CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

site: http://users.unimi.it/cirme

CIRME CELEBRATING 10 Years

Analytical performance specifications two years after Milan conference

Prof Mauro Panteghini

CIRME Scientific Coordinator

10th International Scientific Meeting. November 17-18, 2016

Definition

- Analytical performance specifications: Criteria that specify (in numerical terms) the quality required for analytical performance in order to deliver laboratory test information that would satisfy *clinical needs* for improving *health outcomes*.

Steps of the process and different responsibilities in implementing traceability of patient results and defining their uncertainty

Profession (e.g., JCTLM, IFCC, EFLM):

Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)

↓

Diagnostic manufacturers:

Implement suitable analytical systems (platform, reagents, calibrators, controls) fulfilling the above established goals

↓

End users (clinical laboratories):

Survey assay and laboratory performance through IQC and EQA redesigned to meet metrological criteria

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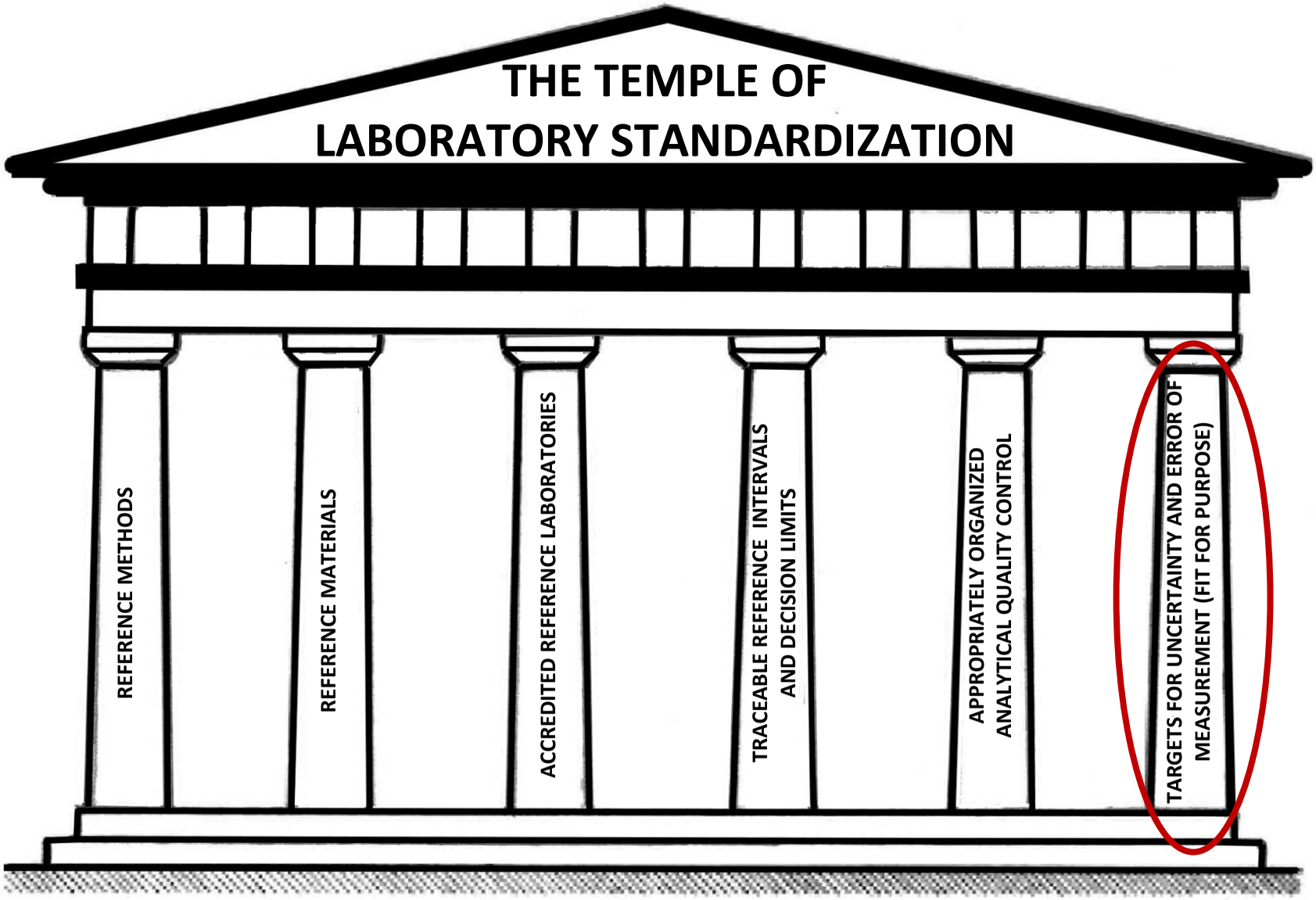
Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

THE TEMPLE OF LABORATORY STANDARDIZATION



Braga F & Panteghini M, Clin Chim Acta 2014;432:55

MANIFESTO
MANIFESTO
MANIFESTO
MANIFESTO

"THE TRACEABILITY REVOLUTION MANIFESTO"

Braga F & Panteghini M, Clin Chim Acta 2014;432:55

- **Definition and approval of reference measurement systems, possibly in their entirety;**
- **Implementation by IVD industry of traceability to such reference systems in a scientifically sound and transparent way;**
- **Definition by the profession of the clinically acceptable measurement uncertainty for each of the analytes used in the clinical field;**
- **Adoption by EQAS providers of commutable materials and use of an evaluation approach exclusively based on trueness;**
- **Monitoring of the analytical performance of individual laboratories by the participation in EQAS that meet metrological criteria and application of clinically acceptable limits;**
- **Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality.**

CI
CE

The definition and use of the reference system concept for standardization of measurements must be closely associated with the setting of targets for uncertainty and error of measurement in order to make it clinically acceptable.

Braga F & Panteghini M, Clin Chim Acta 2014;432:55

If these goals are not objectively defined and fulfilled, there is a risk of letting error gain the upper hand, thus obscuring the clinical information supplied by the result and possibly nullifying the theoretical advantages of metrological traceability and even causing negative effects on patients' outcome.

L Thienpont et al., Clin Chem Lab Med 2004;42:842

Barriers to practical achievement of traceability scope

- Lack of definition of the clinically allowable uncertainty for validation of the metrological traceability chain of each measurand

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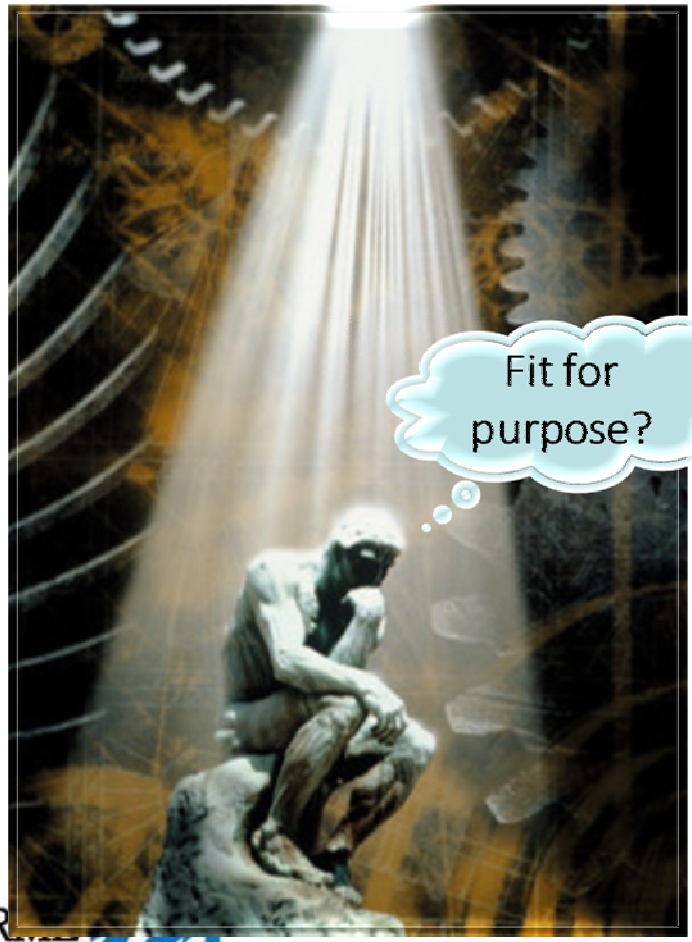
The Essential Question…



"What amount of medical harm due to analytical error is it OK to let go undetected?"

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Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

Model 1: Based on the effect of analytical performance on clinical outcomes

a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes;

b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g., by simulation or decision analysis.

Model 2: Based on components of biological variation of the measurand.

Model 3: Based on state of the art of the measurement (i.e., the highest level of analytical performance technically achievable).

DE GRUYTER Clin Chem Lab Med 2015; 53(6): 829–832

Editorial

Mauro Panteghini and Sverre Sandberg

Defining analytical performance specifications 15 years after the Stockholm conference

The most innovative aspect of the new consensus is that it is recognized that some models are better suited for certain measurands than for others; the attention is therefore primarily directed towards the measurand and its biological and clinical characteristics.

Conference conclusions

Defining Analytical Performance Specifications

- Three models: outcome, biology, state of the art
- Important: w. high quality studies and updated data
- Measurands can have different performance specifications depening on its use

- More work to be done to produce high quality data that can be used for performance specifications
- More work to be done to judge how to apply the performance specifications

An **EFLM Task Force on Performance Specifications in Laboratory Medicine (TF-PS)** has been created to coordinate the activities of the Task & Finish Group (TFG) established as outcome of the 1st Strategic Conference

DE GRUYTER Clin Chem Lab Med 2016; aop

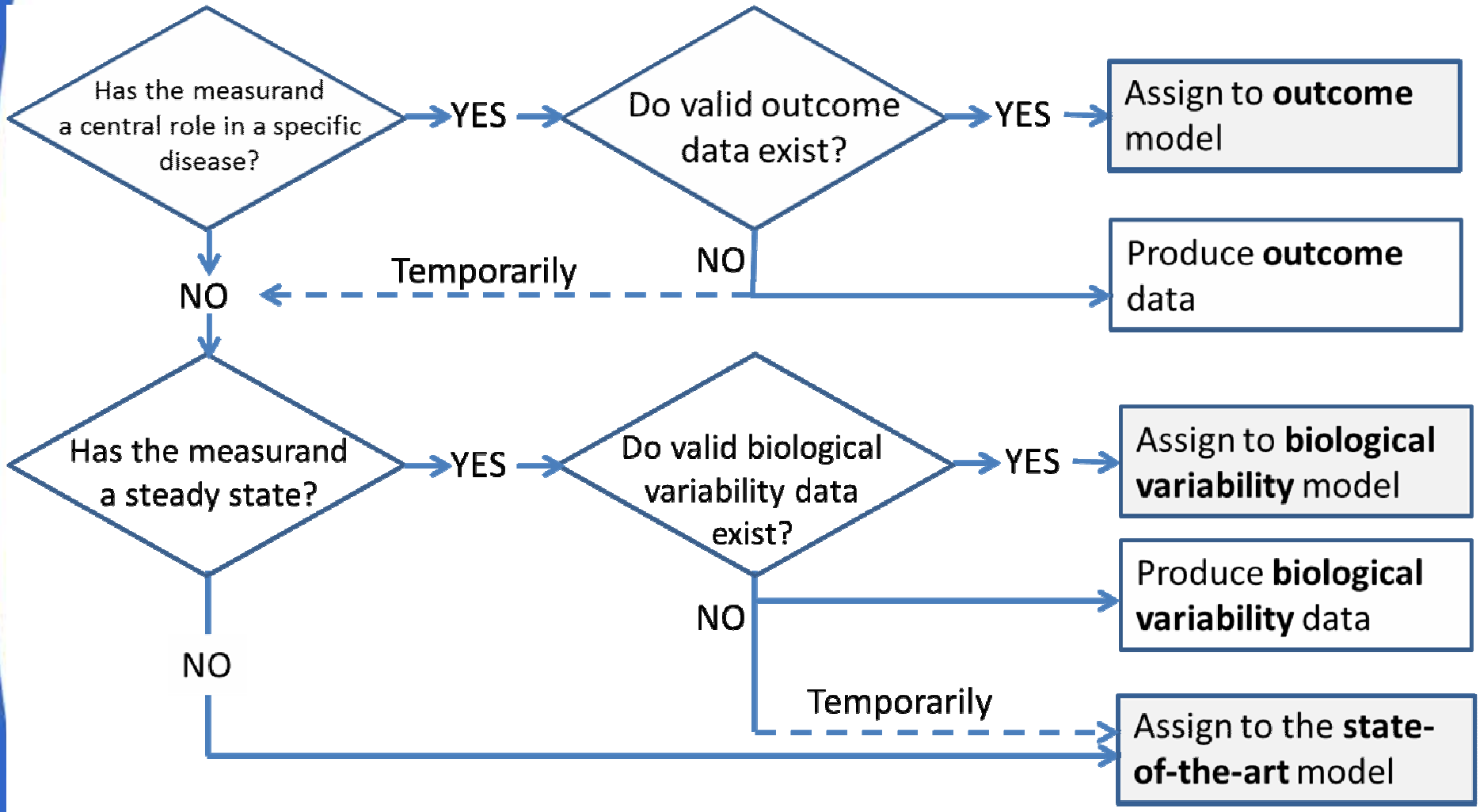
Opinion Paper

Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

Criteria for assigning laboratory measurands to models for analytical performance specifications defined in the 1st EFLM Strategic Conference

