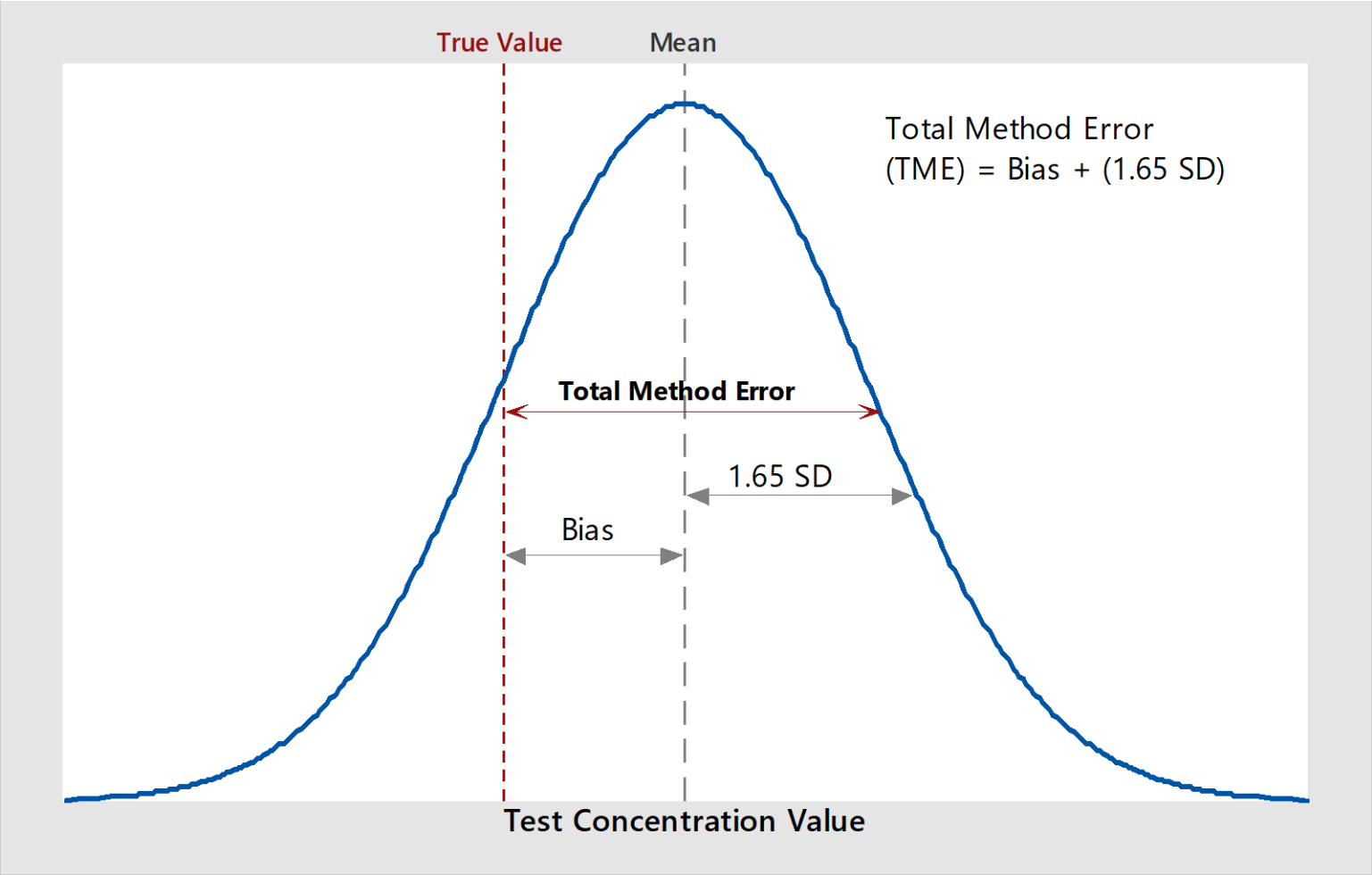
Method performance validation, concept of total error

- ✓ Establish or verify analytical performance prior to use in patient care

- ✓ Determine:
  - Precision
  - Bias
  - Total method error (TME)

- ✓ TME compared to Total Allowable Error (abbreviated TEa, or TAE)
  - When TME < TAE, test method is considered to meet goals for patient care use

Concept of Total Method Error (TME)



Establishing TAE goals

How are TAE goals determined?

