Serum Creatinine Measurement Specificity

NKDEP Lab Working Group

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Problem Summary

From: Myers, et al, Recommendations for Improving Serum Creatinine Measurement, *Clinical Chemistry* 52:1, 5–18 (2006)

- Endogenous and exogenous interfering substances contribute to lack of analytical specificity of Jaffe (alkaline picrate) creatinine methods
- Interfering substances in serum and/or plasma, particularly proteins, can lead to overestimation of 15%–25% with various Jaffe methods
- Interference from glucose and ketoacids particularly important in diabetics who are at high-risk for CKD.

Problem Summary

From: Myers, et al, Recommendations for Improving Serum Creatinine Measurement, *Clinical Chemistry* 52:1, 5–18 (2006)

- Most Jaffe interference studies dated 10-30 years ago
- Several modifications to Jaffe method reported to improve specificity (e.g. use of kinetic assays or early read times)
- An offset of 21 µmol/L (0.234 mg/dL) was needed to further correct "compensated" Jaffe method for non-creatinine Jaffe-reacting chromogens (Junge W, et al. Clin Chim Acta 2004; 344:137-48)
  - …even with low imprecision and assay standardized to IDMS reference measurement procedure
  - If analytical non-specificity bias remains, errors in estimating GFR will occur.

Problem Summary (cont)

From: Myers, et al, Recommendations for Improving Serum Creatinine Measurement, *Clinical Chemistry* 52:1, 5–18 (2006)

- Although enzymatic creatinine methods are reported to have fewer interferences than Jaffe methods, reports are published of various interferents with enzymatic methods
- HPLC methods have greater analytical specificity than conventional methods.
  - Sample de-proteinization combined with selectivity of mobile-phase conditions make it unlikely that many substances will interfere
- GC-IDMS is method of choice for establishing true concentration of creatinine in serum due to excellent specificity and relative SD (0.3%)

Creatinine Analytical Performance Goals

From: Myers, et al, Recommendations for Improving Serum Creatinine Measurement, *Clinical Chemistry* 52:1, 5–18 (2006)

Performance Goals Based on Biological Variability, creat = 1.0 – 1.5 mg/dL

CVi	CVg	Goal Level	CVa Goal Basis	CVa Goal	Bias Goal Basis	Bias Goal	TE Goal*
4.30%	12.90 %	**Minimum Acceptable**	(0.75 CVi)	3.20%	$0.375\ (CVi^2 \_\ CVg^2)^{1/2}$	5.10%	11.40%
		Desirable	(0.5 CVi)	2.20%	$0.25\ (CVi^2 \_\ CVg^2)^{1/2}$	3.40%	7.60%
		Optimum	(0.25 CVi)	1.10%	$0.125\ (CVi^2 \_\ CVg^2)^{1/2}$	1.70%	3.80%

* TE (total error) goal calculation: Bias Goal + (1.96 X CVa goal)

Issue:

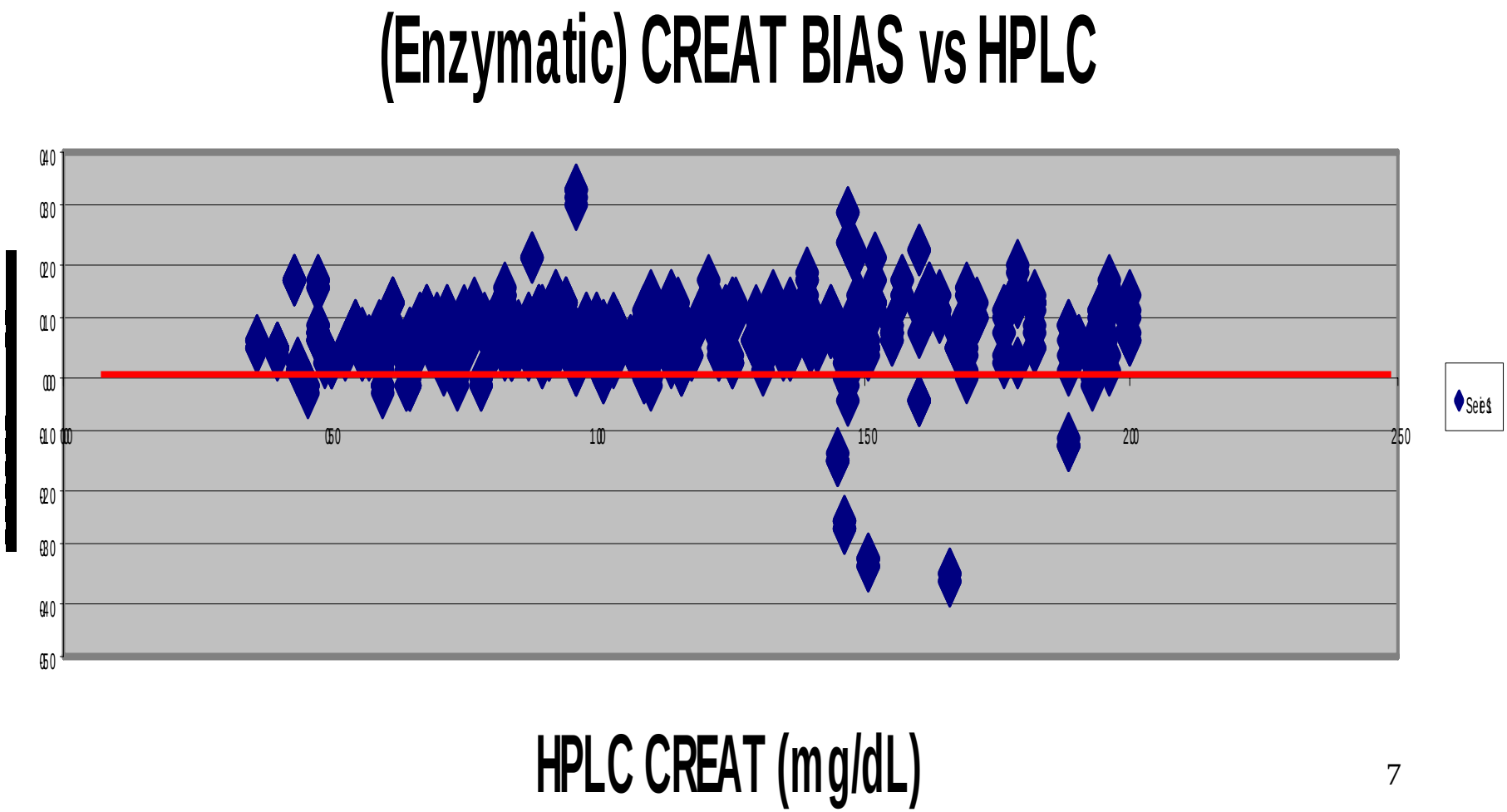
No goal/limit has been defined for sample-dependent random bias (specificity) performance.

Creatinine Analytical Performance Goals - Specificity

Problem/Issue:

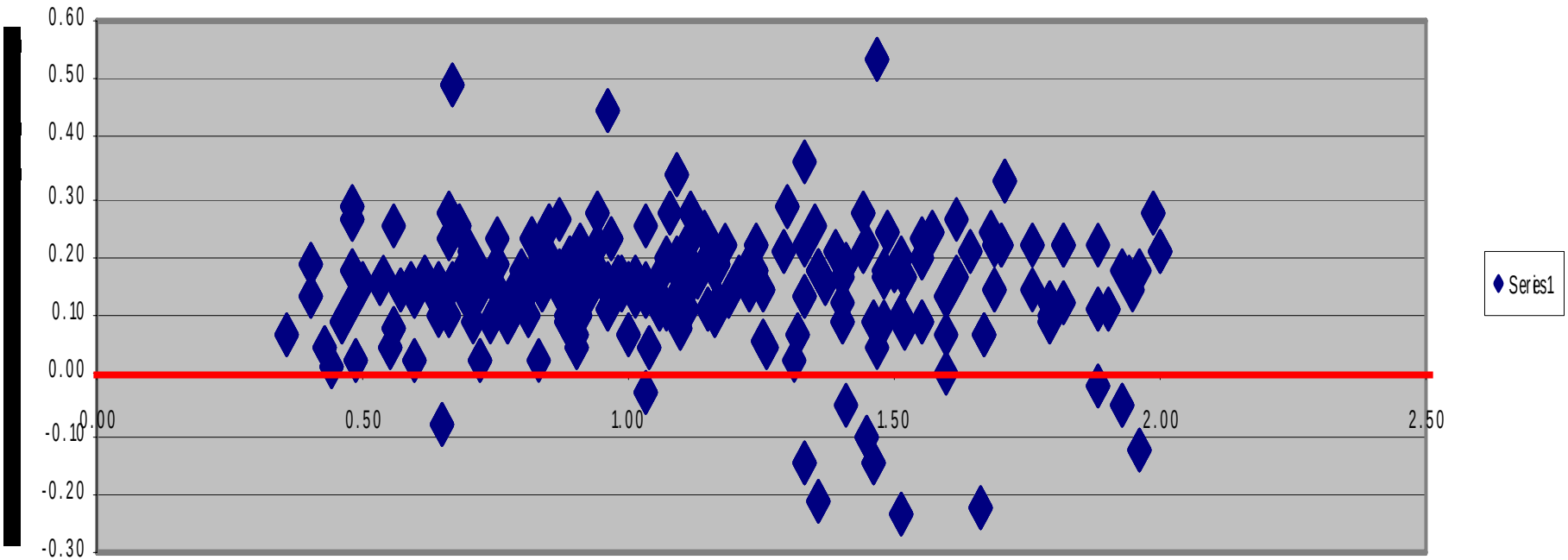
For serum/plasma creatinine measurements, especially in context of using serum creatinine values for determination of GFR with estimating equations, what are appropriate acceptance criteria for individual sample random biases due to interferents and other sample-dependent factors?

