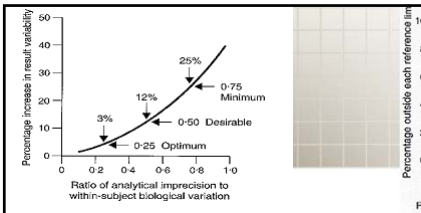
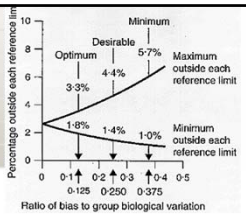
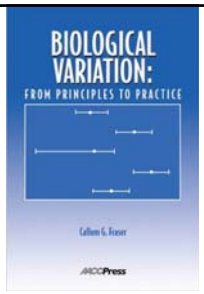






Biologic Variation

The ultimate context for test results

October 25th, 2015
EFLM Continuing Postgraduate Course in Clinical Chemistry
and Laboratory Medicine

Dubrovnik Zagreb Course

15th EFLM Continuing Postgraduate Course in Clinical Chemistry and Laboratory Medicine:
"How to assess the quality of your method?"
October 24-25, 2015,Zagreb, Croatia

Sten Westgard, MS
Westgard QC, Inc.

Westgard QC

Outline of the Talk

- What is biologic variation?
  Do we need to worry about it?
- Setting Goals for Performance from Biologic Variation information
- Reference Change Value
- Current Challenges and Debate on Biologic Variation (Milan Meeting 2014)
- Tools for integrating test results into biologic variation
  - Reference Change Value (RCV)
  - Number of tests required to detect a significant change

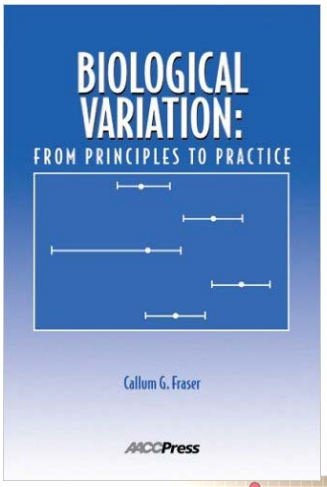
Westgard QC

Disclosure: Almost all discussion of Biologic Variation derives from Callum Fraser

Biologic Variation Data for Setting Quality Specifications
https://www.westgard.com/guest12.htm

James O. Westgard Foreword:
https://www.westgard.com/guest19.htm

Fraser: Are "Scientific Statements" the Scientific Truth?
https://www.westgard.com/callumfraser.htm



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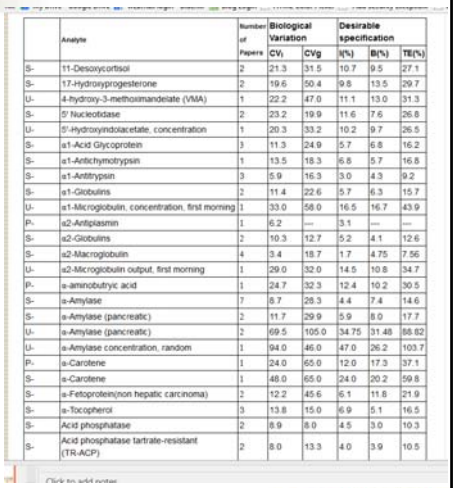
Disclosure: The Biologic Variation Database is housed (but not calculated) on Westgard Web

- Biologic Variation Database is compiled and updated by SEQC and Dr. Carmen Ricos
- Sometimes called "Ricos Goals" as a shorthand and tribute to her leadership
- Most popular resource = **Desirable specifications** for Imprecision, Bias, and Allowable Total Error: https://www.westgard.com/biodatabase1.htm
- **Minimum** Specifications: https://www.westgard.com/minimum-biodatabase1.htm
- **Optimal** Specifications: https://www.westgard.com/optimal-biodatabase1htm.htm
- Specifications for **patients w/disease**: https://www.westgard.com/biodatabasedisease.htm



	Analyte	Number of Papers	Biological Variation		Desirable specification		
			CVI	CVg	I(%)	B(%)	TE(%)
S-	11-Desoxycortisol	2	21.3	31.5	10.7	9.5	27.1
S-	17-Hydroxyprogesterone	2	19.6	50.4	9.8	13.5	29.7
U-	4-hydroxy-3-methoxymandelate (VMA)	1	22.2	47.0	11.1	13.0	31.3
S-	5' Nucleotidase	2	23.2	19.9	11.6	7.6	26.8
U-	5'-Hydroxyindolacetate, concentration	1	20.3	33.2	10.2	9.7	26.5
S-	α1-Acid Glycoprotein	3	11.3	24.9	5.7	6.8	16.2
S-	α1-Antichymotrypsin	1	13.5	18.3	6.8	5.7	16.8
S-	α1-Antitrypsin	3	5.9	16.3	3.0	4.3	9.2
S-	α1-Globulins	2	11.4	22.6	5.7	6.3	15.7
U-	α1-Microglobulin, concentration, first morning	1	33.0	58.0	16.5	16.7	43.9
P-	α2-Antiplasmin	1	6.2	---	3.1	---	---
S-	α2-Globulins	2	10.3	12.7	5.2	4.1	12.6
S-	α2-Macroglobulin	4	3.4	18.7	1.7	4.75	7.56
U-	α2-Microglobulin output, first morning	1	29.0	32.0	14.5	10.8	34.7
P-	α-aminobutryic acid	1	24.7	32.3	12.4	10.2	30.5
S-	α-Amylase	7	8.7	28.3	4.4	7.4	14.6
S-	α-Amylase (pancreatic)	2	11.7	29.9	5.9	8.0	17.7
U-	α-Amylase (pancreatic)	2	69.5	105.0	34.75	31.48	88.82
U-	α-Amylase concentration, random	1	94.0	46.0	47.0	26.2	103.7
P-	α-Carotene	1	24.0	65.0	12.0	17.3	37.1
S-	α-Carotene	1	48.0	65.0	24.0	20.2	59.8
S-	α-Fetoprotein(non hepatic carcinoma)	2	12.2	45.6	6.1	11.8	21.9
S-	α-Tocopherol	3	13.8	15.0	6.9	5.1	16.5
S-	Acid phosphatase	2	8.9	8.0	4.5	3.0	10.3
S-	Acid phosphatase tartrate-resistant (TR-ACP)	2	8.0	13.3	4.0	3.9	10.5