1. The measurand has a central role in diagnosis and monitoring of a specific disease ⇒ outcome model
2. The measurand has a high homeostatic control ⇒ biological variability model
3. Neither central diagnostic role nor sufficient homeostatic control ⇒ state-of-the-art model

Workflow for allocation of laboratory measurands to different models for performance specifications



Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

The application of the analytical performance specifications can be modulated depending on its use. For example:

- Reference material providers
- Manufacturers producing calibrators
- Individual laboratories who provide patient results
- EQAS organizations

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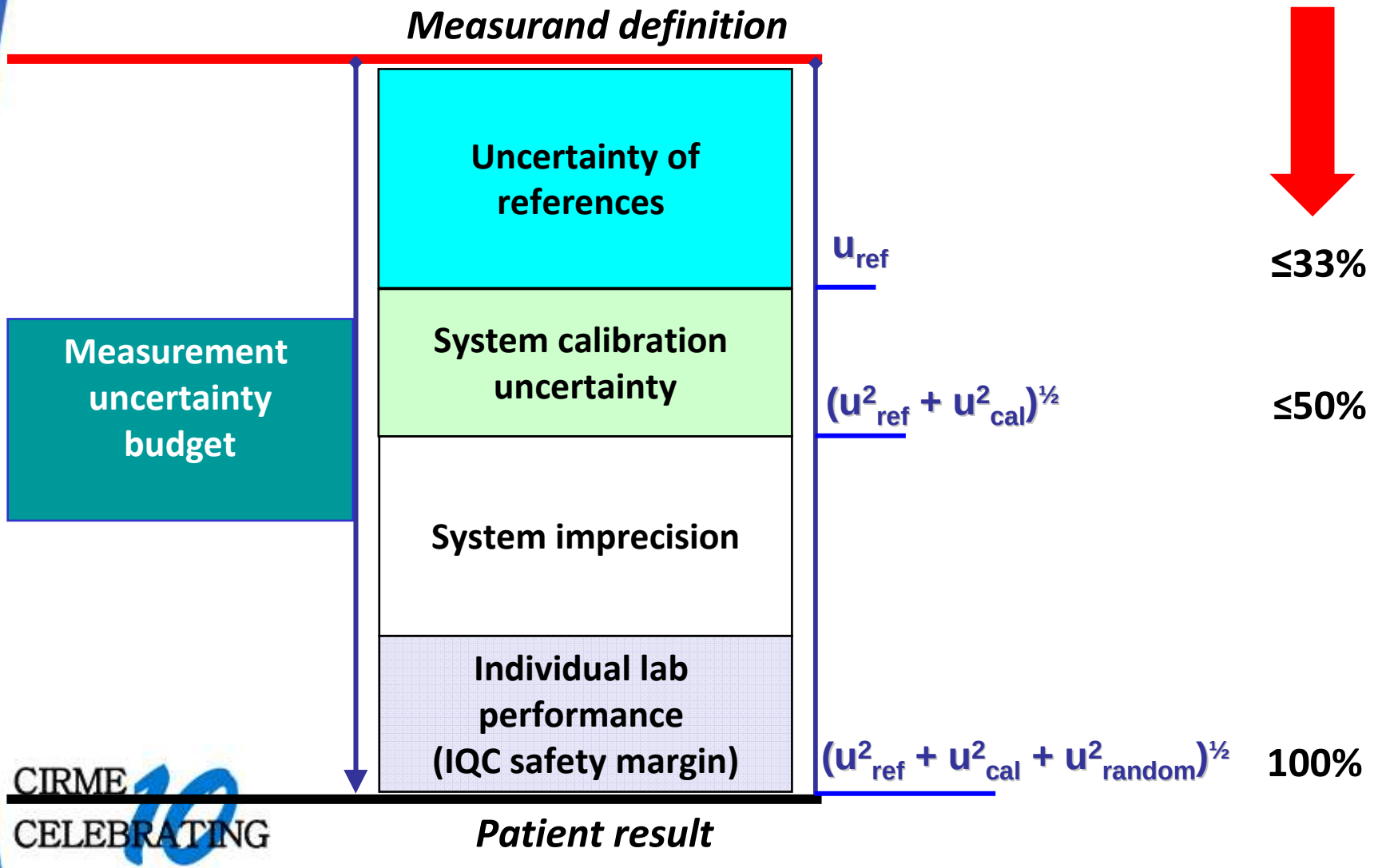
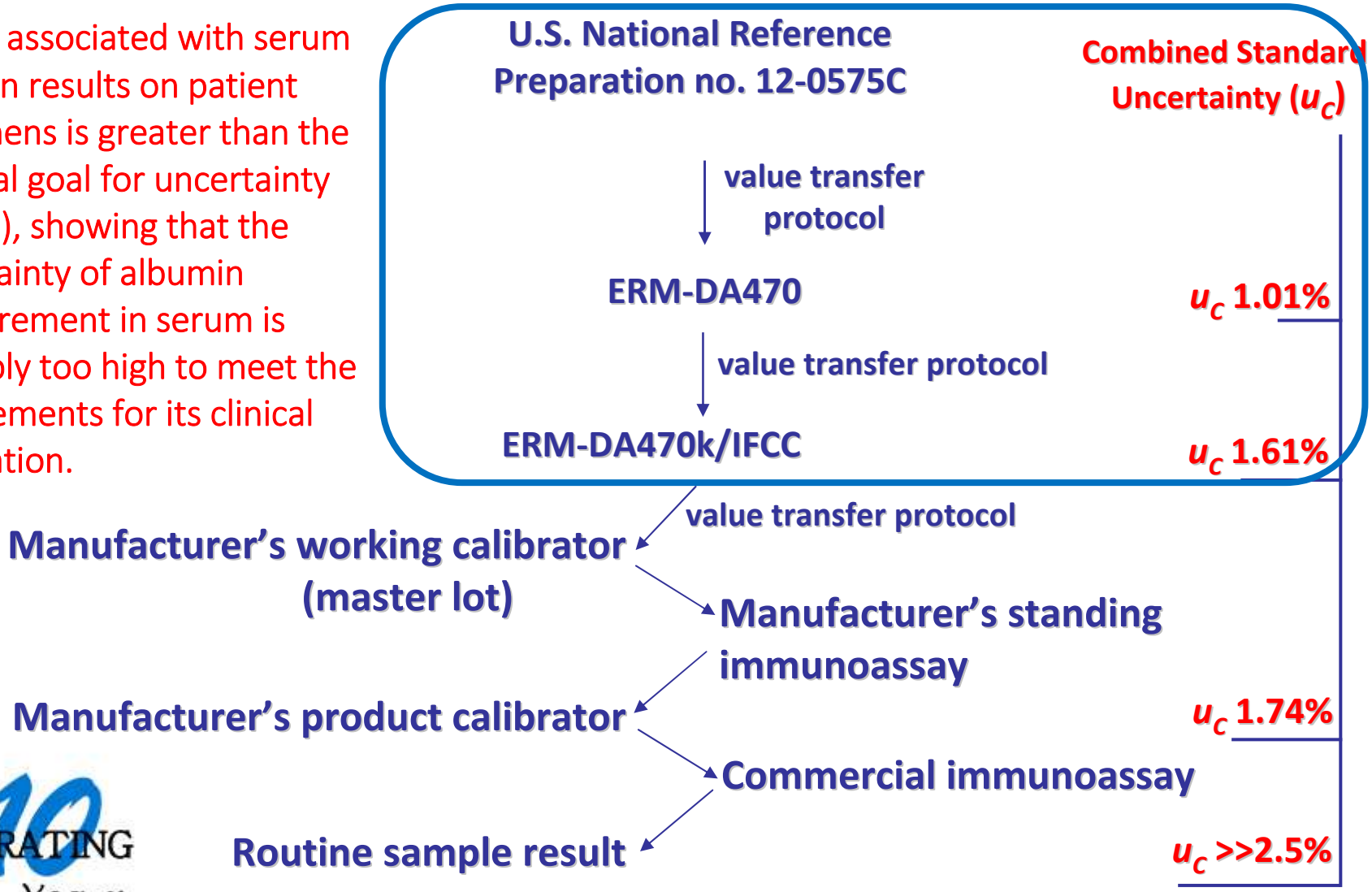
Recommended limits for combined uncertainty budget (expressed as percentage of total budget goal) in traceability implementation



[Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905]

Serum albumin: An example

The u_C associated with serum albumin results on patient specimens is greater than the minimal goal for uncertainty (≤2.4%), showing that the uncertainty of albumin measurement in serum is probably too high to meet the requirements for its clinical application.



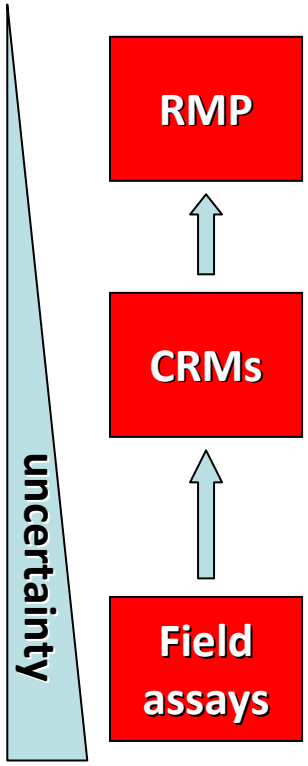
Panteghini M, Clin Chem Lab Med 2012;50:1237
Infusino I & Panteghini M, Chim Clin Acta 2013;419:15
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Turning the problem upside down
Focus first on the field assays

Specifications of reference measurement procedure defined by intended use…

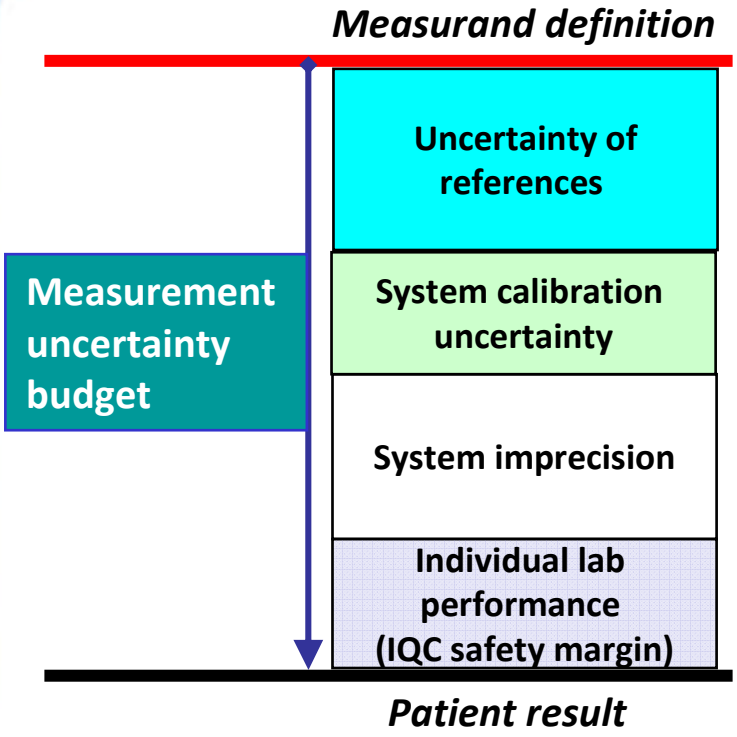
…intended use is the certification of reference materials…

…the specifications of certified reference materials are defined by the performance needs of the clinical assays.



