Deriving performance criteria for laboratory tests: which model should be used?

Wytze Oosterhuis

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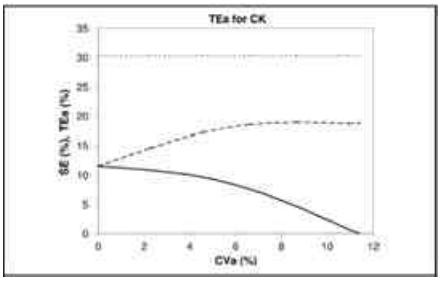
Gross Overestimation of Total Allowable Error Based on Biological Variation

To the Editor:



Wytze P. Oosterhuis*

Department of Clinical Chemistry
Atrium Medical Centre
Heerlen, the Netherlands

Clin Chem 2011; 57: 1334

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Stockholm criteria

Consensus agreement

D. KENNY,* C. G. FRASER,† F. HYLTOFT PETERSEN,‡ & A. KALLNER§

*Department of Clinical Biochemistry, Our Lady's Hospital for Sick Children, Dublin, Ireland, †Directorate of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, ‡Department of Clinical Chemistry, Odense University Hospital, Odense, Denmark, and §Department of Clinical Chemistry, Karolinska Hospital, Stockholm, Sweden

CONSENSUS STATEMENT*

The main outcome of the Conference was agreement that the following hierarchy of models should be applied to set analytical quality specifications.

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings
2. Evaluation of the effect of analytical performance on clinical decisions in general:
   a. Data based on components of biological variation
   b. Data based on analysis of clinicians' opinions
3. Published professional recommendations
   a. From national and international expert bodies
   b. From expert local groups or individuals
4. Performance goals set by
   a. Regulatory bodies
   b. Organizers of External Quality Assessment (EQA) schemes
5. Goals based on the current state of the art
   a. As demonstrated by data from EQA or Proficiency Testing scheme
   b. As found in current publications on methodology.

Desirable routine analytical goals for quantities assayed in serum

Stöckl et al. Eur J Clin Chem 1995; 33: 157

"A stricking feature is the fact that all of the individuel approaches described recommend numbers for analytical standard deviation near or equal to 0.5 times the biological standards deviation"

Imprecision $< 0{,}5SD_b$

Total SD = $(SD_a^2 + SD_b^2)^{1/2}$ $\quad SD_a = 0{,}5SD_b \rightarrow$

Total SD = $((0{,}5SD_b)^2 + SD_b^2)^{1/2}$

Total SD = $(0{,}25SD_b^2 + SD_b^2)^{1/2}$

Total SD = $(1{,}25SD_b^2)^{1/2}$

Total SD = $1{,}12SD_b$

→ **analytical variation < 12% total variation**

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Total Error concept

Westgard:
One measure for uncertainty of the test result

Criteria for Judging Precision and Accuracy in Method Development and Evaluation

James O. Westgard, R. Neill Carey, and Svante Wold[1]

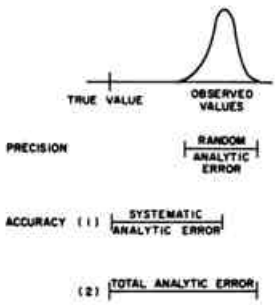

Fig. 1. Definitions of precision and accuracy in terms of random, systematic, and total analytic errors

$$TE = Z \times SD_a + bias$$

Clin Chem 1974;20:825

Quality goals in external quality assessment are best based on biology

C. G. FRASER & P. HYLTOFT PETERSEN

$\pm [1.65\ (^1/_2 CV_I) + {}^1/_4 (CV_I^2 + CV_G^2)^{1/2}]$

$$\underline{TE_a = 1{,}65(0{,}5CVi) + 0{,}25(CV_i^2 + CV_g^2)^{1/2}}$$

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There are many data [3] on within-subject (CV_I) and between-subject (CV_G) biological variation which allow generation of quality goals for EQAS as:

allowable imprecision $< {}^1/_2 CV_I$

allowable inaccuracy $< {}^1/_4 (CV_I^2 + CV_G^2)^{1/2}$

These specifications should be fulfilled separately and EQAS appropriately designed. However, when only a single determination of each survey material is used or allowed, the 95% acceptance range (for total error) for each laboratory from the target value is:

$\pm [1.65\ (^1/_2 CV_I) + {}^1/_4 (CV_I^2 + CV_G^2)^{1/2}]$

$TE = Z \times CV_a + bias$

$Z=1,65$

$TE_a = 1,65\, CV_a + bias$

$CV_a=0,5CV_i$

$TE_a = 1,65(0,5CV_i) + bias$

$bias=0,25CV_b$

$TE_a = 1,65(0,5CV_i) + 0,25CV_b$

$CV_b=0,25(CV_i^2 + CV_g^2)^{½}$

$$\underline{TE_a = 1,65(0,5CV_i) + 0,25(CV_i^2 + CV_g^2)^{½}}$$

The estimate for bias: (Gowans et al.)

- IFCC guideline for calculation of reference values.
- N=120
- maximum of 4,6% outside the reference limit

SD_a <0,58SD_{biol} (with bias=0)
Bias <0,25SD_{biol} (with SD_a=0)

The reference values are based on both with- as between individual variation.

Scan J Clin Lab Invest 1988; 48: 757

Scand J Clin Lab Invest 1988; 48: 757–764

Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area

E. M. S. GOWANS,*† P. HYLTOFT PETERSEN,† O. BLAABJERG† & M. HØRDER†

*Department of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, and †Department of Clinical Chemistry, Odense University Hospital, Odense C, Denmark

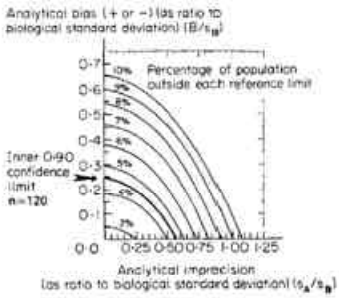
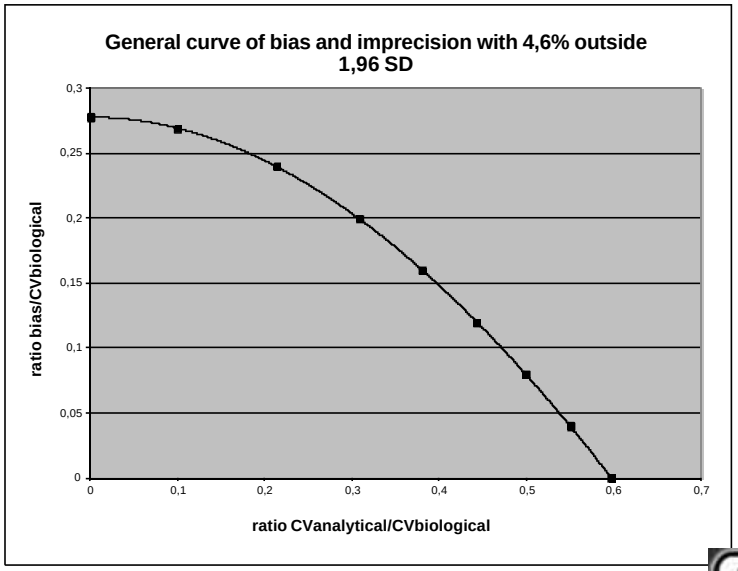
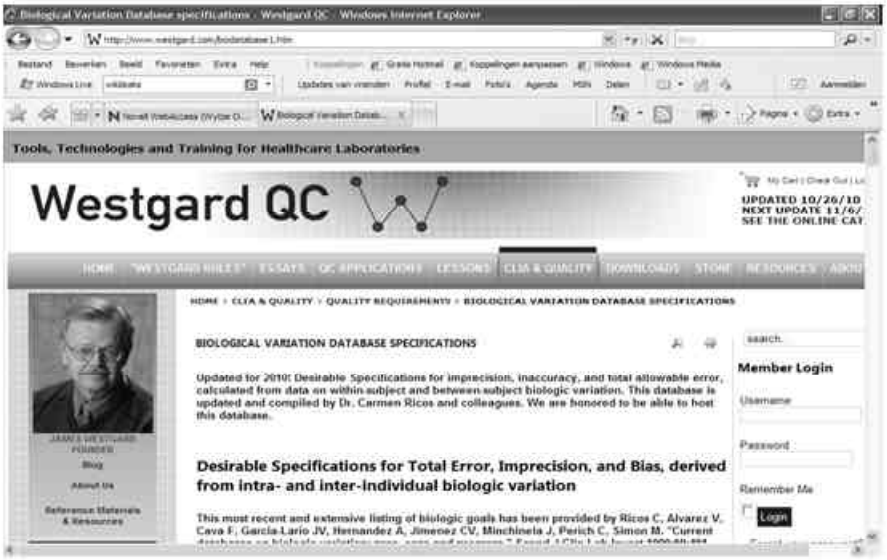