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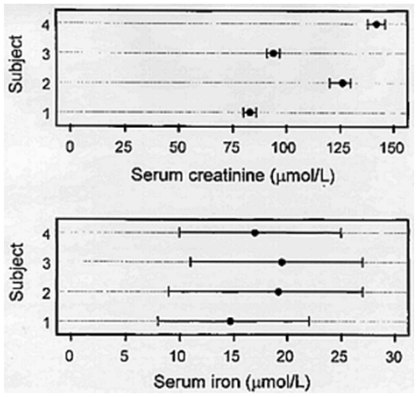
Biologic Variation: One reason Why we never get the same number twice

- CVG: Within-group variation: people are different from other people
- CVI: Within-subject variation: you are never exactly the same



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Why biologic variation matters: it impacts test results

- The "noise" of the body may obscure the signal of the patient's clinical state
- We want the clinician to treat on signal not noise
- We want to make sure our analytical method variation doesn't add too much additional "noise" and make it even harder for the clinician to determine what's happening with the patient.
- [Which raises the question: how much noise is acceptable?]

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Outline of the Talk

- **Setting Goals for Performance from Biologic Variation information**
- Reference Change Value
- Current Challenges and Debate on Biologic Variation (Milan Meeting 2014)

- Tools for integrating test results into biologic variation
  - Reference Change Value (RCV)
  - Number of tests required to detect a significant change

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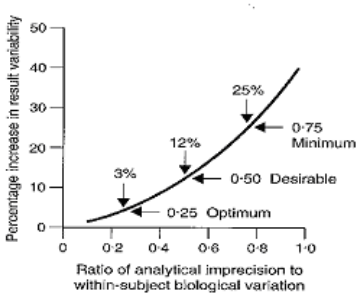
Setting Quality Specifications from Biologic Variation: **Imprecision**

- Optimal: ONE-QUARTER of CVI
- Desirable: HALF of CVI
- Minimum: THREE-QUARTERS OF CVI

WHY?

- Optimal imprecision will only increase result variability by 3%
- Desirable imprecision will only increase result variability by 12%
- Minimum imprecision will only increase result variability by 25%



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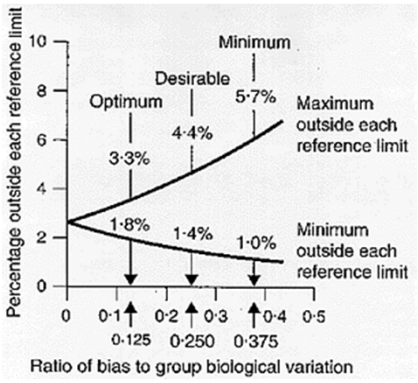
Setting Quality Specifications from Biologic Variation: **Bias**

- *desirable* < **0.250**$[CV_I^2 + CV_G^2]^{0.5}$
- *optimum* < **0.125[**$CV_I^2 + CV_G^2]^{0.5}$
- *minimum* < **0.375**$[CV_I^2 + CV_G^2]^{0.5}$

WHY?

- Optimal bias increases results outside reference interval by 3.3%
- Desirable bias increases results outside reference interval by 4.4%
- Minimum bias increases results outside reference interval by 5.7%



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Setting Quality Specifications from Biologic Variation: **Total Allowable Error**

- Total Allowable (Analytical) Error:
  TEa or ATE = (1.65*SD) + Bias

- **TE < k * 0.5 CV_I + 0.25$(CV_I^2 + CV_G^2)^{1/2}$**
  where k= 1.65 at a=0.05
  (limiting chance of a significant error to 5%)

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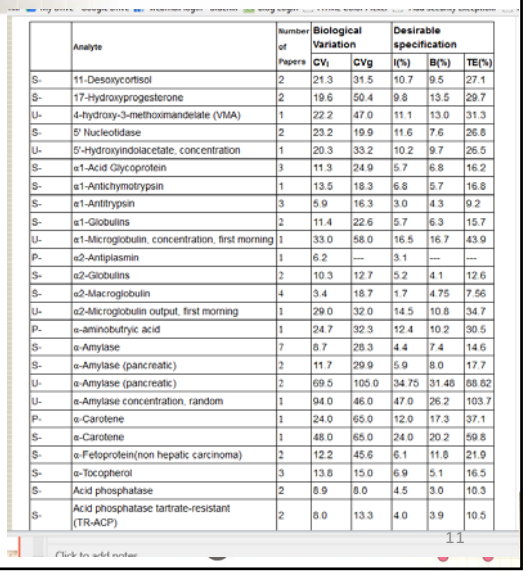
Disclosure: The Biologic Variation Database is housed (but not calculated) on Westgard Web

- Estimates of CV_I and CV_G are compiled through a review of all relevant studies of biologic variation
- Updated every two years
- As new analytes are introduced, and new studies added, the size and specifications of the database changes
- Unlike all other EQA/PT surveys and government regulations, these are "evidence-driven" quality specifications
- Latest edition covers more than 350 analytes



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S-	Acid phosphatase	2	8.9	8.0	4.5	3.0	10.3
S-	Acid phosphatase tartrate-resistant (TR-ACP)	2	8.0	13.3	4.0	3.9	10.5

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Outline

- **Reference Change Value and Number of Tests Required**
- Current Challenges and Debate on Biologic Variation (Milan Meeting 2014)
- Tools for integrating test results into biologic variation
  - Reference Change Value (RCV)
  - Number of tests required to detect a significant change

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Callum Fraser: Reference Change Value (RCV)

Are serial test results clinically different? Or is it just noise?

$$RCV = \sqrt{2} * z * \sqrt{CV_a^2 + CV_i^2}$$

- 2 samples
- need estimates of analytical imprecision and within-subject biologic variation
- Z-value of 1.96 for P <0.05 or 95% probability (use 2.56 for P <0.01 or 99% probability)
- No bias included in the calculation

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What's the deal with the RCV?

- When changes are **bigger** than the **RCV**,
  it is a real difference
- When changes are **smaller** than the RCV,
  it may only be noise (imprecision and/or inaccuracy)
- Callum Fraser suggests the following notation on the report
  * = significant change;
  ** = highly significant change
- **RCV is NOT used to set an analytical goal, but to help interpret test results**

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Systemic Impact on Clinical Diagnosis: Callum Fraser's Number of tests/samples required

$$\#\ \text{Tests} = \left(\frac{z * \sqrt{CV_a^2 + CV_i^2}}{D} \right)^2$$

How many tests required to detect a significant change in a patient?