2002 OCD Internal Study, Rate Jaffe and (enzymatic) method compared to HPLC, 410 random patient samples, creatinine range = 0.4 – 2.0 mg/dL



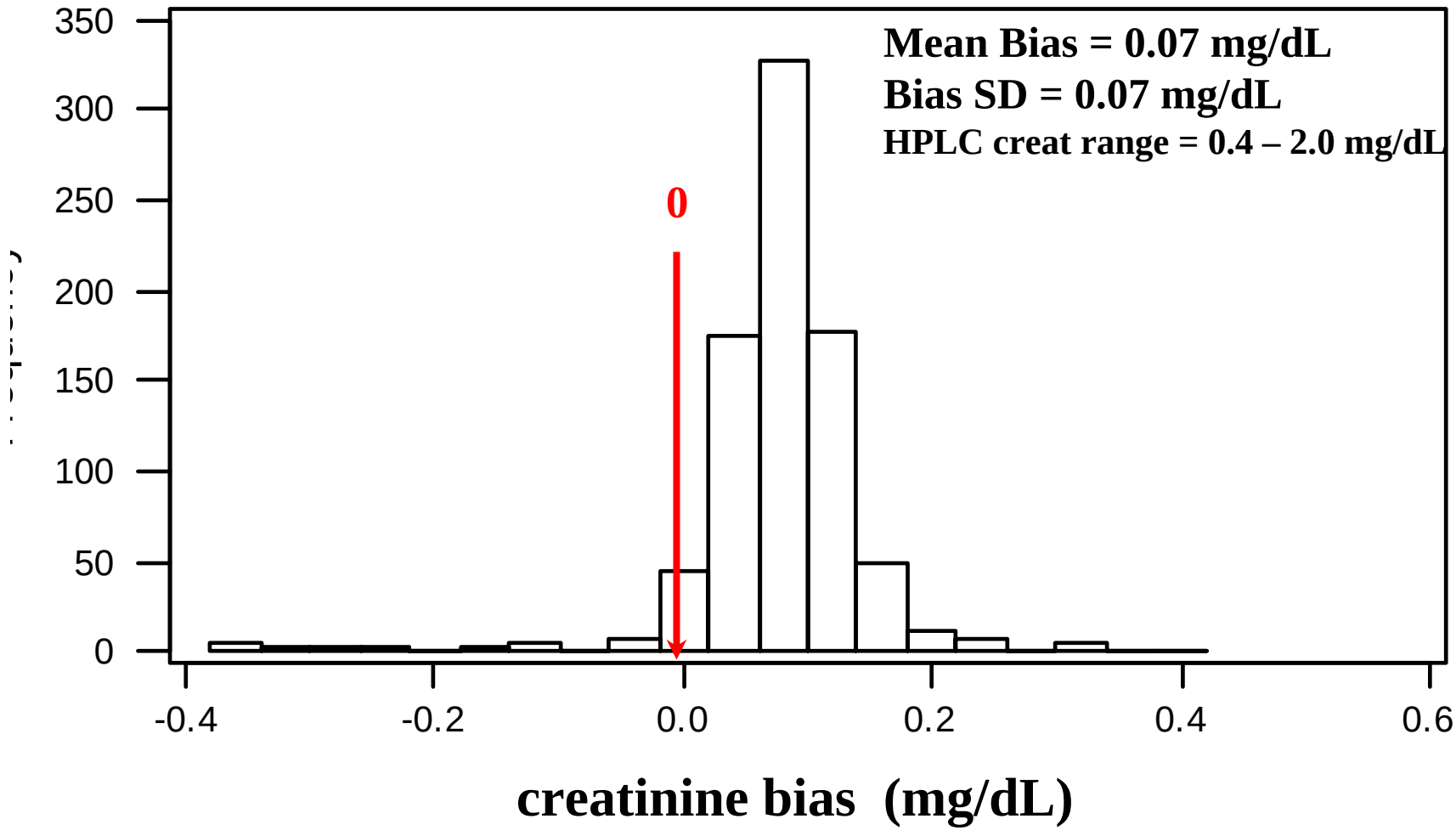
Example Rate JAFFE CREAT Bias vs. HPLC