- Countries with specified legal criteria
  - e.g., CLIA acceptable limits used for regulated analytes (USA)
- Targets set by providers of proficiency testing (PT) / external quality assessment schemes (EQAS)
  - USA, Canada, European Union, Australia, *more*
- ***Using Biological Variation data***

- Miller WG, Myers GL, Ashwood ER, Killeen AA, Wang E, Ehlers GW, et al.. Arch Path Lab Med 2008;132:838-46.
- Jones GRD, Albarede S, Kesseler D, MacKenzie F, Mammen J, Pedersen M, et al. Clin Chem Lab Med 2017;55:949-55.

Terms to describe biological variation data

CV_G %

- Between-subject biological variation
- (think: **G**roup variation)

Recall:

$$\text{CV}\ (\%) = {}^{SD}/_{Mean} \text{ x } 100\%$$

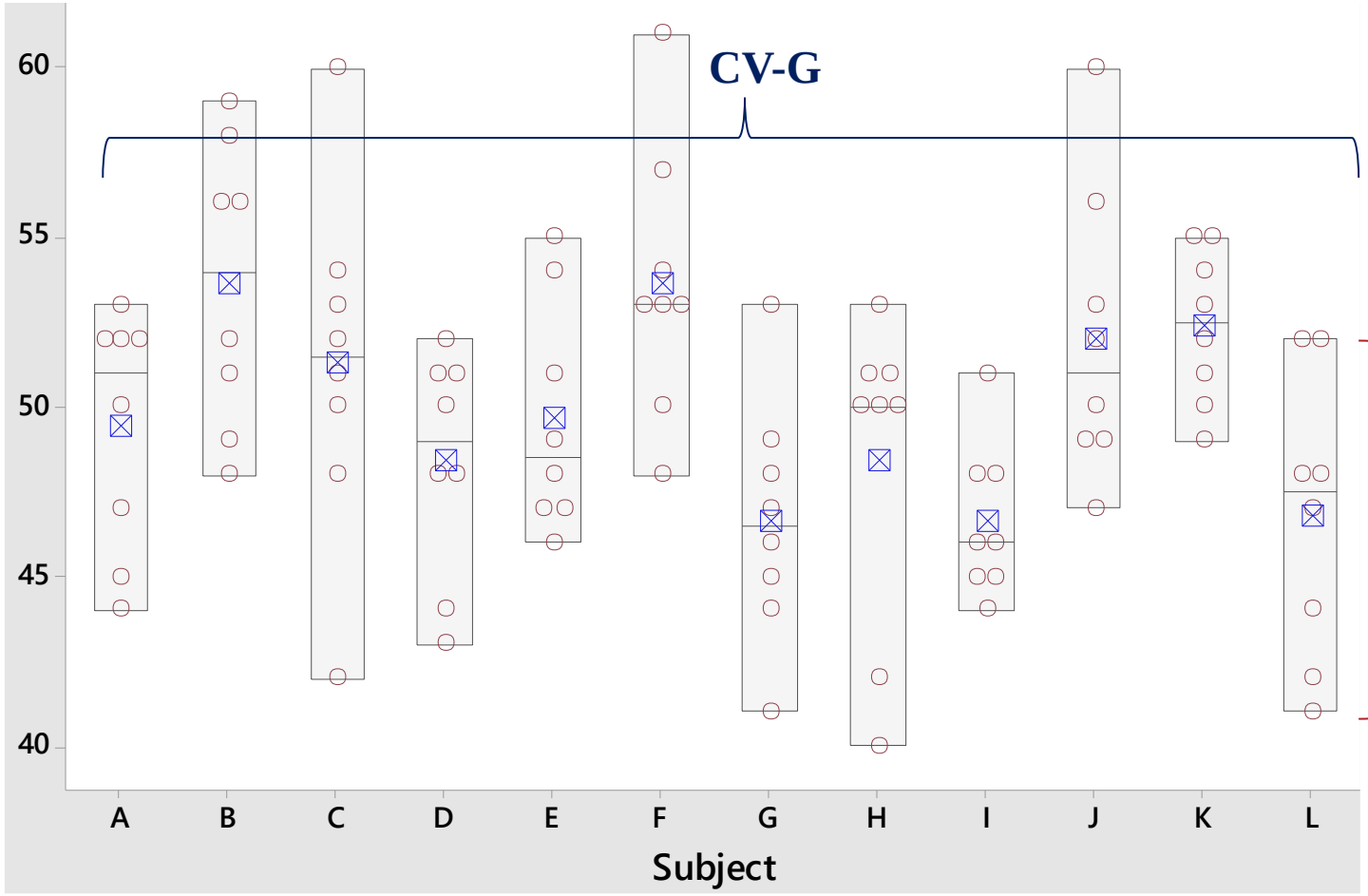
$$\text{RSD}(\%) = {}^{SD}/_{Mean} \text{ x } 100\%$$