- D is the % deviation allowed from homeostatic set point (input the quality requirement here)
- value of <1 means only 1 test is needed to detect a significant change in patient status.

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Example Using Validation, Six Sigma and Biologic Variation calculations: Homocysteine

Performance Characteristics of Six Homocysteine Assays

Sonia L. La'ulu,[1] Mindy L. Rawlins,[1] Christine M. Pfeiffer, PhD,[2] Mindy Zhang, MD,[2] and William L. Roberts, MD, PhD[3]

Key Words: Homocysteine; Method comparison; Imprecision

DOI: 10.1309/AJCP64BJIPNPSQDJ

American Journal of Clinical Pathology 2008; 130:969-975
Comparison of Six Homocysteine methods on 5 instruments

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Homocysteine:

Determining the Size and Shape of the Target

- Sigma-metrics as an assessment tool
- Find the quality requirement:
  - Non-regulated analyte by CLIA
  - Ricos *et al* database gives 17.7%
- Pick critical level of performance: 15 umol/L

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Homocysteine:

Measuring the Method Performance (arrow)

- CV: total imprecision study performed
  - Method A at mean of 17 umol/L, **2.1% CV**

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Homocysteine:

Measuring the Method Performance (arrow)

- How to calculate Bias?
  (comparison study with HPLC reference method, Deming Regression used)
  - Use the Regression equation:

    NewMethod= (slope * OldMethod) + Y-intercept

    Bias (in units) = (NewMethod – OldMethod)

    Bias% = |Bias| / OldMethod

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Homocysteine:

Measuring the Method Performance (arrow)

- Bias: comparison study with HPLC reference method, Deming Regression used
  - Method A: **slope = 0.93, Y-Intercept = 0.64**
  - Bias = NewMethod – OldMethod
    = (((15*0.93)+0.64) – 15)
    = (13.95 + 0.64) - 15
    = 14.59 – 15
    = - 0.41
  - **Bias %** = abs(-0.41) / 15 = **2.73%**

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Homocysteine:
Measuring the Method Performance (arrow)

- **Sigma-metric: (TEa – Bias) / CV**
  - (17.7 – 2.73) / 2.1
  - 14.97 / 2.1 = 7.1
  - Method A Sigma-metric: **7.1**

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Homocysteine:
Data table

Method	Imprecision	Bias	Sigma-metric
A	2.1	2.73	7.1
B	4.3	11.3	1.5
C	3.4	4.93	3.8
D	3.4	5.33	3.6
E	2.5	11.2	2.6
F	8.3	9.1	1.0

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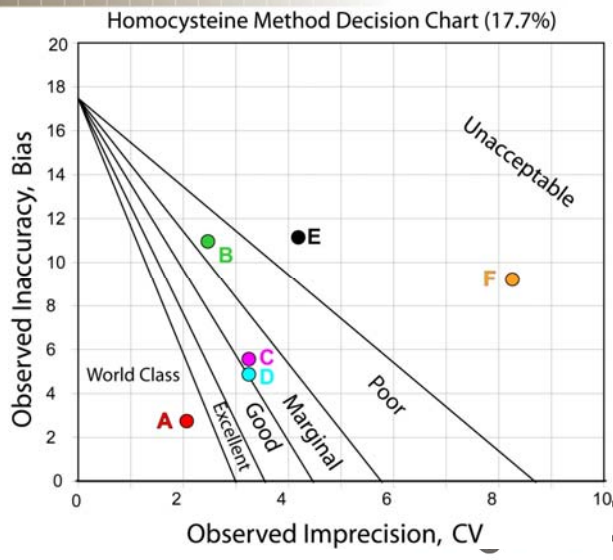
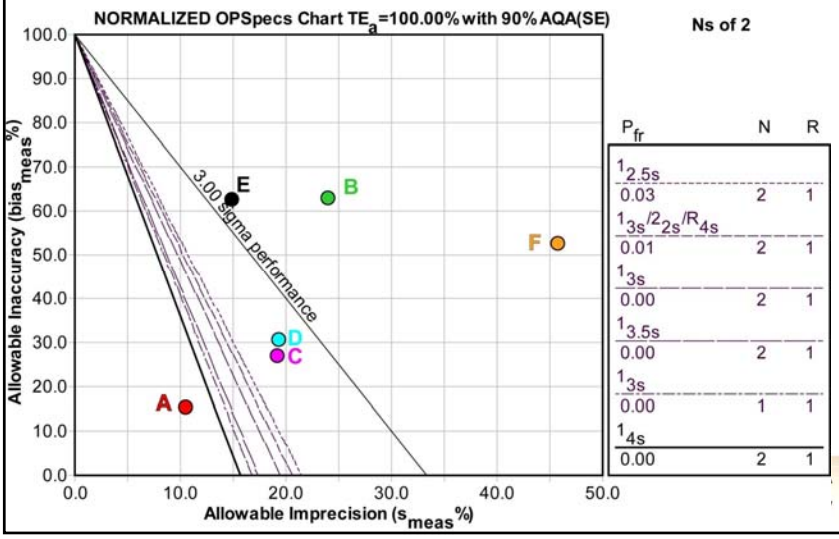
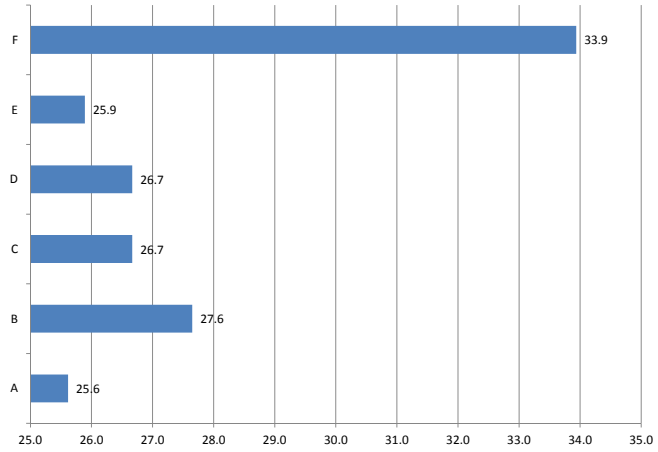
Sigma-metrics: Homocysteine