2002 OCD Internal Study, Rate Jaffe and (enzymatic) compared to HPLC, 410 random patient samples, creatinine range = 0.4 – 2.0 mg/dL



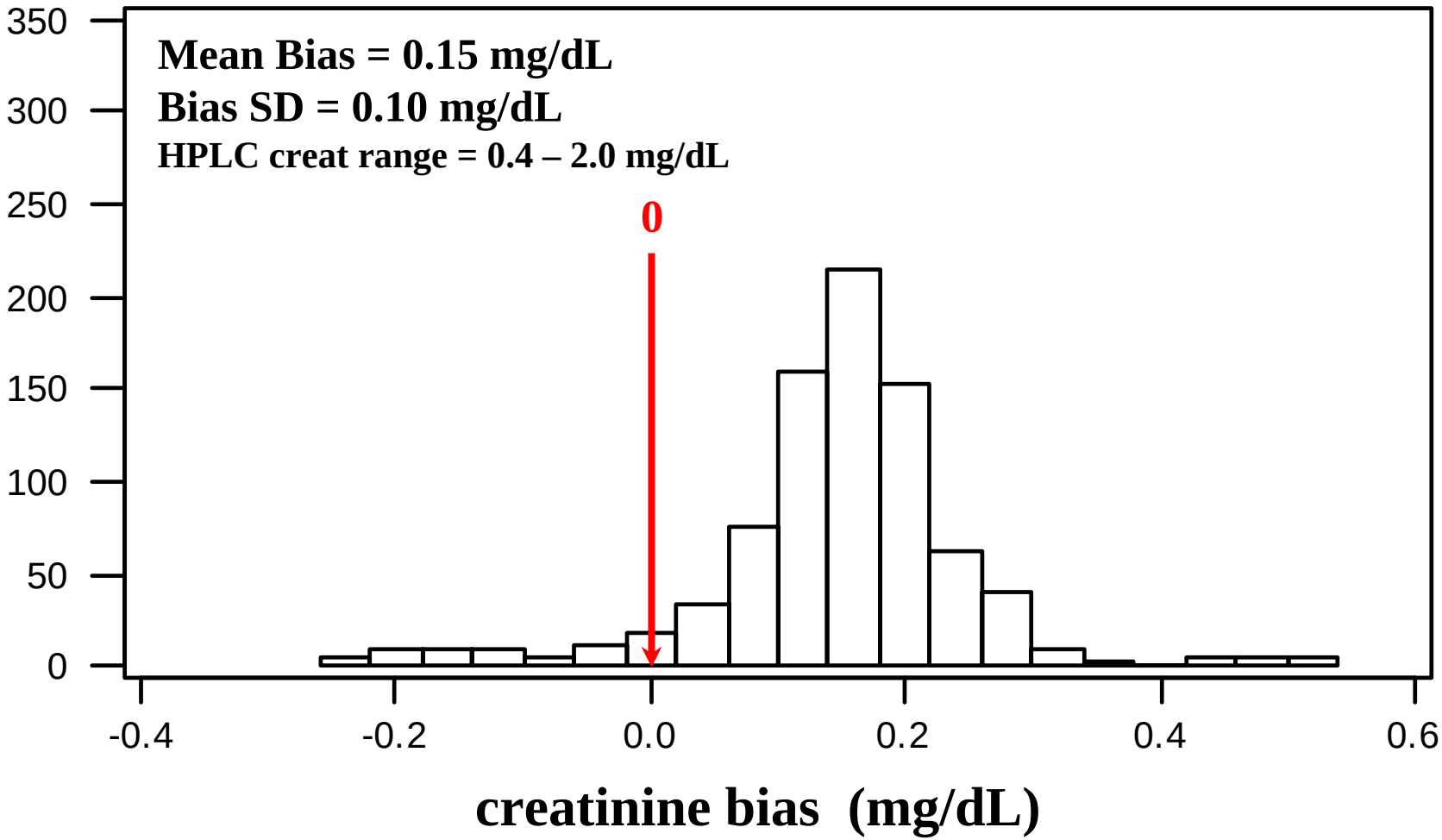
HPLC CREAT (mg/dL)