To assure that the expanded combined uncertainty associated with patient results fulfill the total budget goal, the higher order references should display uncertainty at most equal to 1/3 of the total budget goal.

IFCC WG-TNI Technical Discussion
Value assignment of NIST SRM 2922 and measurement uncertainty



≤33% of uncertainty budget due to SRM uncertainty (~4.5%).

Anticipate 50% of uncertainty budget (6.5%) at manufacturer's calibration and value transfer level.

According to the outcome-based study of misclassification rates, the maximum allowable goal for 100% total uncertainty budget of cTnI assays is 13% (minimum quality goal) for the clinical result and which allows for <2% result misclassification.

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The application of the analytical performance specifications can be modulated depending on its use. For example:

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- Manufacturers producing calibrators
- Individual laboratories who provide patient results
- EQAS organizations

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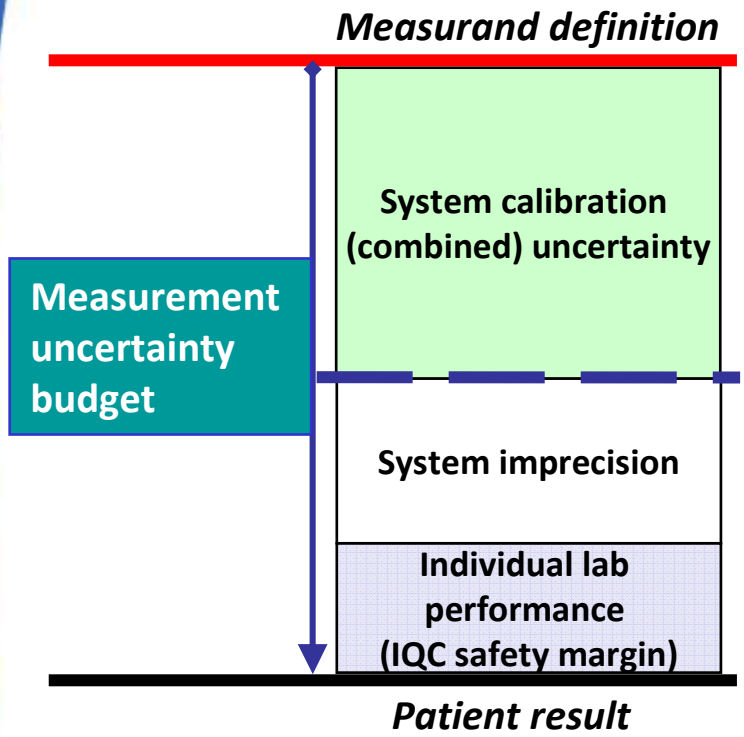
Need to define criteria for manufacturers that can be achieved for their calibrators leaving enough uncertainty budget for the laboratories to produce clinically acceptable results.



→ **Allowable limit for the expanded (combined) uncertainty of manufacturer's commercial calibrators @ 50% of the goals**

[note that these are goals for random variability, as at the calibrator level the systematic error (bias), in agreement with the metrological traceability theory, must be corrected if present in a non negligible amount]

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10th International Scient

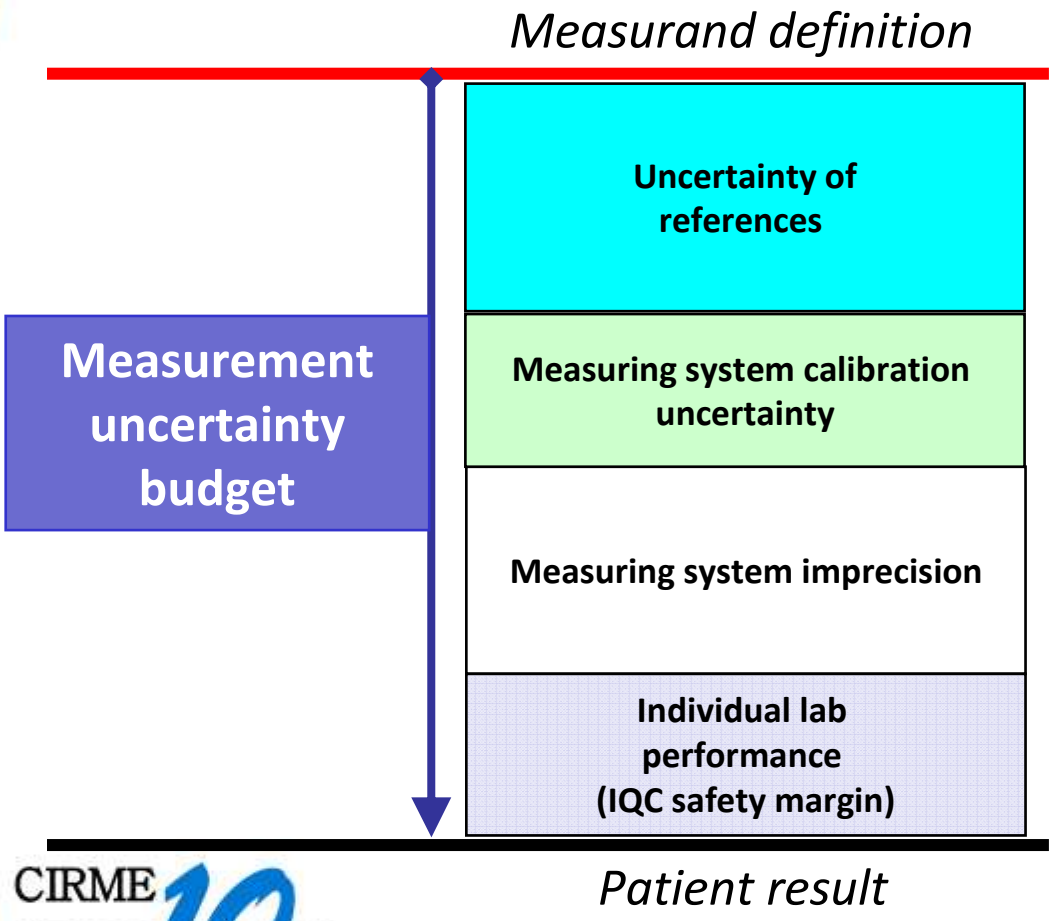
Opinion Paper

Clin Chem Lab Med 2013; 51:973

Renze Bais*, Dave Armbruster, Rob T. P. Jansen, George Klee, Mauro Panteghini, Joseph Passarelli and Ken A. Sikaris on behalf of the IFCC Working Group on Allowable Error for Traceable Results (WG-AETR)

Defining acceptable limits for the metrological traceability of specific measurands

IVD MANUFACTURER contribution to the measurement uncertainty budget



IVD Manufacturer

The manufacturer must indicate the combined uncertainty associated with calibrators when used in conjunction with other components of the analytical system (platform and reagents).
Such uncertainty estimates provided by the manufacturer must include the uncertainty associated with higher levels of the metrological traceability chain.

INVITED CRITICAL REVIEW

Table 1

Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring blood glucose marketed by four IVD companies.

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty[a]	Higher-order reference employed		Type of traceability chain used[b]	Combined standard uncertainty associated with the used chain[c]
					Method	Material		
Abbott	Architect	ND	Multiconstituent calibrator	2.70%	IDMS	NIST SRM 965	A	1.22-1.45%[d]
Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22-1.45%[d]
	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60-3.00%[e]
Roche	Cobas c	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
	Integra	Hexokinase	C.f.a.s.	0.62%	IDMS	ND	B	1.70%
	Modular	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
		GOD		0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]
		GOD		0.80%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]

Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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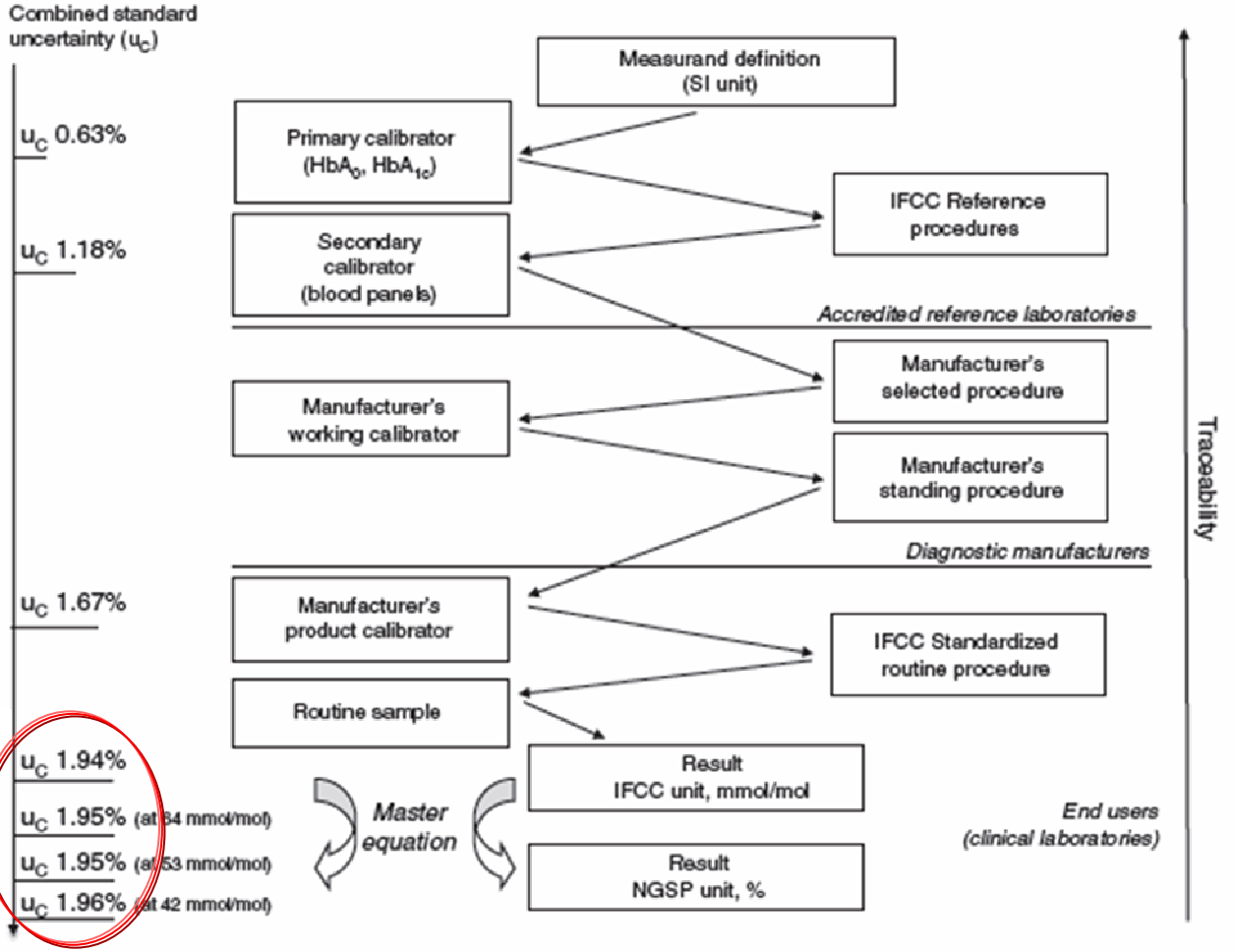
HbA1c reference system and associated combined standard uncertainty