OPSpecs: Homocysteine



Homocysteine: RCV



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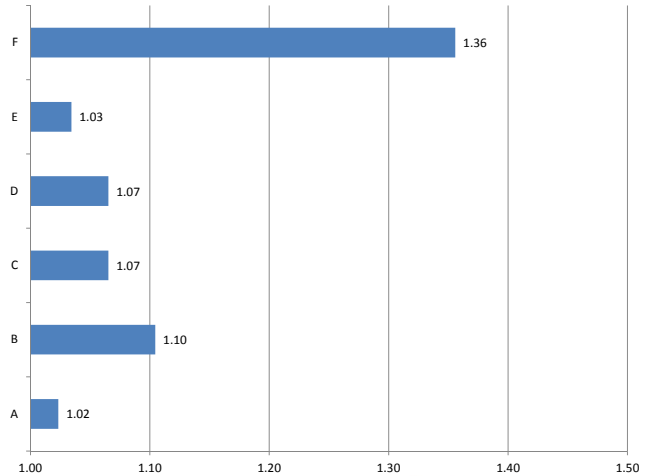
Homocysteine: # Tests Required



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Outline

- **Current Challenges and Debate on Biologic Variation (Milan Meeting 2014)**
- Tools for integrating test results into biologic variation
  - Reference Change Value (RCV)
  - Number of tests required to detect a significant change

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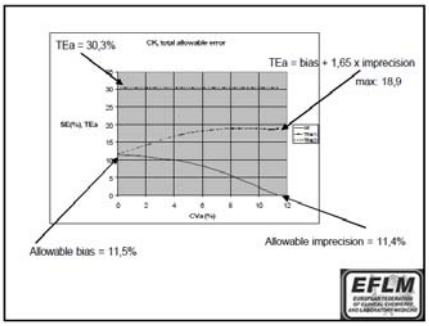
Milan 2014, Oosterhuis Outcry

Gross Overestimation of Total Allowable Error Based on Biologic Variation, Wytze P. Oosterhuis, Clin Chem 2011; 57:1334

- Biologic I and B specifications are maximums that should not be combined in traditional Tea format
- Example CK, biodatabase estimates 30.3% TEa while Oosterhuis model projects maximum of 18.9% Tea
- Essentially, Biodatabase goals are too big



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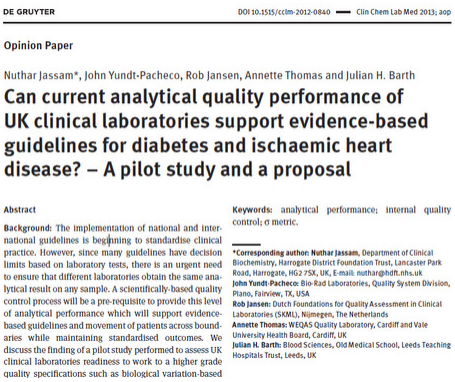
Milan 2014, Carobene Correction

- Around 40-80% of analytes have their quality requirements specified on the basis of just one paper = ***TOO FEW***
- Only 25% of the papers have been published in last 14 years (after 2000) = ***TOO OLD***
- It is unknown whether all of the papers in the database adhered to the proper study protocol = ***TOO UNRELIABLE***
- Impossible to calculate confidence intervals

Can labs hit the *current* Ricos Goals?

UK MAPS project estimates:

- < 25% labs achieve HbA1c goals (7.0%)
- < 25% labs achieve glucose goals (7.0%)
- *NO* labs achieve creatinine goals (8.2%)
- Half of labs achieve cholesterol goals (8.5%)
- Less than half of labs achieve HDL goals (11.1%)



DE GRUYTER DOI 10.1515/cclm-2012-0840 — Clin Chem Lab Med 2013; aop

Opinion Paper

Nuthar Jassam*, John Yundt-Pacheco, Rob Jansen, Annette Thomas and Julian H. Barth

Can current analytical quality performance of UK clinical laboratories support evidence-based guidelines for diabetes and ischaemic heart disease? – A pilot study and a proposal

Abstract

Background: The implementation of national and international guidelines is beginning to standardise clinical practice. However, since many guidelines have decision limits based on laboratory tests, there is an urgent need to ensure that different laboratories obtain the same analytical result on any sample. A scientifically-based quality control process will be a pre-requisite to provide this level of analytical performance which will support evidence-based guidelines and movement of patients across boundaries while maintaining standardised outcomes. We discuss the finding of a pilot study performed to assess UK clinical laboratories readiness to work to a higher grade quality specifications such as biological variation-based

Keywords: analytical performance; internal quality control; σ metric.

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John Yundt-Pacheco: Bio-Rad Laboratories, Quality System Division, Plano, Fairview, TX, USA
Rob Jansen: Dutch Foundations for Quality Assessment in Clinical Laboratories (SKML), Nijmegen, The Netherlands
Annette Thomas: WEQAS Quality Laboratory, Cardiff and Vale University Health Board, Cardiff, UK
Julian H. Barth: Blood Sciences, Old Medical School, Leeds Teaching Hospitals Trust, Leeds, UK

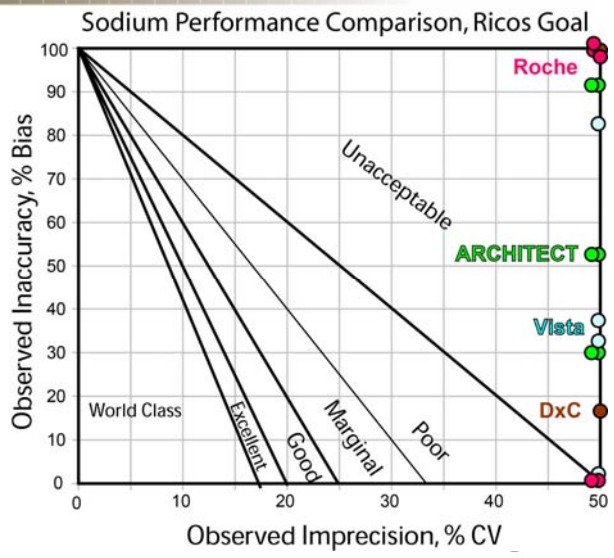
Sodium goals

Analyte	Quality Goal				
	CLIA	Desirable Biologic Goal	RCPA	Rilibak	Spanish Minimum Consensus
Sodium	± 4 mmol/L	± 0.9%	± 3 mmol/L ≤ 150 mmol/L; ± 2% > 150 mmol/L	± 5.0%	± 5.0%