(enzymatic) Creatinine method
Distribution of Biases (mg/dL) vs. HPLC



Example Rate Jaffe Creatinine Method

Distribution of biases (mg/dL) vs HPLC



Creatinine Analytical Performance Goals - Specificity

Statistical Model for Total Error including Random Bias

Lawton WH, Sylvester EA, Young-Ferraro BJ. Statistical comparison of multiple analytic procedures: application to clinical chemistry. *Technometrics* 21:397-409 (1979)

%TE (total error) goal =

%FB Goal + 1.96 X SQRT[$\%CV_A^2$ goal + $\%CV_{RB}^2$ goal]

Where…

%FB = allowable (systematic) calibration %bias

$\%CV_A$ = allowable analytical imprecision, CV%

$\%CV_{RB}$ = allowable random bias (non specificity), CV%

Creatinine Analytical Performance Goals - Specificity

Rationale for Proposed Goal – Random Bias (non-specificity)

Following the statistical model defined by Lawton, et al…

$$\%TE = \%FB + 1.96 \times SQRT[\%CV_A^2 + \%CV_{RB}^2]$$

Given that (from biological variability), $\%CV_{B\text{-}G} = 12.9\%$

(where $\%CV_{B\text{-}G}$ = % biological variation among individuals), allow that %TE can be as large as 12.9%.

Example 1: Where allowable TE= 12.9%, %FB = 5% and $\%CV_A$ =3%…

- $12.9\% = 5\% + 1.96 \times SQRT[(3\%)^2 + \%CV_{RB}^2]$
- then allowable $\%CV_{RB}$ = 2.7%

Creatinine Analytical Performance Goals - Specificity

Rationale for Proposed Goal – Random Bias (non-specificity)

Following the statistical model defined by Lawton, et al…

$$\%TE = \%FB + 1.96 \times SQRT[\%CV_A^2 + \%CV_{RB}^2]$$

Example 2: Where allowable TE= 12.9%, %FB = 1% and $\%CV_A$ =3%…

- $12.9\% = 1\% + 1.96 \times SQRT[(3\%)^2 + \%CV_{RB}^2]$
- then allowable $\%CV_{RB}$ = 5.3

Example 3: Where allowable TE= 11%, %FB = 1% and $\%CV_A$ =3%…

- $11\% = 1\% + 1.96 \times SQRT[(3\%)^2 + \%CV_{RB}^2]$
- then allowable $\%CV_{RB}$ = 4.1%