FIG. 6. Relationship between maximal acceptable analytical bias and imprecision for fixed percentages of the population outside either of the $\bar{x} \pm 1.96\ s$ reference limits. This is a more operational transformation of the information detailed by the horizontal inner confidence limits shown in Fig. 5.



Example

TE_a calculation CK

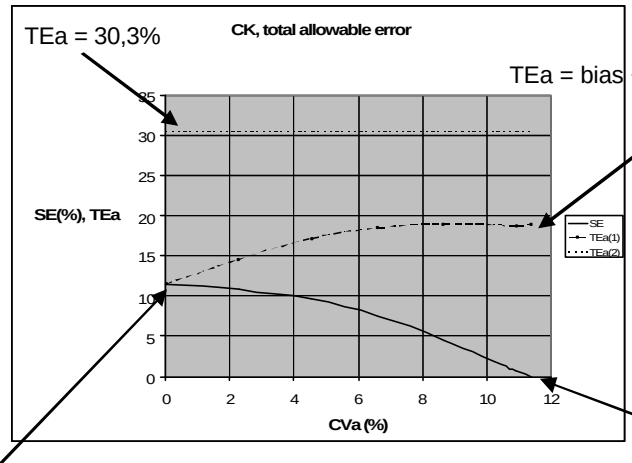


U-	C-Telopeptide of type I collagen/creatinine, 1st morning	32.8	48.0	16.4	14.5	41.6
U-	C-Telopeptide type I collagen/creatinine, 2nd morning	23.4	--	11.7	--	--
S-	Creatine kinase (CK)	22.8	40.0	11.4	11.5	30.3
S-	Creatine kinase MB, %	6.9	48.2	3.45	2.17	17.37
S-	Creatine kinase MB, activity	16.7	24.3	8.9	7.8	24.1

CK:
CV_{within} = **22,8%**
$Cv_{between}$ = **40.0%**

Imprecision = 0,5 x CV_{within} = **11,4%**
Bias= 0,25 v($CV_{wihin}^2 + CV_{between}^2$) = **11,5%**

$TE_{allowable}$ = Bias + 1,65 x imprecision = 11,5% + 1,65 x 11,4% = **30,3%**



TEa = 30,3%

TEa = bias + 1,65 x imprecision

max: 18,9

Allowable bias = 11,5%

Allowable imprecision = 11,4%

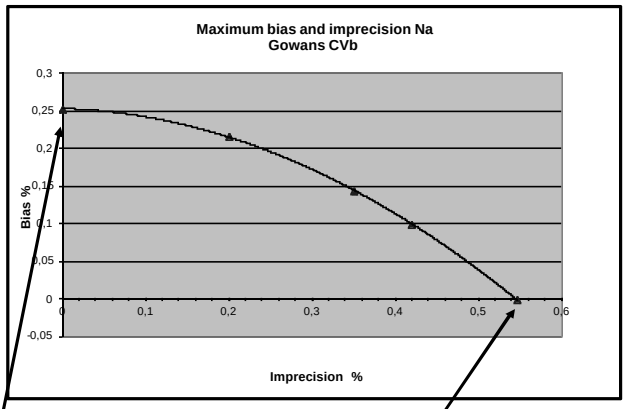
Conclusion

Comparing 18.9% with 30.3%, we see that TEa is overestimated in the latter model. For different purposes, the maximum allowable imprecision and bias have been derived separately from data on biological variation. To combine these maximum values into a single expression has no theoretical basis and leads to gross overestimation of TEa.