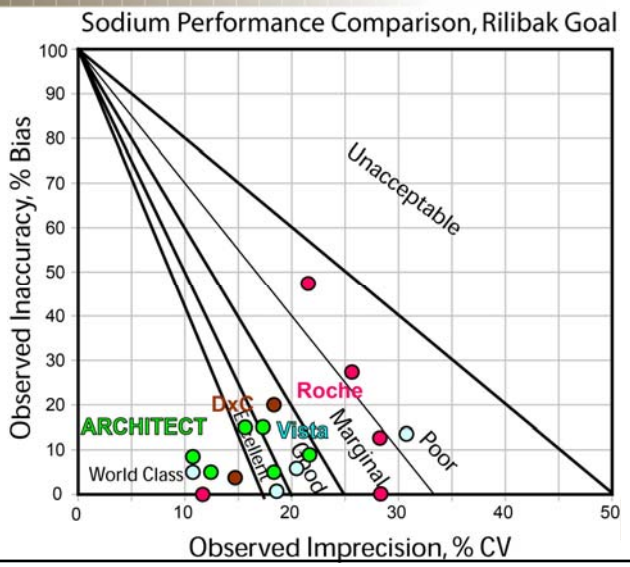
Data Sources

- Evaluation des performances analytiques du systeme Unicel DXC 600 (Beckman Coulter) et etude de la transferabilite des resultats avec l'Integra 800 (Roche diagnostics), A. Servonnet, H. Thefenne, A. Boukhira, P. Vest, C. Renard. Ann Biol Clin 2007: 65(5): 555-62
- Validation of methods performance for routine biochemistry analytes at Cobas 6000 series module c501, Vesna Supak Smolcic, Lidija Bilic-Zulle, elizabeta Fisic, Biochemia Medica 2011;21(2):182-190
- Analytical performance evaluation of the Cobas 6000 analyzer – special emphasis on trueness verification. Adriaan J. van Gammeren, Nelley van Gool, Monique JM de Groot, Christa M Cobbeart. Clin Chem Lab Med 2008;46(6):863-871.
- Analytical Performance Specifications: Relating Laboratory Performance to Quality Required for Intended Clinical Use. [cobas 8000 example evaluated] Daniel A. Dalenberg, Patricia G. Schryver, George G Klee. Clin Lab Med 33 (2013) 55-73.
- The importance of having a flexible scope ISO 15189 accreditation and quality specifications based on biological variation – the case of validation of the biochemistry analyzer Dimension Vista, Pilar Fernandez-Calle, Sandra Pelaz, Paloma Oliver, Maria Josa Alcaide, Ruben Gomez-Rioja, Antonion Buno, Jose Manuel Iturzaeta, Biochemia Medica 2013;23(1):83-9.
- External Evaluation of the Dimension Vista 1500 Intelligent Lab System, Arnaud Bruneel, Monique Dehoux, Anne Barnier, Anne Bouten, Journal of Clinical Laboratory Analysis 2012;23:384-397.
- Evaluation of the Vitros 5600 Integrated System in a Medical Laboratory, Baum H, Bauer I, Hartmann C et al, poster PDF provided at Ortho-Clinical Diagnostics website. Accessed December 10th, 2013.
- Evaluation of the VITROS 5600 Integrated System - Validation and Comparison Studies. Chen LS, Sakpal M, Kwong T. poster PDF provided at Ortho-Clinical Diagnostics website. Accessed March 23, 2014.
- Sigma metrics used to access analytical quality of clinical chemistry assays: importance of the allowable total error (TEa) target. Hens K, Berth M, Armbruster D, Westgard S. Clin Chem Lab Med 2014 (July issue)

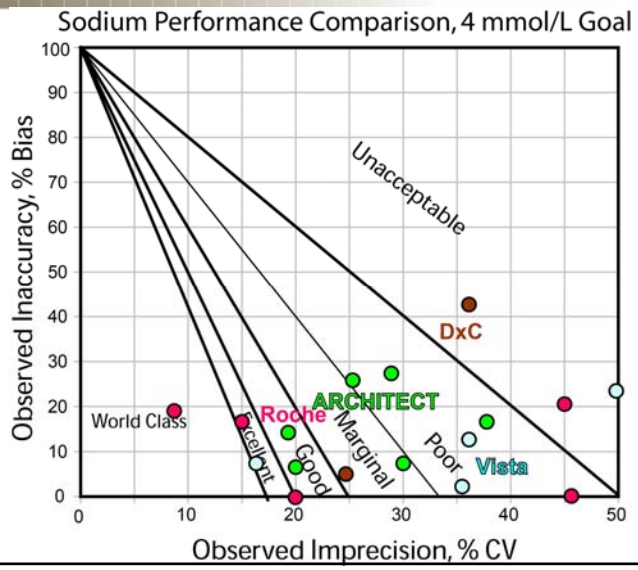
Sodium: Ricos Goal



Sodium: Rilibak Goal



Sodium: CLIA Goal



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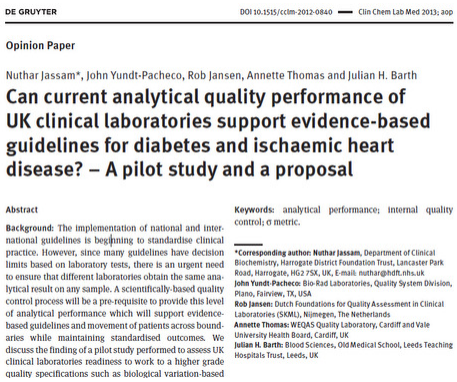
What about glucose?

UK MAPS project estimates:

- < 25% labs achieve HbA1c goals (7.0%)
- < 25% labs achieve glucose goals (7.0%)
- *NO* labs achieve creatinine goals (8.2%)
- Half of labs achieve cholesterol goals (8.5%)
- Less than half of labs achieve HDL goals (11.1%)



DE GRUYTER DOI 10.1515/cclm-2012-0840 — Clin Chem Lab Med 2013; aop

Opinion Paper

Nuthar Jassam*, John Yundt-Pacheco, Rob Jansen, Annette Thomas and Julian H. Barth

Can current analytical quality performance of UK clinical laboratories support evidence-based guidelines for diabetes and ischaemic heart disease? – A pilot study and a proposal

Abstract

Background: The implementation of national and international guidelines is beginning to standardise clinical practice. However, since many guidelines have decision limits based on laboratory tests, there is an urgent need to ensure that different laboratories obtain the same analytical result on any sample. A scientifically-based quality control process will be a pre-requisite to provide this level of analytical performance which will support evidence-based guidelines and movement of patients across boundaries while maintaining standardised outcomes. We discuss the finding of a pilot study performed to assess UK clinical laboratories readiness to work to a higher grade quality specifications such as biological variation-based

Keywords: analytical performance; internal quality control; σ metric.