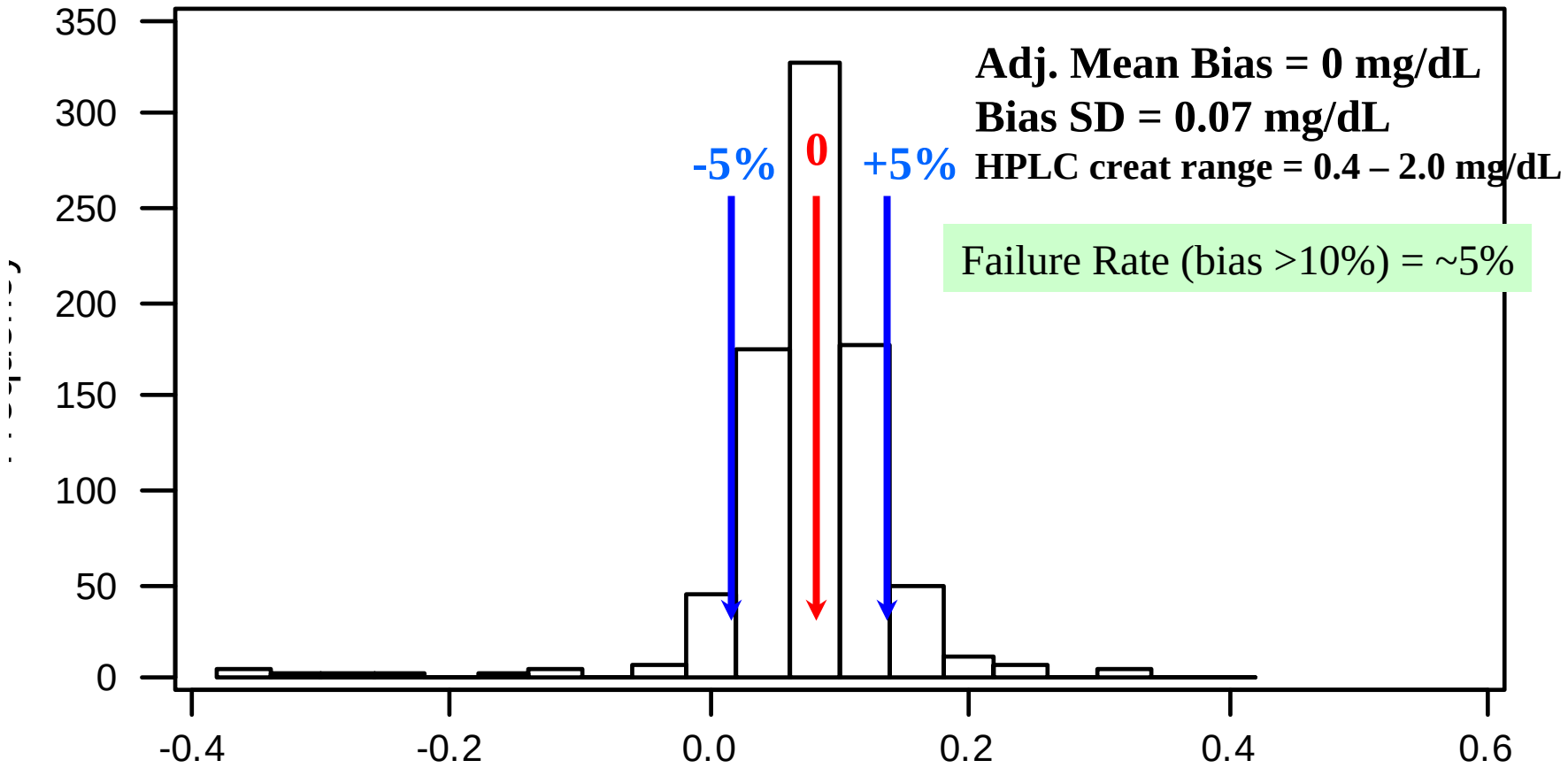
Creatinine Analytical Performance Goals - Specificity

Proposed rationale and approach for development of acceptance criteria – specificity

- If systematic bias can be controlled to within ±1% from IDMS reference target, allowable random bias ($\%CV_{RB}$) can be ~± 5% without compromising "minimally acceptable" TE% goals
- Defined criteria should be stated as…
  - When a creatinine method is calibrated to be traceable to the IDMS reference method, for the indication of screening patients for CKD (using MDRD or other estimating equations), random sample-dependent bias should be within ± 2*X% for 95% of samples tested, where X = $\%CV_{RB}$ Goal.
  - Possible Criteria:
    - 5% "minimally acceptable";
    - 3% "desirable"
  - Need to recognize that 3% ($\%CV_{RB}$) performance may not be achievable with state-of-the art methods

Enzymatic creatinine method
Distribution of Biases (mg/dL) vs. HPLC

Mean value = 1.1 mg/dL with bias compensation; Proposed Allowable Random Bias = 5%



Example Rate Jaffe Creatinine Method

Distribution of biases (mg/dL) vs HPLC

Mean value = 1.1 mg/dL with bias compensation; Proposed Allowable Random Bias = 5%