CV = coefficient of variation
RSD = relative standard deviation

CV_I %

- Within-subject biological variation
- (think: **I**ndividual variation)

Two components of BV: CV-G, CV-I



Observed variation across subjects (**CV-G**) and within each subject (**CV-I**)

Biological variation database

		Biological Variation	
Analyte	***N***	**CV-I**	**CV-G**
Albumin	42	2.6	5.1
Apolipoprotein A1	20	5.8	11.2
Aspartate aminotransferase (AST)	16	9.5	21.0
Chloride	29	1.0	1.3
Cholesterol	95	5.9	14.4
Creatinine	58	4.9	11.7
Glucose	45	4.8	5.8
HDL cholesterol	68	7.5	23.0
Potassium	29	3.9	4.1
Protein, total	34	2.6	4.5
Sodium	31	0.5	1.2

CV-I = within-subject biological variation

CV-G = between-subject biological variation

EFLM. Biological variation database. https://biologicalvariation.eu/(Accessed 11 July 2019)

Setting "Desirable" Limits

CV-I = within-subject biological variation

CV-G = between-subject biological variation

I = desirable specification for imprecision

B = desirable specification for bias

TE = desirable specification for total allowable error

		Biological Variation		Desirable Limits		
Analyte	***N***	**CV-I**	**CV-G**	**I(%)**	**B(%)**	**TE(%)**
Albumin	42	2.6	5.1	1.3	1.4	3.6
Apolipoprotein A1	20	5.8	11.2	2.9	3.2	7.9
Alanine aminotransferase (ALT)	14	9.6	28.0	4.8	7.4	15.3
Aspartate aminotransferase (AST)	16	9.5	21.0	4.8	5.8	13.6
Chloride	29	1.0	1.3	0.5	0.4	1.2
Cholesterol	95	5.9	14.4	3.0	3.9	8.8
Creatinine	58	4.9	11.7	2.5	3.2	7.2
Glucose	45	4.8	5.8	2.4	1.9	5.8
HDL cholesterol	68	7.5	23.0	3.8	6.0	12.2
Potassium	29	3.9	4.1	2.0	1.4	4.6
Protein, total	34	2.6	4.5	1.3	1.3	3.4
Sodium	31	0.5	1.2	0.3	0.3	0.7