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Annette Thomas: WEQAS Quality Laboratory, Cardiff and Vale University Health Board, Cardiff, UK
Julian H. Barth: Blood Sciences, Old Medical School, Leeds Teaching Hospitals Trust, Leeds, UK

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Glucose goals

Analyte	Quality Goal				
	CLIA	Desirable Biologic Goal	RCPA	Rilibak	Spanish Minimum Consensus
Glucose	± 10%	± 6.9%	± 0.4 mmol/L ≤ 5.0 mmol/L; ± 8% > 5.0 mmol/L	± 15.0%	± 11%

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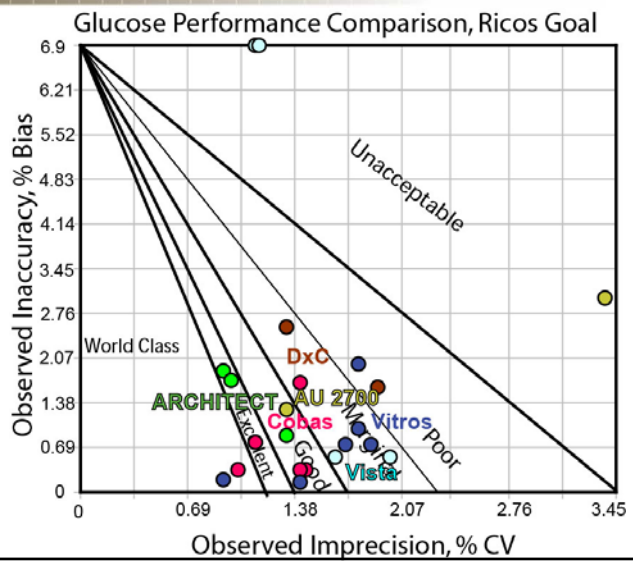
Glucose: Ricos Goals



QC

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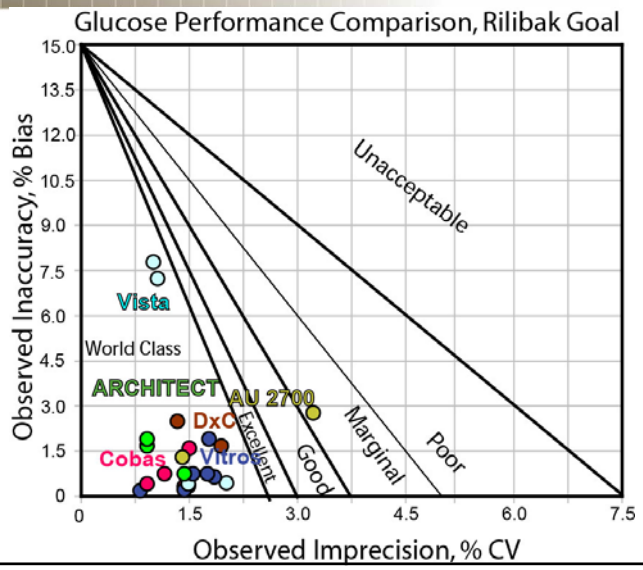
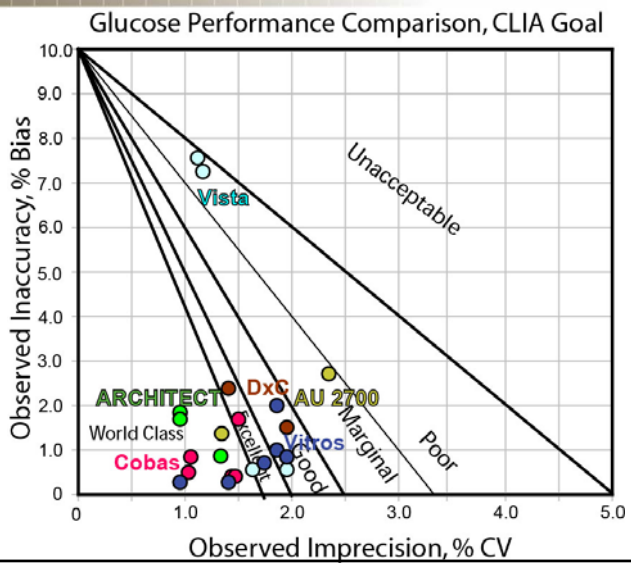
Glucose: Rilibak Goal



Glucose: CLIA Goals



Potassium Goals

Analyte	Quality Goal				
	CLIA	Desirable Biologic Goal	RCPA	Rilibak	Spanish Minimum Consensus
Potassium	± 0.5 mmol/L	± 5.8%	± 0.2 mmol/L ≤ 4.0 mmol/L; ± 5% > 4.0 mmol/L	± 8.0%	± 8.0%

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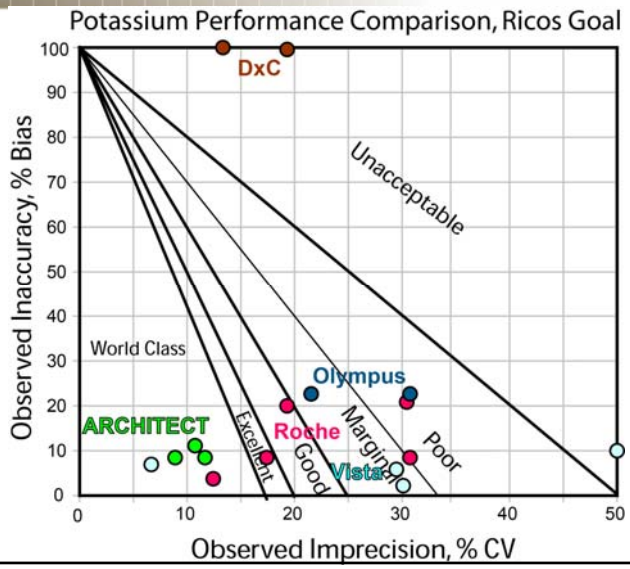
Potassium Goals: Ricos