Analytical goals for HbA_{1c} measurement

Quality level	U_C
Optimal	≤0.6
Desirable	≤1.3
Minimal	≤1.9

[Braga F & Panteghini M, Clin Chem Lab Med 2013;51:1719]

Federica Braga* and Mauro Panteghini

Standardization and analytical goals for glycated hemoglobin measurement

Clin Chem Lab Med 2013;51:1719–26

Further advances are needed to:

1. reduce uncertainty associated with higher-order metrological references (reference materials and procedures)
2. increase the precision of commercial HbA1c assays

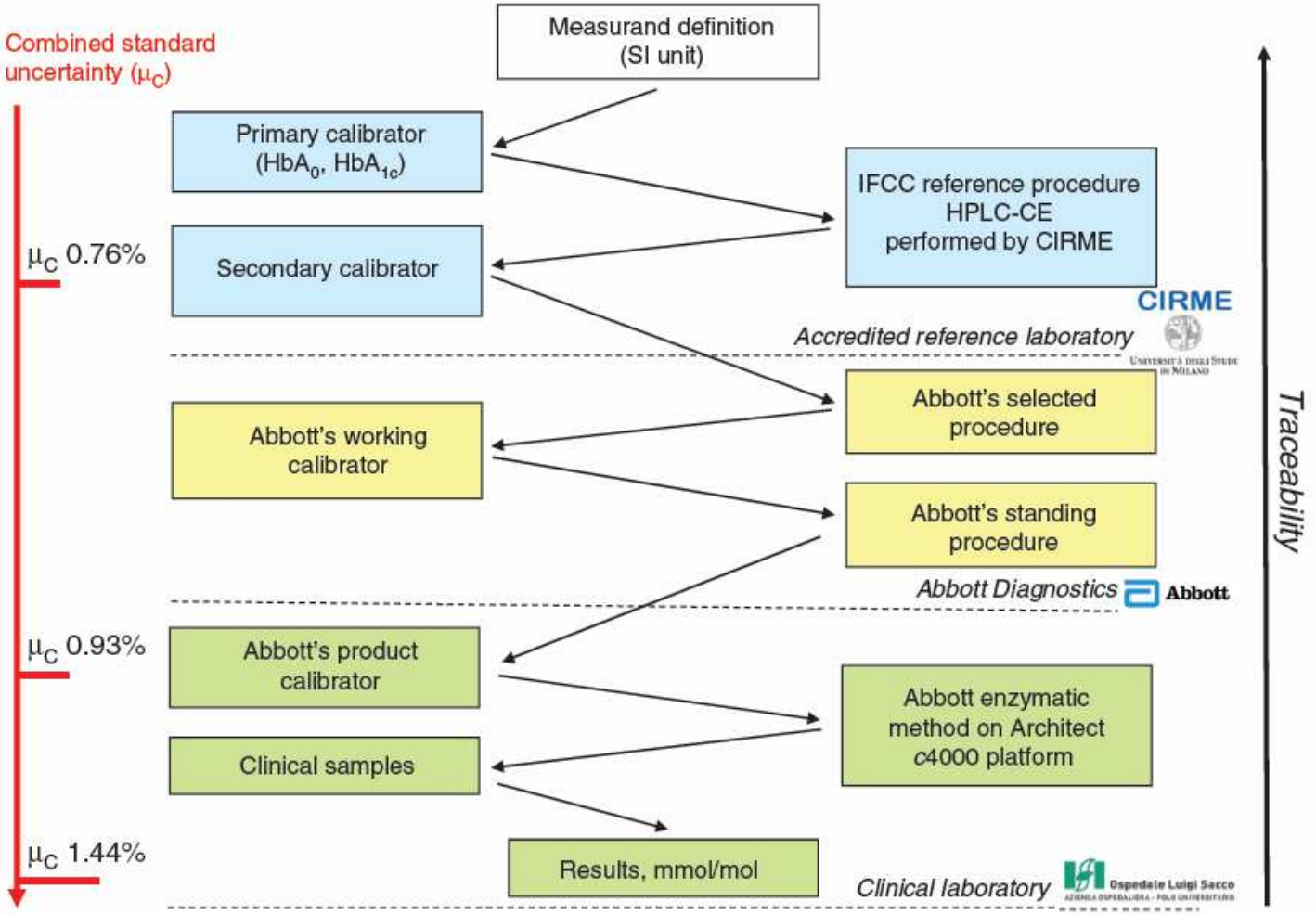
DE GRUYTER

Clin Chem Lab Med 2016; 54(3): e71–e73

Letter to the Editor

Dominika Szőke*, Assunta Carnevale, Sara Pasqualetti, Federica Braga, Renata Paleari and Mauro Panteghini

More on the accuracy of the Architect enzymatic assay for hemoglobin A_{1c} and its traceability to the IFCC reference system



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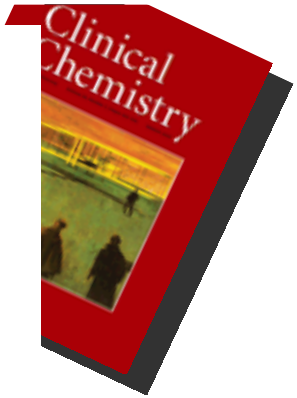
Clinical Chemistry 62:9
1255–1263 (2016)

Evidence-Based Medicine and Test Utilization



Analytical Bias Exceeding Desirable Quality Goal in 4 out of 5 Common Immunoassays: Results of a Native Single Serum Sample External Quality Assessment Program for Cobalamin, Folate, Ferritin, Thyroid-Stimulating Hormone, and Free T_4 Analyses

Gunn B.B. Kristensen,[1*] Pål Rustad,[1] Jens P. Berg,[2] and Kristin M. Aakre[3]

Table 1. Bias from the target value (Mt or the concentrations measured by the reference method[a]) for the concentrations of serum X.

	Serum X	Quality goal[b]	Abbott Architect	Beckman Coulter Unicel	Roche Cobas	Roche Modular	Siemens ADVIA Centaur
Cobalamin, pmol/L	329	±58	6	**−108**	15	15	−21
Folate, nmol/L	14.0	±2.7	−1.4	−1.5	2.1	0.6	0.1
Ferritin, μg/L	62.4	±3.2	−1.5	**−13.8**	**9.4**	**11.1**	**−8.7**
TSH, mU/L	1.69	±0.13	−0.15	0.01	**0.16**	**0.20**	−0.03
Free T_4, pmol/L	14.3	±0.5	**−1.2**	**−3.1**	**0.8**	**0.7**	0.4
Free T_4, pmol/L[a]	19.7	±0.7	**−6.5**	**−8.4**	**−4.5**	**−4.6**	**−4.9**

[a] Reference method values (IFCC *(6)*).
[b] The quality goal (±absolute values) for desirable bias is based on biological variation data: cobalamin 17.7%, folate 19.2%, ferritin 5.2%, free T_4 3.3%, and TSH 7.8% *(11)*. Biases exceeding the quality goal are shown in bold.

DE GRUYTER Clin Chem Lab Med 2016; aop

Cas Weykamp*, Sandra Secchiero, Mario Plebani, Marc Thelen, Christa Cobbaert, Annette Thomas, Nuthar Jassam, Julian H. Barth, Carmen Perich, Carmen Ricós and Ana Paula Faria

Analytical performance of 17 general chemistry analytes across countries and across manufacturers in the INPUtS project of EQA organizers in Italy, the Netherlands, Portugal, United Kingdom and Spain

Conclusions: The overall performance of the measurement of 17 general chemistry analytes in European medical laboratories met the minimum performance specifications. In this general picture, there were no significant differences per country and no significant differences per manufacturer. There were major differences between the analytes. There were six analytes for which the minimum quality specifications were not met and manufacturers should improve their performance for these analytes. Standardization of results of enzymes requires ongoing efforts.

The application of the analytical performance specifications can be modulated depending on its use. For example:

- Reference material providers
- Manufacturers producing calibrators
- Individual laboratories who provide patient results
- EQAS organizations

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Analytical performance specification (APS) derivation should be added to the Miller's EQAS categorization

[Miller WG et al. Clin Chem 2011;57:1670]

	Sample characteristics			Evaluation capability				
				Accuracy				
				Individual laboratory				
					Relative to participant results		Reproducibility	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV
1	Yes	Yes	Yes	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X

Category 1/2A → Milan model 1 or 2 as basis for APS

Category 1/2B → Other models

Infusino I et al. Clin Chem Lab Med 2016;in press.

Basis for performance specifications

PROVIDER	MODELS
RCPAQAP Australia	Combination of BV and state of the art
SKML The Netherlands	Combination of BV and state of the art
NOKLUS Norway	Fixed percentage limits and based on a combination of BV, state of the art and expert opinion
SEQC Spain	Combination of BV and statistical results
WEQAS UK	Combination of BV and state of the art
SEHH Spain	Statistical/state of the art/BV
CTCB France	z-score/state of the art/limits given by scientific societies or other/limits based on clinical impact

TFG on Performance Specifications for EQAS

- Apply Milan models to describe EQAS performance specifications
- Develop common performance specifications based on Milan models
- Focus on “type 1” EQAS (commutable materials, reference measurement for target, repeated samples)

TFG on EQAS: Actions

- Develop terminology to describe EQAS performance specifications
- Use terminology to describe current limits
- Support EQAS using descriptions to communicate specifications (and meaning of specifications) to users
- Consider best specifications to meet goals (may be different for different schemes)

Single results in EQAS: the interpretation

- A single result includes effects of both bias and imprecision
- Bias and imprecision effects cannot be separated
- Quality standards assess "total error"
- Applies to multiple samples, if they are analysed separately