Gowans' model is exact but:

- Only 'CV_b' used for calculation of reference values. CV_a?

Example Sodium



CV_i= 0,6%
CV_g=0,7%
CV_b=0,92

CV_a = 1,06%

Max. Bias = 0.27 * CV_b= 0.25%

Max. CV_a= 0.59 * CV_b= 0.55%

Gowans' model is exact but:

- Only 'CV_b' used for calculation of reference values.

  Alternative: $(CV_{a0}^2 + CV_i^2 + CV_g^2)^{1/2}$!

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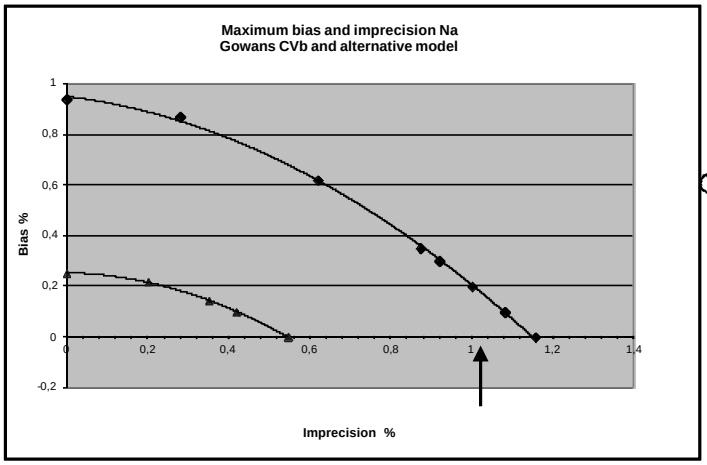

CV_i= 0,6%
CV_g=0,7%
CV_b=0,92

CV_{a0} = 1,06%

Gowans' model is exact but:

- Only 'CV_b' used for calculation of reference values.
  Alternative: $(CV_{a0}^2 + CV_i^2 + CV_g^2)^{½}$

- To use for monitoring:
  Alternative: change to reference change model:
  $RCV = v2 \times Z \times (CV_i^2 + CV_{a0}^2)^{½}$

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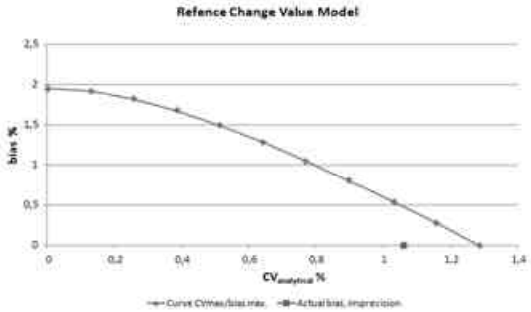
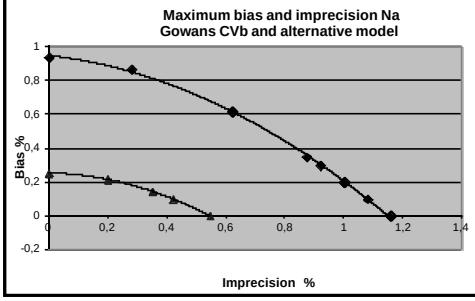
Calculation Bias-Imprecision Curve According to Reference Change Value Model

Test	Na	
CVi (CV within)	0,60	%
Imprecision,CVa0	1,06	%
Actual bias	0,00	%
Actual total imprecision, CVa	1,06	%

Imprecision max.(bias=0)	1,29	%
Bias max.(actual CVa)	0,48	%





Summary: different steps:

1) Decision to use test based on: e.g. CV_a<0,5CV_i (or other) - CV_{a0} and reference values present

2) Apply RCV model, test should remain within curve

3) Develop ICQ !

4) Keep bias close to zero with EQA (1st grade QC material)