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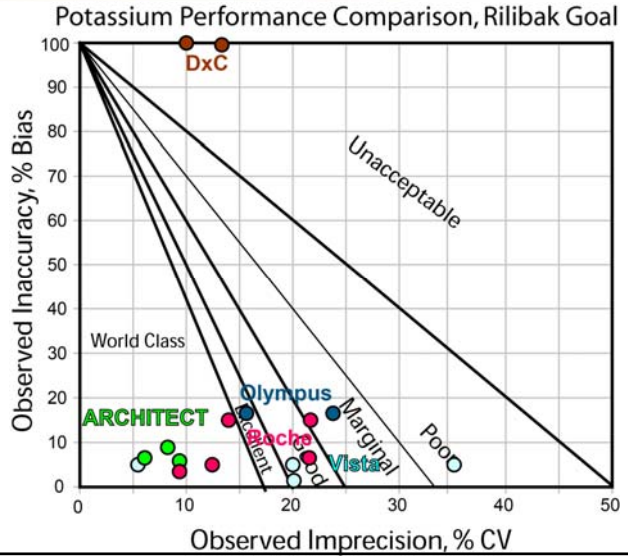
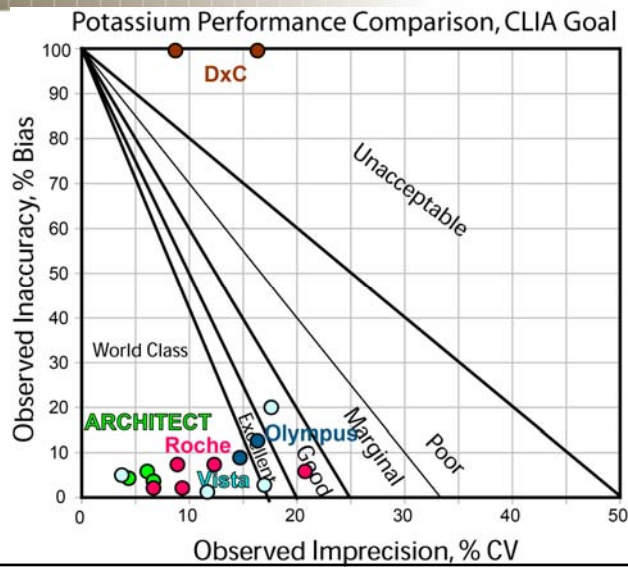
Potassium Goals: Rilibak



Potassium Goals: CLIA



Chloride Goals

Analyte	Quality Goal				
	CLIA	Desirable Biologic Goal	RCPA	Rilibak	Spanish Minimum Consensus
Chloride	± 5.0%	± 1.5%	± 3.0 mmol/L	± 8.0%	± 9.0%

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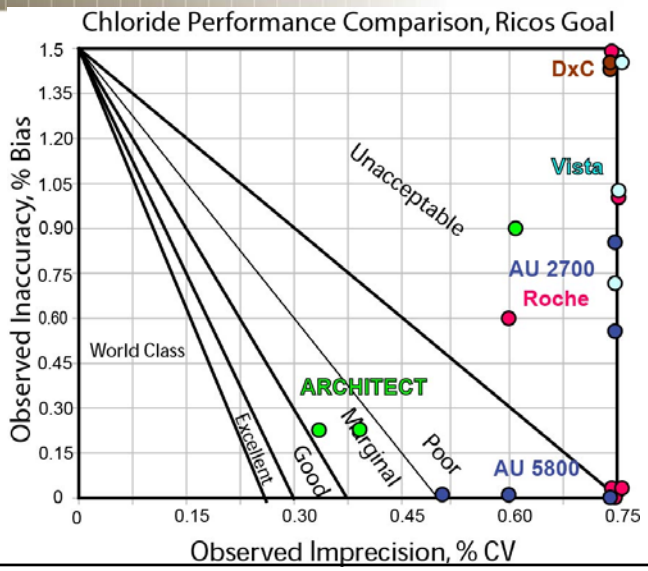
Chloride: Ricos Goal



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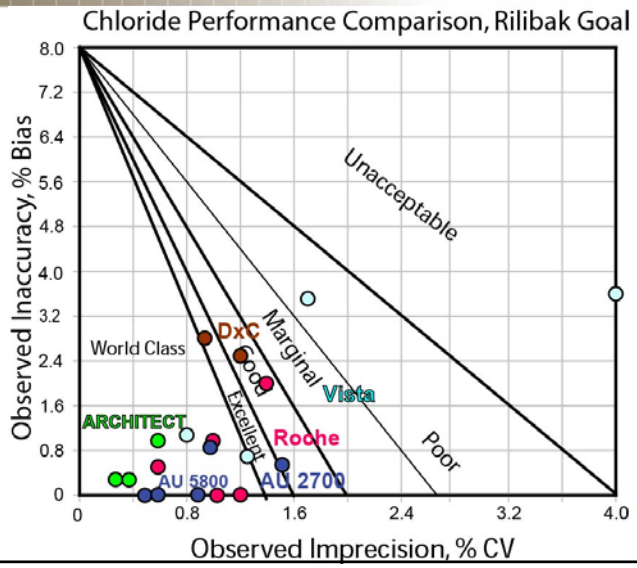
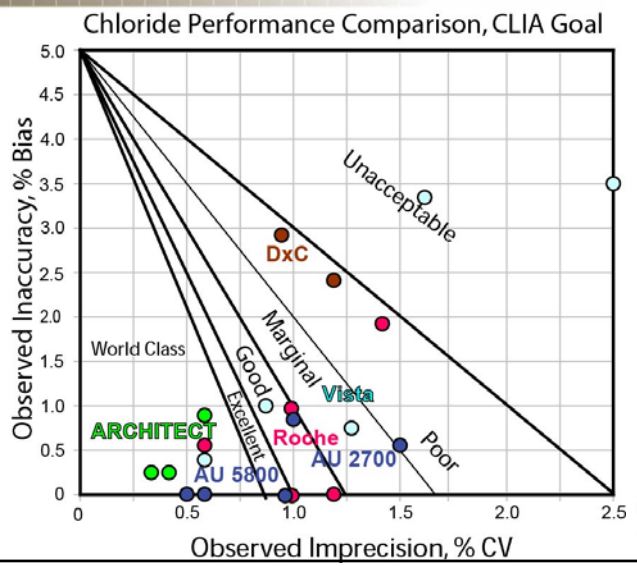
Chloride: Rilibak Goal

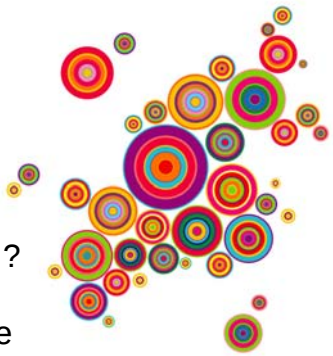


Chloride: CLIA Goal



So, What to do?