Clin Chem 1974;20:825

Criteria for Judging Precision and Accuracy in Method Development and Evaluation

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

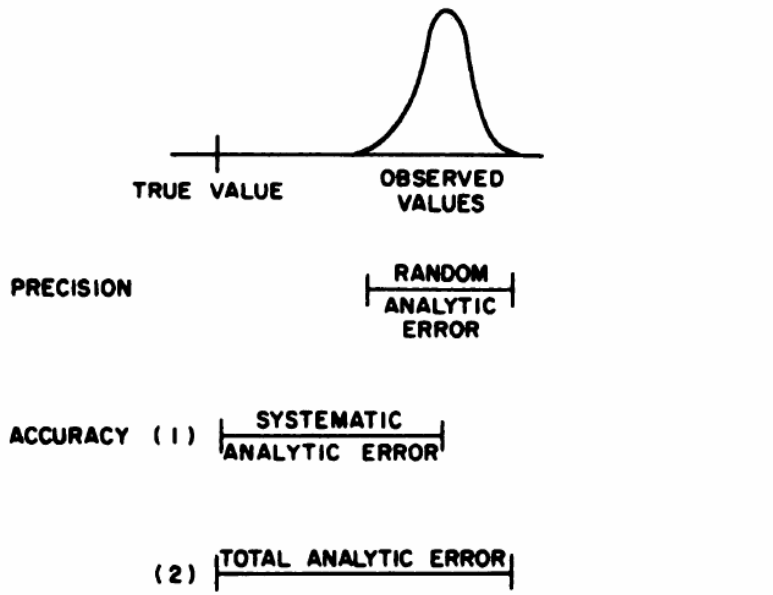


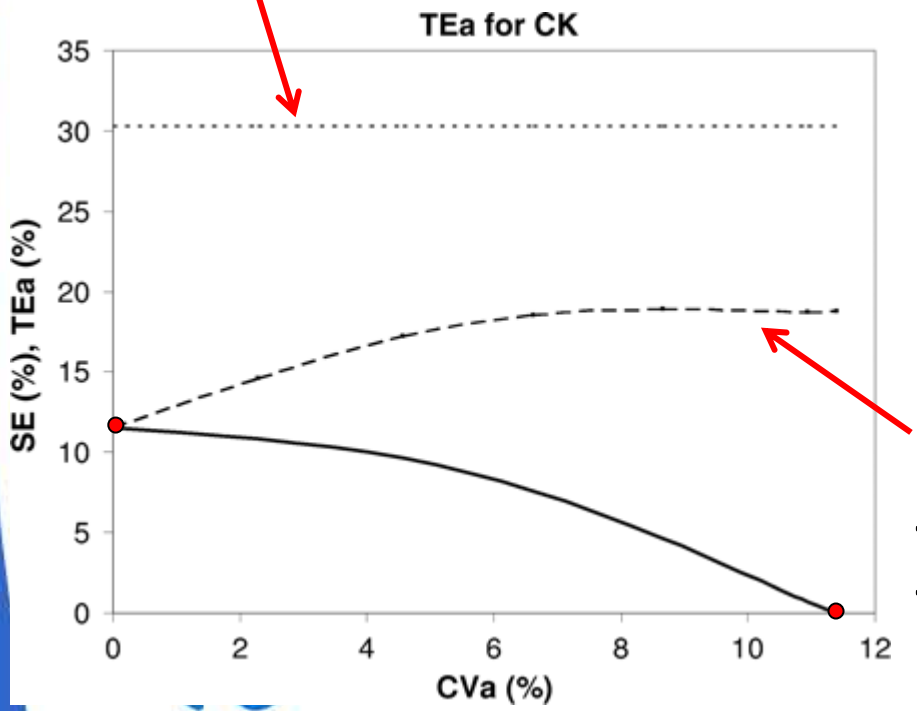
Fig. 1. Definitions of precision and accuracy in terms of random, systematic, and total analytic errors

TE = bias + Z x SDA

Z=1.65

Conventional model is flawed:
TEA = 0,25 CVB + 1,65 (0,5 CVI)

Summing of mutual exclusive terms



Gross Overestimation of Total Allowable Error Based on Biological Variation

To the Editor:

Oosterhuis WP. Clin Chem 57 (2011):1334

Gowans et al. proposed an alternative model in which the maximum allowable bias and imprecision are interrelated and described in a curve and the allowable total error calculated from each point of the graph.

Years

DE GRUYTER Clin Chem Lab Med 2016; 54(2): 195–196

Editorial

Mauro Panteghini and Sverre Sandberg

Total error vs. measurement uncertainty: the match continues

DE GRUYTER Clin Chem Lab Med 2016; 54(2): 235–239

Opinion Paper

Wytze P. Oosterhuis* and Elvar Theodorsson

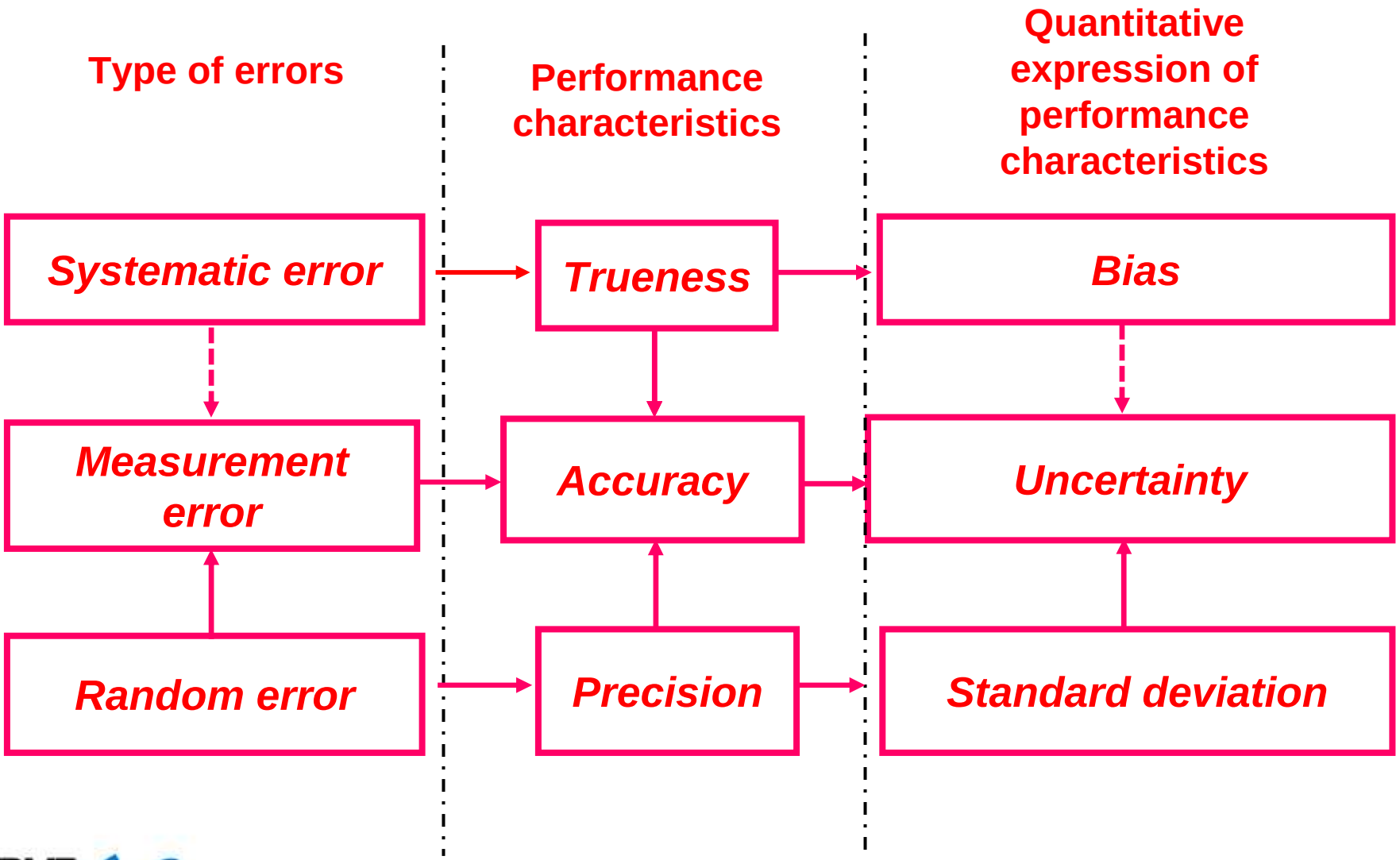
Total error vs. measurement uncertainty: revolution or evolution?

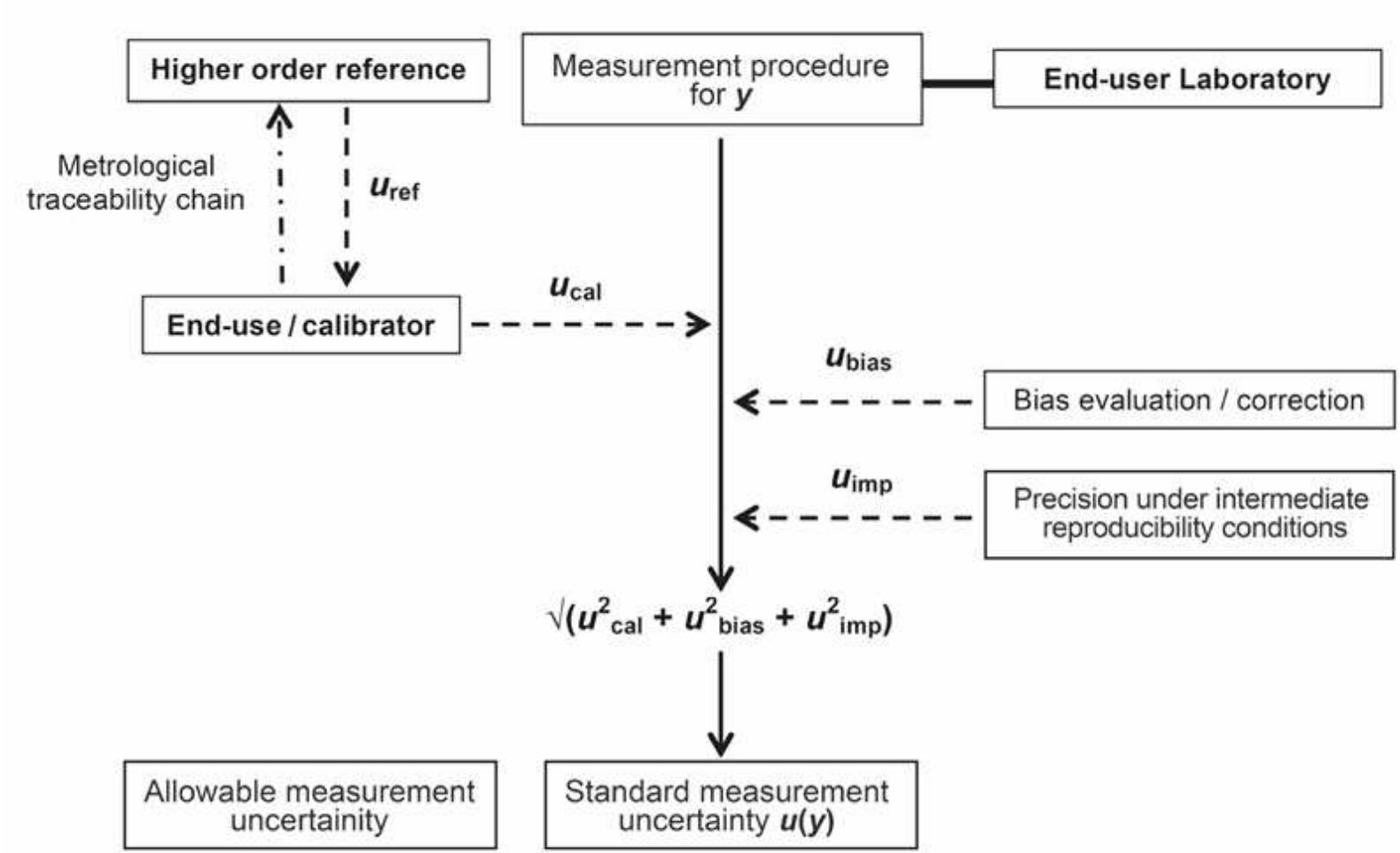
Clin Chem Lab Med 2010;48(1):7–10 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.020

Editorial

Application of traceability concepts to analytical quality control may reconcile total error with uncertainty of measurement

Mauro Panteghini


Type of errors
Performance characteristics
Quantitative expression of performance characteristics
Systematic error
Trueness
Bias
Measurement error
Accuracy
Uncertainty
Random error
Precision
Standard deviation


Higher order reference
Measurement procedure for y
End-user Laboratory
Metrological traceability chain
u_{ref}
u_{cal}
End-use / calibrator
u_{bias}
Bias evaluation / correction
u_{imp}
Precision under intermediate reproducibility conditions
$\sqrt{(u^2_{cal} + u^2_{bias} + u^2_{imp})}$
Allowable measurement uncertainity
Standard measurement uncertainty $u(y)$

SIMPLIFY: What do we say

- ”Acceptable limits were established using clinical criteria”
- ”The limits were based on biological variation”
- ”The limits were established using the state of the art”

Table 1: Proposal for assignment of some commonly requested laboratory measurands to the three models for analytical performance specifications (APS) as defined in the Milan Consensus.[a]

APS model 1: outcome-based	APS model 2: biological variation	APS model 3: state-of-the-art
P-Cholesterol+ester	P-Sodium ion	U-Sodium ion
P-Cholesterol+ester in LDL	P-Potassium ion	U-Potassium ion
P-Cholesterol+ester in HDL	P-Chloride	U-Chloride
P-Triglycerides	P-Bicarbonate	U-Calcium ion
P-Glucose	P-Calcium ion	U-Magnesium ion
B-Hemoglobin A_{1c}	P-Magnesium ion	U-Phosphate (inorganic)
P-Albumin	P-Phosphate (inorganic)	U-Creatinine
P-Troponin T and P-troponin I	P-Creatinine	U-Urate
P-Thyrotropin	P-Cystatin C	
B-Hemoglobin	P-Urate	
B-Platelets	P-Proteins	
B-Neutrophil leukocytes	B-Erythrocytes	
	B-Erythrocyte volume fraction	
	B-Erythrocyte volume	
	P-Prothrombin time	
	P-activated partial thromboplastin time	

Defining analytical performance specifications using *indirect* outcome data (Model 1b)

- Impact of analytical performance of test on clinical classifications or decisions and thereby on probability of outcomes (simulation or decision analysis).
- To model the clinical outcomes of misclassification requires clinical evidence about the consequences for patients.
- Where clinical evidence about these consequences is not available, the model estimates will be based on *assumptions* drawn from what evidence there is about disease prognosis, treatment benefits, harms, etc.