Calculating "Desirable" Imprecision Goal

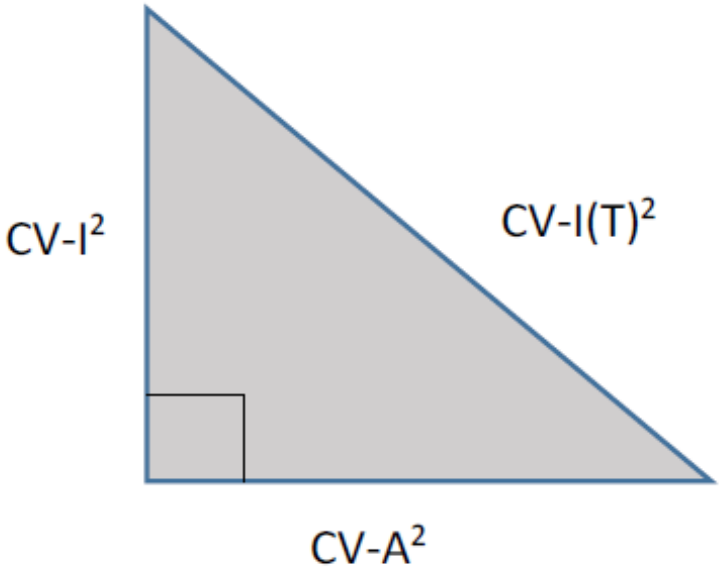
- Under normal circumstances, random fluctuation (imprecision) *within* a subject is the CV-I

- Analytical method imprecision should be less than one-half of within-subject biological variation:

$$\text{Imprecision } (CV_A) < 0.5\ CV_I$$

- Fraser CG, et al. Ann Clin Biochem 1997;34 (Pt 1):8-12
- Fraser CG. Change in serial results. Biological variation: From principles to practice, Vol. 1: AACC Press; 2001. p. 67-90

Analytical imprecision adds variability to within-subject variation



$$CV.I(T) = \sqrt{CV.I^2 + CV.A^2}$$

"Total" within-subject variation

Let: CV-A = 0.5 CV-I
(substitute terms into equation shown on left-side panel)

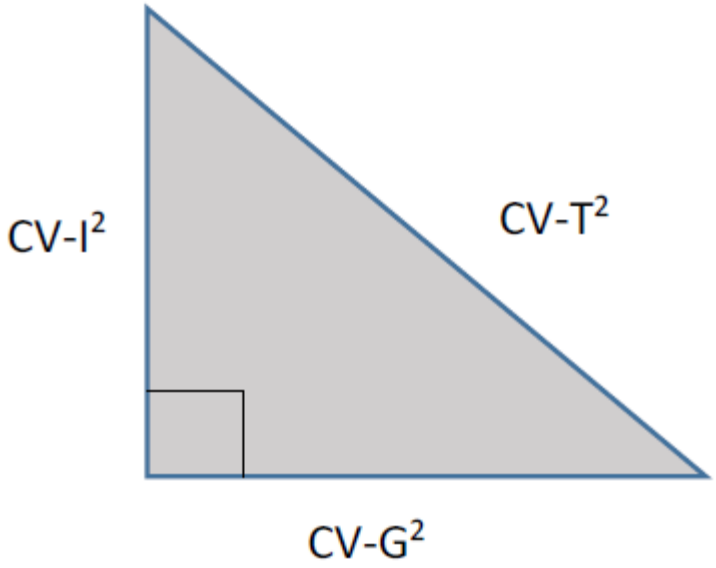
$$= \sqrt{1.25\ CV - I}$$

$$= 1.12\ CV - I$$

= 12% added variability to result

When CV-A is 50% of CV-I (desirable goal limit)

Total biological variation



$$CV.T = \sqrt{CV.I^2 + CV.G^2}$$

Sum of variances: within-subject and between-subject BV

Calculating "Desirable" Bias Goal

Bias, or inaccuracy, should be less than one-fourth of total biological variation (combined within-subject and between-subject)

$$\text{Bias} < 0.25 \times \sqrt{CV_I^2 + CV_G^2}$$

- "Bias" can be thought of as differences between people
- **Compare method bias data to *total* biological variation**

- Fraser CG, et al. Ann Clin Biochem 1997;34 (Pt 1):8-12
- Fraser CG. Change in serial results. Biological variation: From principles to practice, Vol. 1: AACC Press; 2001. p. 67-90

Total Allowable Error Goals

Combine the previous two equations to get:

$$TAE < (1.65 \; x \; \text{Imprecision goal}) + \text{Bias goal}$$

-or-

$$TAE < [1.65 \; x \; 0.5 \; CV_I] + [0.25 \; x \; \sqrt{CV_I^2 + CV_G^2}]$$

1.65 = one-sided z-value 0.05 significance level (α), 95% probability
2.33 = one-sided z-value 0.01 significance level (α), 99% probability