- Abandon them?
- Ignore them?
- Improve them?
- *Selectively* use them?



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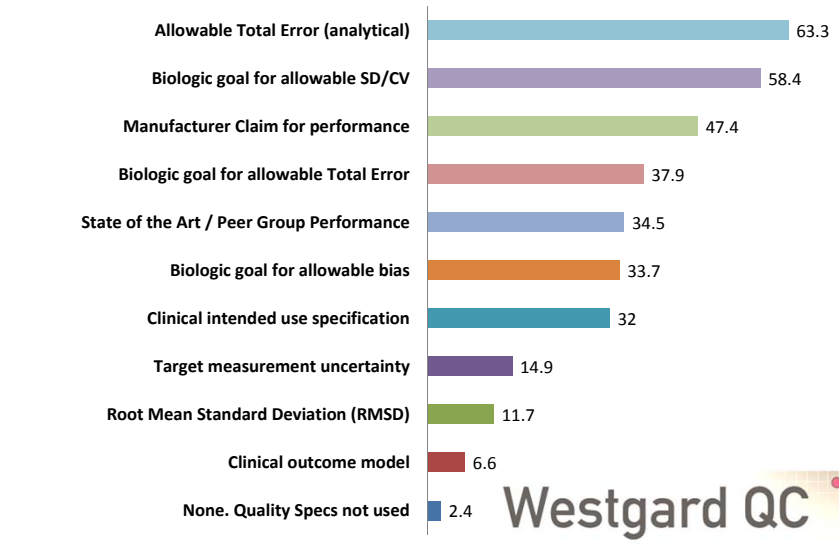
Westgard Global Goal Survey 2014-2015 (80 countries, >400 responses)

Andorra	Ecuador	Lebanon	Serbia
Armenia	Estonia	Lithuania	Singapore
Argentina	Egypt	Macedonia	Slovenia
Austria	Ethiopia	Malaysia	South Africa
Australia	Federated States of Micronesia	Mauritius	Spain
Belgium	Finland	Mongolia	Sudan
Bulgaria	France	Mozambique	Sweden
Bahrain	Greece	Mexico	Switzerland
Brazil	Hong Kong	Nepal	Thailand
Botswana	Indonesia	Netherlands	Turkey
Belarus	Ireland	Nigeria	Uganda
Cambodia	India	Norway	Ukraine
Canada	Iran	Oman	United Kingdom
Cote d'Ivoire	Italy	Philippines	United States
Chile	Jordan	Poland	Uzbekistan
Cameroon	Japan	Portugal	Vietnam
China	Kazakhstan	Qatar	Zambia
Costa Rica	Kenya	Romania	
Croatia	Kuwait	Russia	
Denmark		Saudi Arabia	

Types of Goals used in the Lab (N=409)



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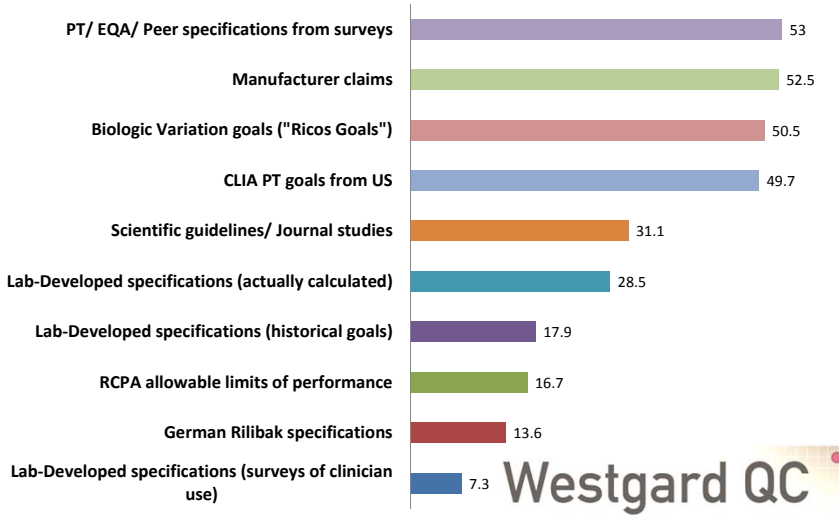
Where do Labs find their Goals? (N=400)



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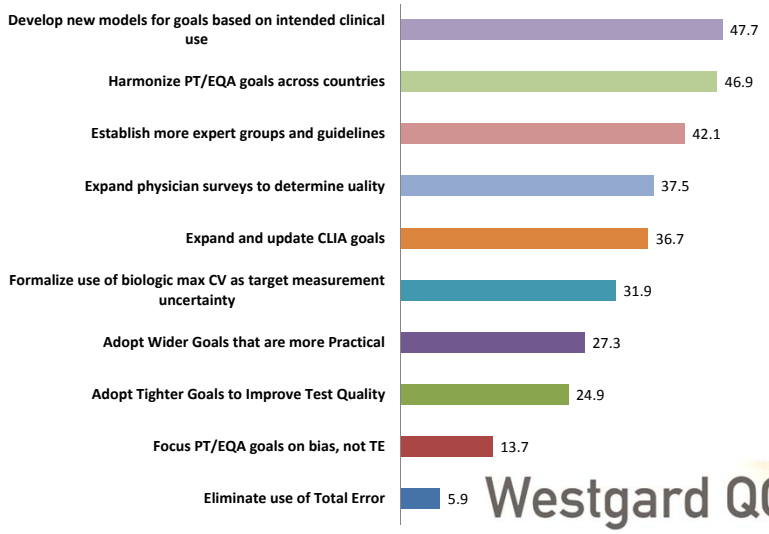
What changes would Labs like to see in analytical goals? (n=377)



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What happens next will depend on *you*

What's the variation in your use of biologic variation?

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