Simulation

Studying the effects of varying analytical performance

Atherosclerosis 233 (2014) 83–90

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

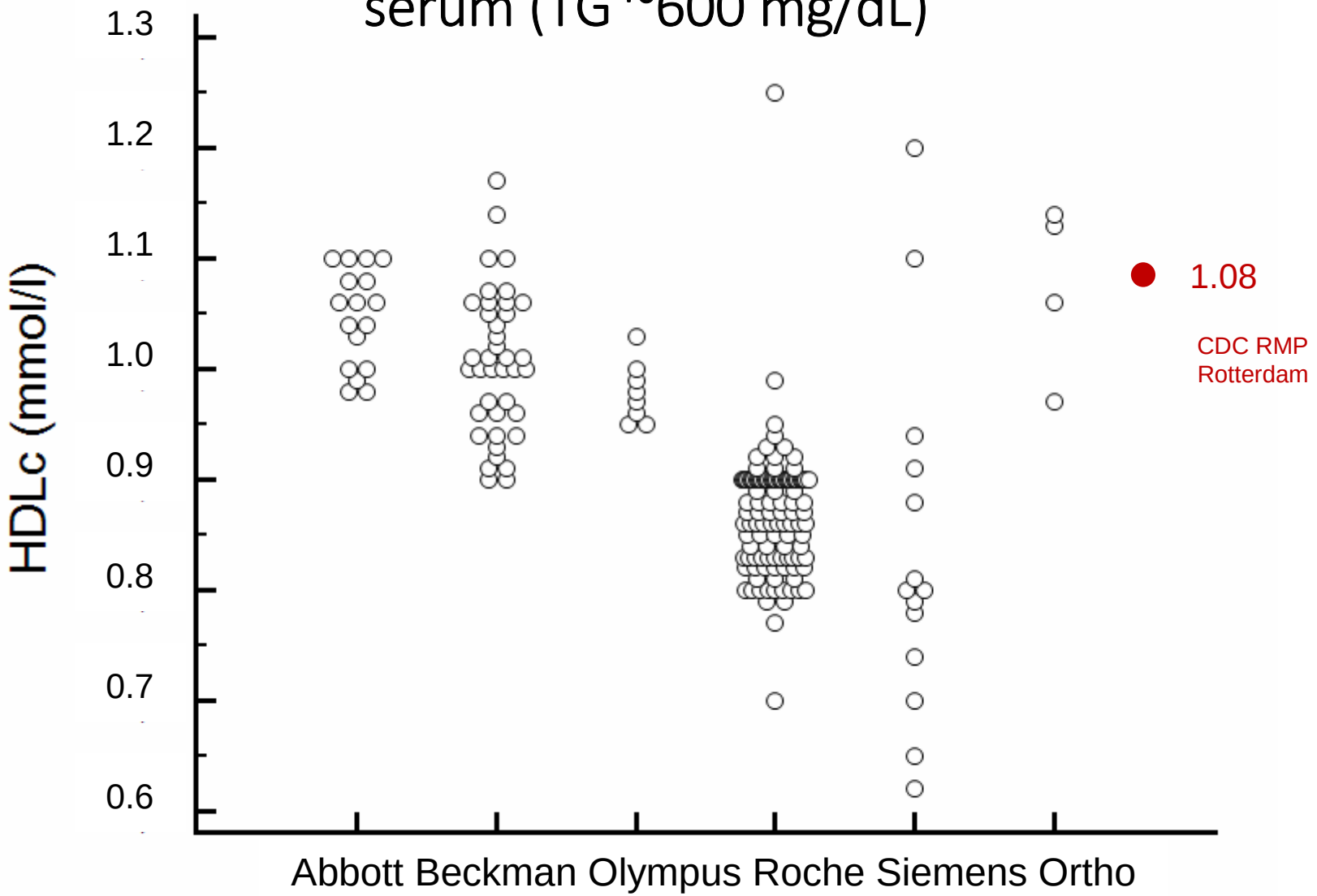
Clinical impact of direct HDLc and LDLc method bias in hypertriglyceridemia. A simulation study of the EAS-EFLM Collaborative Project Group

Michel R. Langlois [a,b,c,*], Olivier S. Descamps [d], Arnoud van der Laarse [e], Cas Weykamp [f], Hannsjörg Baum [a,g], Kari Pulkki [a,h], Arnold von Eckardstein [i], Dirk De Bacquer [j], Jan Borén [k], Olov Wiklund [k], Païvi Laitinen [a], Wytze P. Oosterhuis [b], Christa Cobbaert [l], for the EAS-EFLM Collaborative Project

[a] European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group (WG) Cardiac Markers
[b] WG Guidelines, EFLM

CELEBRATING Years

Dutch EQA survey (n=197 labs) of hypertriglyceridemic serum (TG ~600 mg/dL)



Langlois MR et al. The EAS-EFLM Collaborative Project. *Atherosclerosis* 2014; 233:83

Clinical impact of biased HDLc-risk multipliers, simulated in men with initial SCORE of 4%

Method	Labs (n)	HDL-C median (range) (mg/dL)	Error (mean bias)	SCORE >5% n (%)
Reference	1	42 [HDL multiplier, 1; SCORE = 4%]	-	-
Overall	197	35 (24-48)	-15%	84 (43%)
Abbott	18	41 (38-42)	-3%	0
Beckman	39	39 (31-45)	-7%	2 (5%)
Roche	113	36 (26-48)	-19%	71 (63%)
Siemens	14	31 (24-46)	-22%	10 (71%)

Langlois MR et al. The EAS-EFLM Collaborative Project. *Atherosclerosis* 2014; 233:83

Effect of analytical performance of troponin measurement on diagnostic misclassification

CV assuming unbiased results	% misclassification
36.2%	7.7-15.2
24.6%	3.8-7.7
16.3%	1.8-3.8
13.0%	1.4-1.8
11.2%	1.2-1.4
9.4%	0.9-1.2
6.7%	0.5-0.9

[Sheehan P et al., Ann Clin Biochem 2002;39:213]

Performance specifications for troponin based on clinical needs defined in terms of allowable misclassification rates

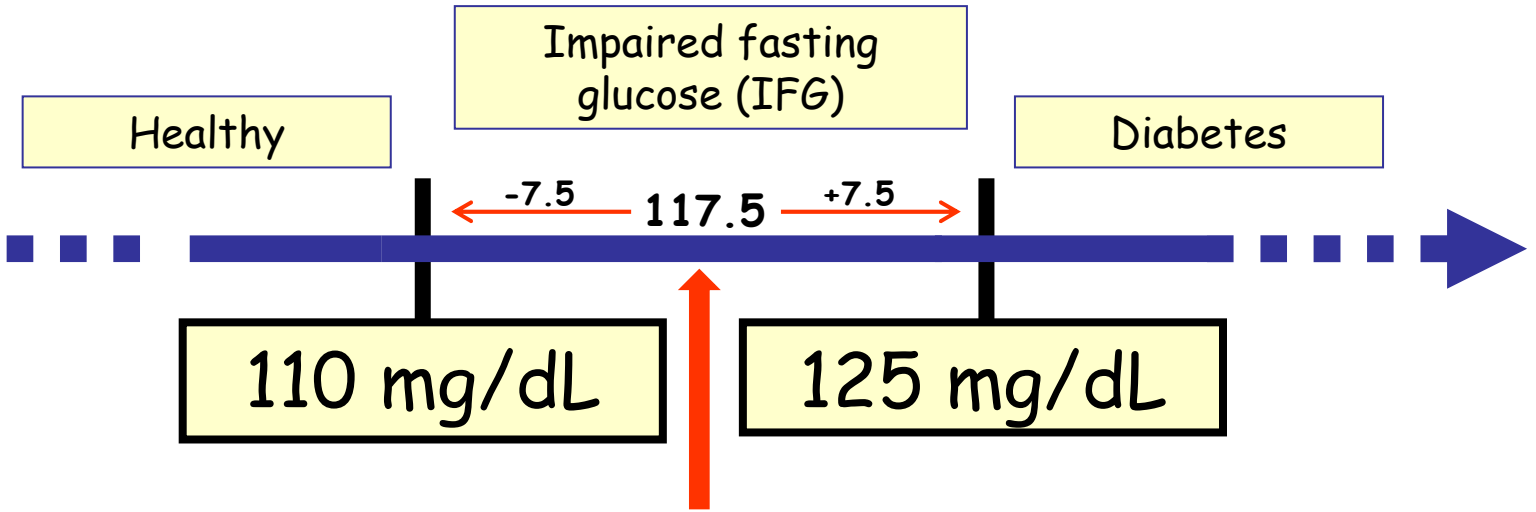
Quality level	Imprecision goal (as CV)		
	Outcome-based	Biological variability[a]	Expert opinion
Minimum	<13%[b]	<7.3%	<20%
Desirable	<10%[c]	<4.9%	<10%
Optimum	<6%[d]	<2.4%	–

[a] Calculated according to Fraser CG, Hyltoft Petersen P, Libeer JC, Ricos C. Proposal for setti quality goals solely based on biology. Ann Clin Biochem 1997;34:8-12.
[b] Assuming a diagnostic misclassification of 1.8%, [c] 1.0%, and [d] 0.5%.

Panteghini M, AACB Troponin Monograph 2012

Defining allowable measurement error for plasma glucose using *indirect* outcome data

Model 1b



A subject with a FPG of 117.5 mg/dL must be differentiate from healthy condition (from one side) and a frank diabetes diagnosis (from the other side).

Therefore, error of FPG measurement should be kept <7.5/117.5 = <6.38%, so that a subject with an IFG cannot be misclassified as diabetic (FPG >125 mg/dL) or healthy (FPG <110 mg/dL).