- Fraser CG, et al. Ann Clin Biochem 1997;34 (Pt 1):8-12
- Fraser CG. Change in serial results. Biological variation: From principles to practice, Vol. 1: AACC Press; 2001. p. 67-90

Alanine aminotransferase (ALT) test, as example

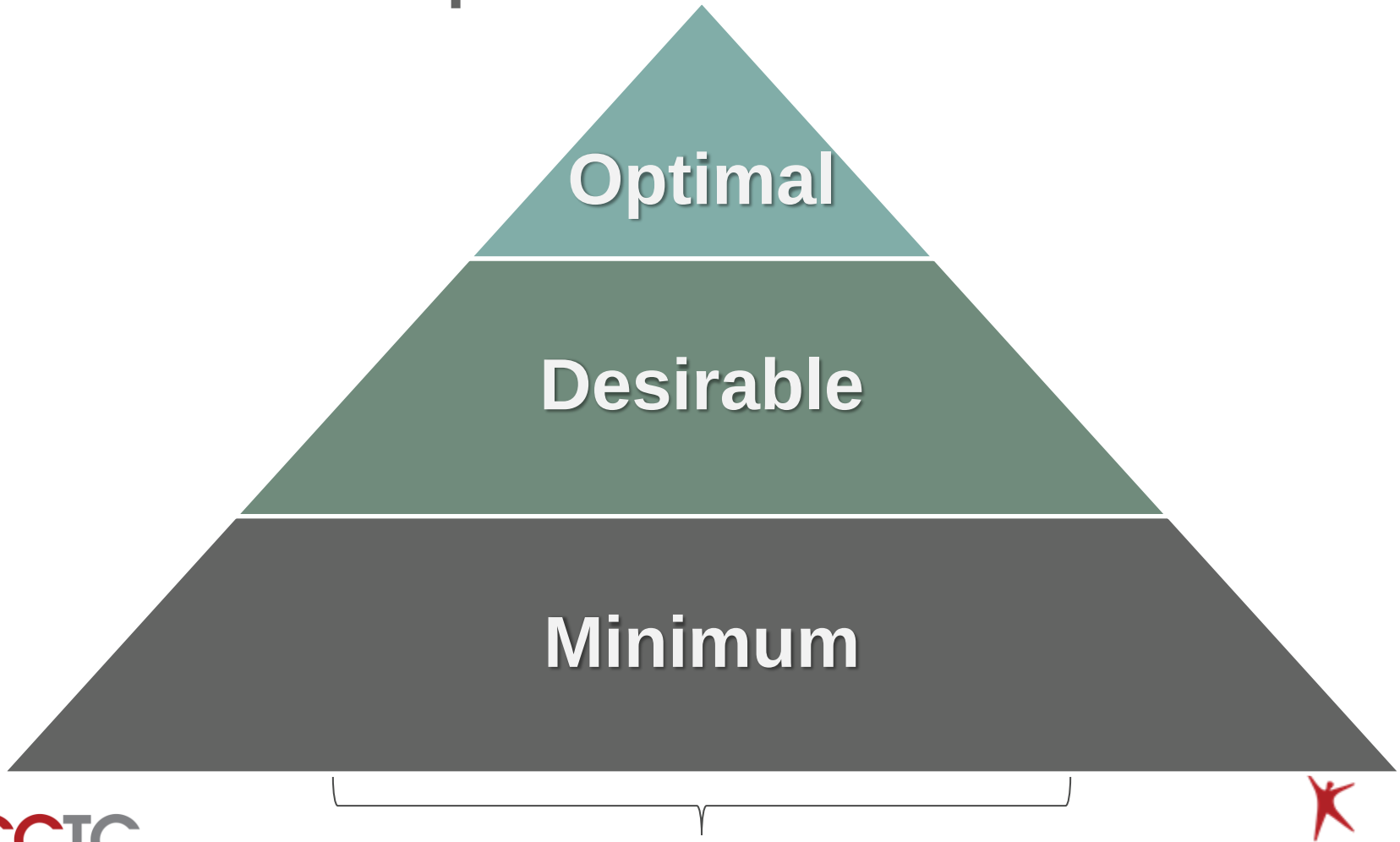
		Biological Variation		Desirable Limits		
Analyte	***N***	**CV-I**	**CV-G**	**I(%)**	**B(%)**	**TE(%)**
Albumin	42	2.6	5.1	1.3	1.4	3.6
Apolipoprotein A1	20	5.8	11.2	2.9	3.2	7.9
Alanine aminotransferase (ALT)	14	9.6	28.0	4.8	7.4	15.3
Aspartate aminotransferase (AST)	16	9.5	21.0	4.8	5.8	13.6
Chloride	29	1.0	1.3	0.5	0.4	1.2
Cholesterol	95	5.9	14.4	3.0	3.9	8.8