Years

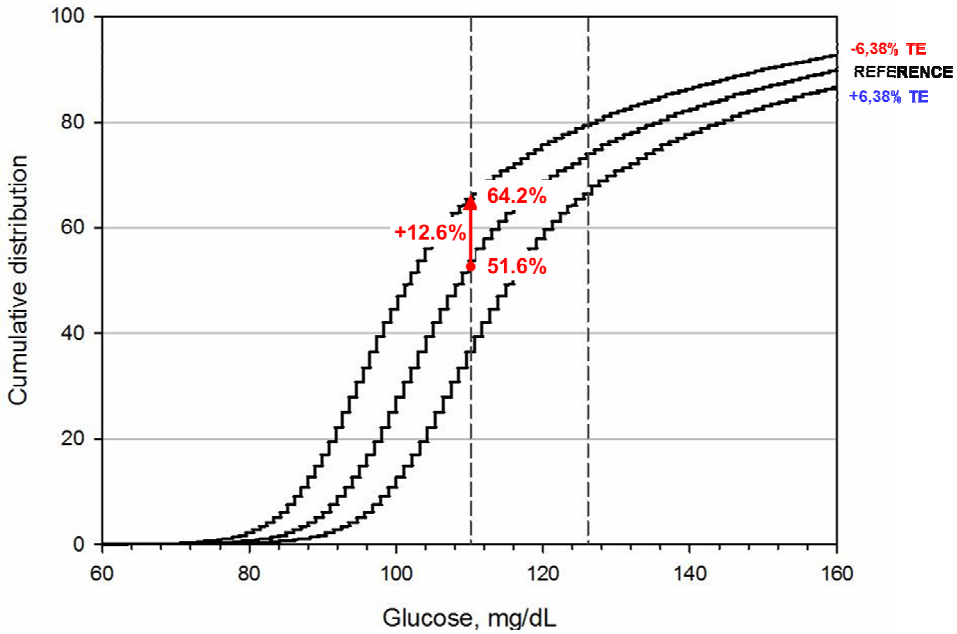
Pasqualetti S et al., submitted

Impact of measurement error of plasma glucose on clinical classification: a simulation analysis

IFG represents a category at increased risk to develop DM. In this condition, the prevention of DM onset as well as of vascular hyperglycaemia-related complications is accomplished with interventions lowering PG over time.

False negatives, i.e., IFG subjects misclassified as normoglycaemic, are therefore the most impacting results.

In our outpatient population, measuring PG with an error of -6.38% would imply that 12.6% of individuals miss interventions necessary to stop the progression to DM and the worsening of related outcomes.



Pasqualetti S et al., submitted

Years

• Considering the *importance of BV data* in laboratory medicine, it is essential to experimentally *derive them in an accurate and reliable way*

• Currently, the most commonly used information on the BV of laboratory analytes is the SEQC compilation (*www.westgard.com/biodatabase1.htm*)

but

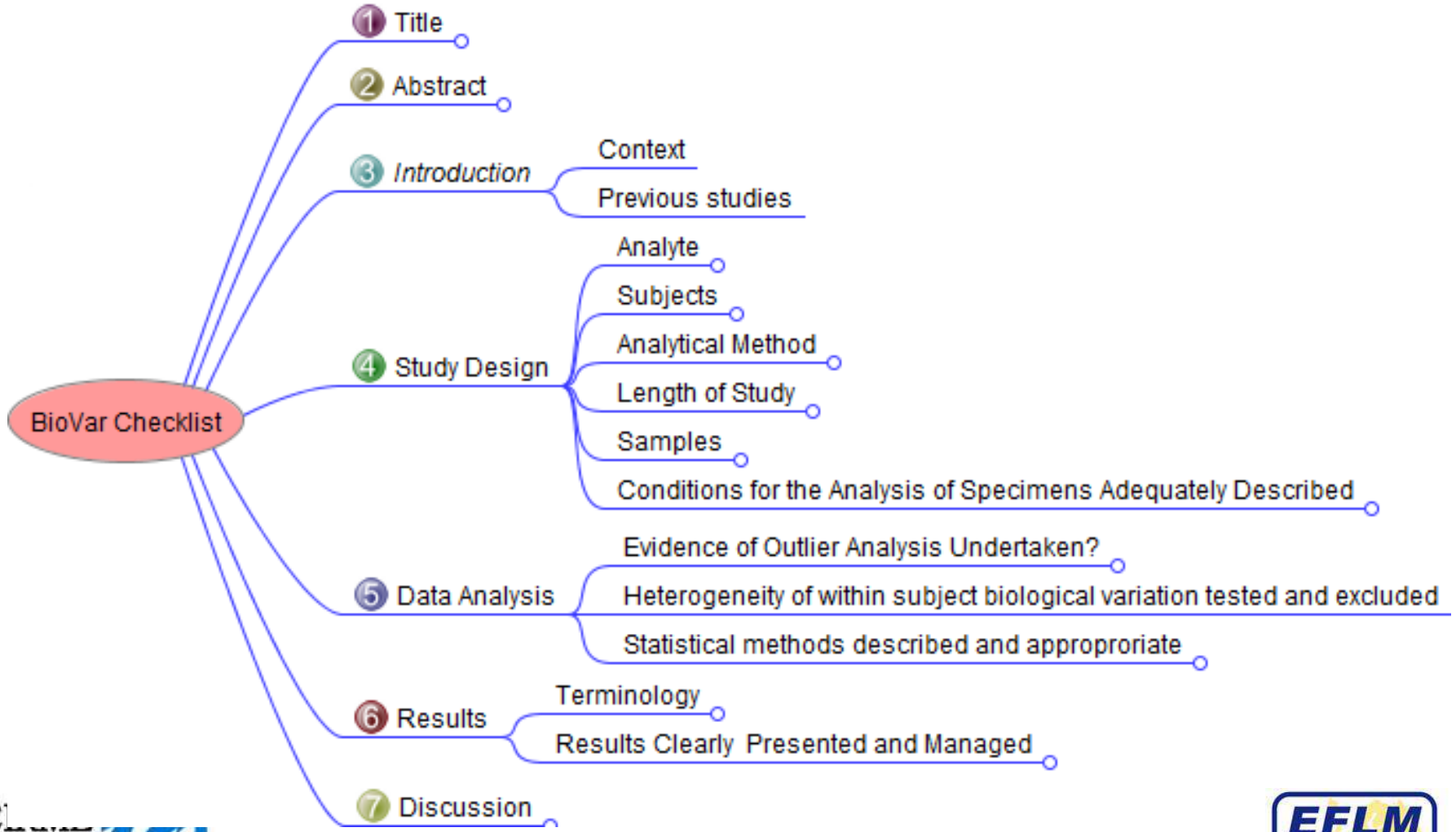
The need to improve it by applying *more stringent criteria* in the selection and review of available BV studies has been recognized…

This is the aim of the TFG created by EFLM under the auspices of the Task Force on Performance Specifications in Laboratory Medicine

CIRME CELEBRATING 10 Years

EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

A checklist for critical appraisal of studies of biological variation



CELEBRATING 10 Years

Bartlett WA et al., Clin Chem Lab Med 2015;53:879

EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Biological Variation Working Group

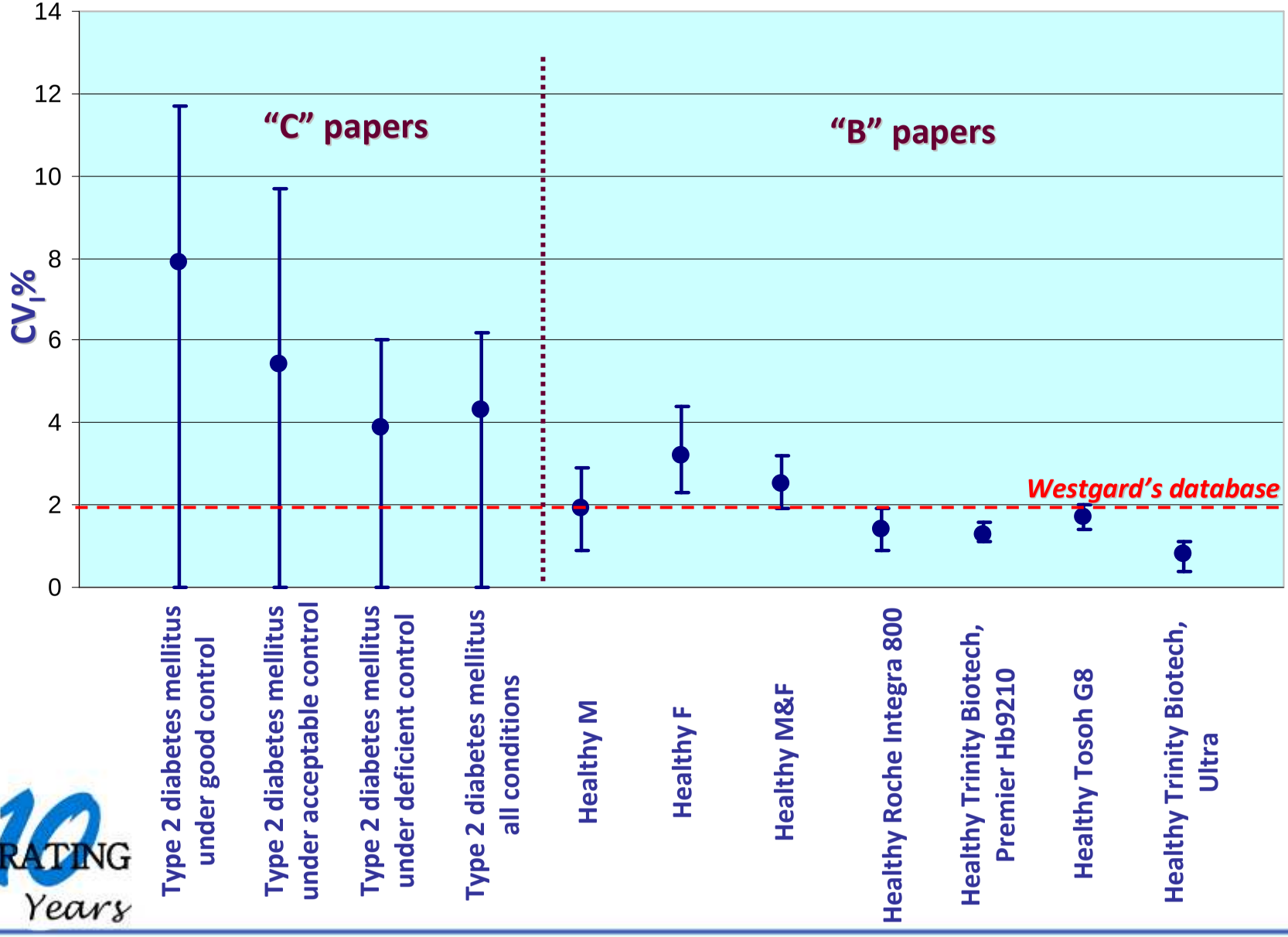
TFG on Biological Variation Database

- ✓ Refining and discussing the checklist
- ✓ Papers categorized as A, B, C and D depending on their methodological quality, with category A papers indicating high quality and D poor quality.
- ✓ The checklist contains 14 items and 22 items will be extracted from each paper and presented in the database.
- ✓ Established groups for different measurands