I (%) = *0.50* x (9.6) = 4.8

B (%) = *0.25* x $\sqrt{(9.6^2 + 28.0^2)}$ = 7.4

TE (%) = (1.65 x 4.8) + 7.4 = 15.3

Additional performance criteria for bias and imprecision



Relative comparisons of allowable error

Comparison of optimal, desirable, and minimal goals

		Biological Variation		Imprecision Factors				Bias Factors	
				0.25	0.50	0.75	0.125	0.250	0.375
Analyte	***N***	**CV-I**	**CV-G**	**Optimal**	**Desirable**	**Minimal**	**Optimal**	**Desirable**	**Minimal**
Albumin	42	2.6	5.1	0.7	1.3	2.0	0.7	1.4	2.1
Apolipoprotein A1	20	5.8	11.2	1.5	2.9	4.4	1.6	3.2	4.7
Alanine aminotransferase (ALT)	14	9.6	28.0	**2.4**	**4.8**	**7.2**	**3.7**	**7.4**	**11.1**
Aspartate aminotransferase (AST)	16	9.5	21.0	2.4	4.8	7.1	2.9	5.8	8.6
Chloride	29	1.0	1.3	0.3	0.5	0.8	0.2	0.4	0.6
Cholesterol	95	5.9	14.4	1.5	3.0	4.4	1.9	3.9	5.8
Creatinine	58	4.9	11.7	1.2	2.5	3.7	1.6	3.2	4.8
Glucose	45	4.8	5.8	1.2	2.4	3.6	0.9	1.9	2.8
HDL cholesterol	68	7.5	23.0	1.9	3.8	5.6	3.0	6.0	9.1
Potassium	29	3.9	4.1	1.0	2.0	2.9	0.7	1.4	2.1
Protein, total	34	2.6	4.5	0.7	1.3	2.0	0.6	1.3	1.9
Sodium	31	0.5	1.2	0.1	0.3	0.4	0.2	0.3	0.5

ALT method comparison data

Method comparison	*Mean (U/L)*		
Instrument A	27.5		
Instrument B	29.8		
	2.3	BIAS	
	8.0%	**% Bias**	
target 30 U/L			
Precision	**Total CV**	Within-Day	Between-Day
Instrument B	**6.5%**	2.5%	6.0%
Total Error	**18.8%**		

Data is generated from method comparison experiments in the laboratory to determine bias and imprecision of “Instrument B”

Conversion factor: U/L x 0.017 = µkat/L

Evaluating method performance

- Compare data obtained from method comparison experiment to desirable and minimum limits based on biological variation *(optimal criteria not shown)*

	Method Performance	Desirable Limits		Minimum Limits		CLIA (USA)	
CV %	6.5	4.8	FAIL	7.2	PASS	N/A	-
Bias %	8.0	7.4	FAIL	11.1	PASS	N/A	-
TME (%)	18.8	15.3	FAIL	23.0	PASS	20.0	PASS

- CLIA proficiency test limits shown for additional comparison

Selected References

1. Miller WG, Myers GL, Ashwood ER, Killeen AA, Wang E, Ehlers GW, et al. State of the art in trueness and interlaboratory harmonization for 10 analytes in general clinical chemistry. Arch Path Lab Med 2008;132:838-46.
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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
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