TFG on Biological Variation Database

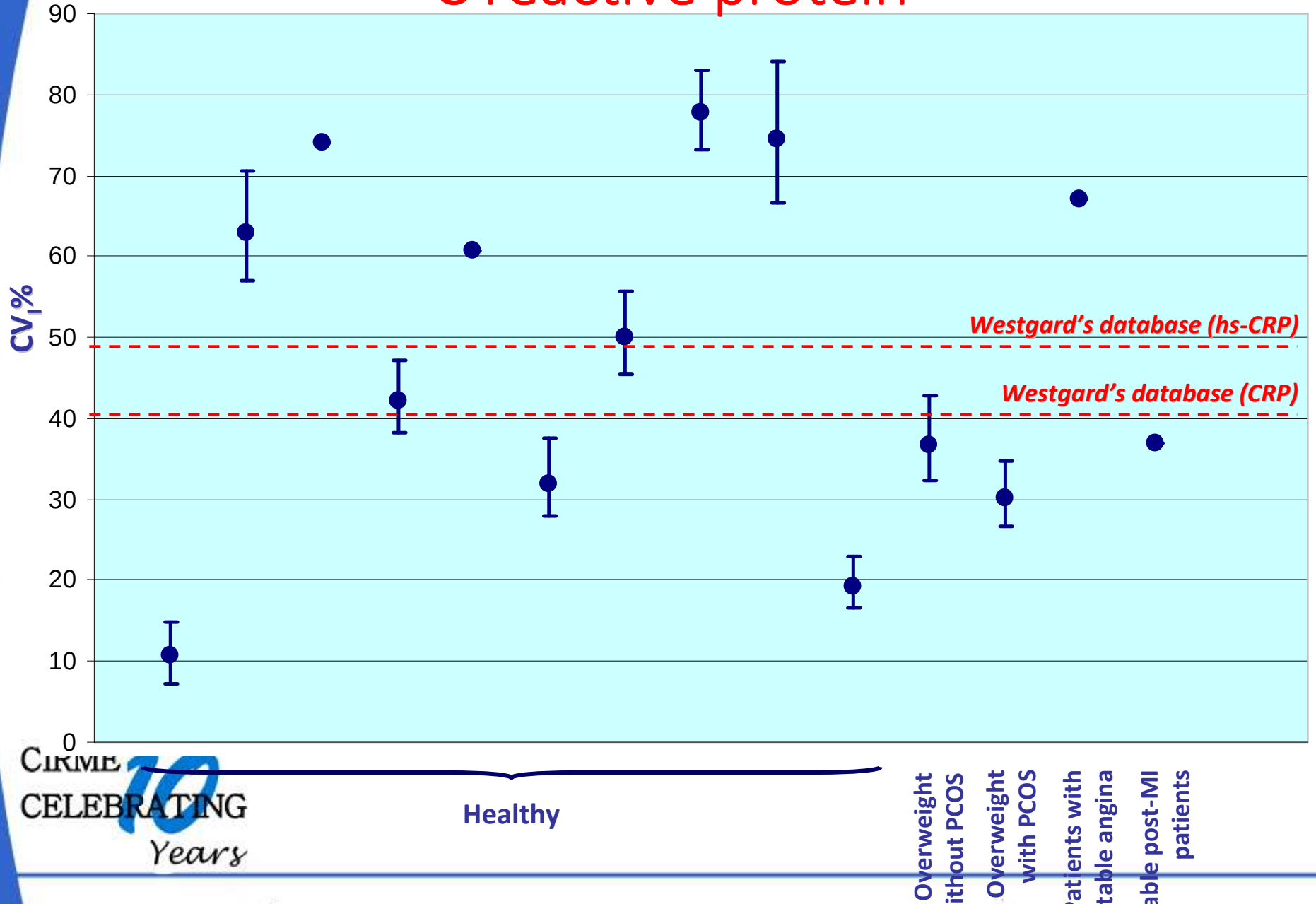
WORKING GROUP	ANALYTE	PARTICIPANTS
1. Kidney	Creatinine, Urea, electrolytes	Niels Jonker (Chair), Bill Bartlett, Carmen Biosca, Virtudes Álvarez
2. Enzymes	ALT, AST, GGT	Anna Carobene (Chair), José Vicente García-Lario, Pilar Fernández-Fernández, Carmen Perich
3. Lipids	Cholesterol, HDL, LDL, triglycerides	Pilar Fernández-Calle (Chair), Jorge Díaz - Garzón, Johana Minchinela, Fernando Cava
4. Diabetes	Glucose, Insulin, C Peptide	Abduhrraman Coskun (Chair), Carmina Ricós, Margarita Simón, Mariví Doménech
5. Other	HbA_{1c} and CRP	Federica Braga (Chair), Elisabeth Gonzalez, Beatriz Boned

HbA1c (IFCC defined measurand)



CIRME CELEBRATING 10 Years

C reactive protein



Biological Variation Database Structure

The database will consist of:

1) an index page for all analytes [analyte, matrix and grading (A, B, C)].

2) a detailed table for each analyte and matrix:

-1st level: with estimates of CVs (CV_I and CV_G), analytical performance specifications for imprecision and bias, grading (with the click you can go to the grading legend)

-2nd level: with all other information and a link to a cloud containing the compiled papers included in the database.

3) a list of articles scored with D.

First group of analytes expected to be published by 2017.

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

Performance specifications for pre- and post-analytical phases

It is acknowledged that, for patient care, optimizing the quality of the total (pre-analytical/analytical/post-analytical) examination process is the ultimate goal and therefore it would be desirable to go beyond setting analytical performance specifications and to establish examination performance specifications. In principle, the performance specifications for the pre- and post-analytical laboratory processes should follow the same models as for analytical performance specifications. When components of these additional phases can be expressed in numerical terms, they should be added in defining examination performance specifications. In other situations, pre- and post-analytical performance specifications will be best represented by separate quality indicators that should reflect models 1 and 3 listed above.

After the 1999 Stockholm Conference

- Evidence has been collected on the frequency and stratification of errors in laboratory medicine.
- The vulnerability of both the pre-analytical and post-analytical phase has been highlighted as well as the risk for quality and patient safety.
- Consensually defined criteria for setting extra-analytical quality indicators have been developed and data collected.
- This, in turn, should provide the way to define reliable performance specifications in the extra-analytical phases.

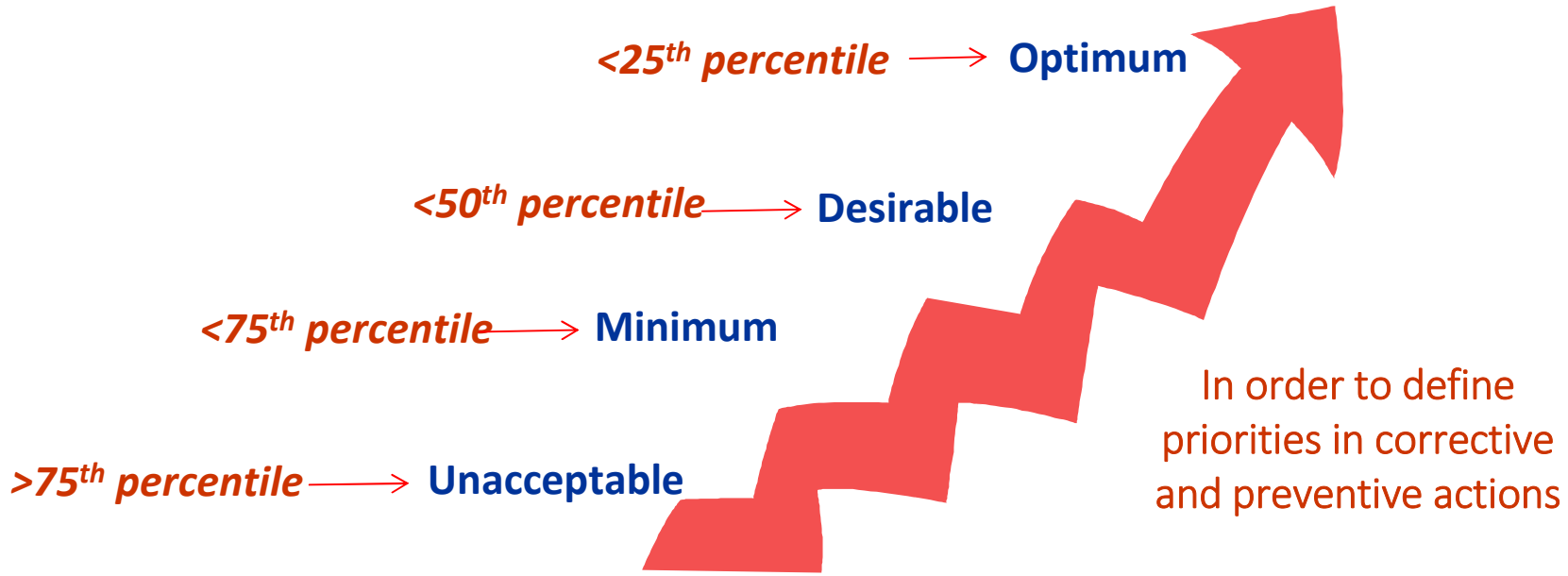
CIRME CELEBRATING 10 Years

Performance specifications

	Analytical Phase	Pre/Post-Analytical Phase
Models for performance specifications	***Defined***	***Not defined*** Possibly based on the State-of-the-Art and on Outcome measures
Metrics	***Well defined***	***Proposed*** - Percentage - Parts per million (ppm) - Six sigma
Tools of measures	***Well defined*** Internal Quality Control External Quality Assessment	***Recently defined*** Quality Indicators

PERFORMANCE SPECIFICATIONS

Three quality levels for each indicator are proposed in order to allow laboratories to evaluate how they are placed in comparison with other labs and if improvement actions are needed.



CIRME CELEBRATING 10 Years

Examples of performance specifications

	Range	Median	Specifications	
Specimen not received	2.0 - 6.1	2.9	2.5	Optimum
			3.0	Desirable
			5.0	Minimum
Insufficient specimen	0.07 - 0.80	0.15	0.10	Optimum
			0.15	Desirable
			0.60	Minimum
Wrong container	0.02 - 0.20	0.11	0.05	Optimum
			0.11	Desirable
			0.17	Minimum

EFLM SYMPOSIUM

Performance specifications in laboratory medicine - Part 1

CHAIR: *Mauro Panteghini (IT)* CO-CHAIR: *TBA*

10.30 - 12.30

ROOM: LAMBRAKIS HALL

COOPERATION WITH: *European Federation of Clinical Chemistry & Laboratory Medicine (EFLM)*

3 LECTURES

LECTURES

Mauro Panteghini (IT)
Defining performance specifications in laboratory testing
(35 min + 5 min discussion)

Sverre Sandberg (NO)
The new EFLM biological variation database based on a critical appraisal check-list
(35 min + 5 min discussion)

Ferruccio Ceriotti (IT)
Criteria for allocation of laboratory tests to the three Milan models for performance specifications
(35 min + 5 min discussion)

SESSION OVERVIEW

The session will provide an overview of different models to set performance specifications in laboratory medicine; 1) based on clinical outcome, on 2) biological variation, and 3) state of the art. In addition, it will address the total error concept, and performance specifications in external quality assessment schemes and in the extra-analytical phases.

LEARNING OBJECTIVES

After this session, participants will be able to:

1. Understand the different principles for setting performance specifications.
2. Achieve practical skills in selecting performance specifications for different measurands (analytes).
3. Understand the total error and uncertainty concepts and their role in judging analytical performance.
4. Understand how to set performance specifications and quality indicators in the extra-analytical phases.

ABOUT THE CHAIRS & SPEAKERS

Ferruccio Ceriotti MD is deputy Director of the Service of Laboratory Medicine of San Raffaele Hospital in Milan. He is Director of the Laboratory for Standardization in Clinical Chemistry of the same Institution and responsible for quality management and quality assurance of the laboratory. He has been chairman of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL) and of the IFCC Committee on Reference System for Enzymes (C-RSE). He is chair of the EFLM Working Group on Harmonisation of the total testing process and of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications. Dr. Ceriotti is the Past President of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology. Dr. Ceriotti has published more than 160 manuscripts and 150 abstracts.

Mauro Panteghini is full Professor of Clinical Biochemistry and Clinical Molecular Biology at University of Milano Medical School. His institutional positions are Director of the Chair of Clinical Biochemistry and Clinical Molecular Biology at the Medical School of the University of Milan, Italy. Director of the Department of Laboratory Medicine and Director of Clinical Pathology Unit of the "Luigi Sacco" University Hospital in Milan, Italy. Director of the Research Centre for Metrological Traceability in Laboratory Medicine (CIRME) of the University of Milan. Prof. Panteghini has served in a number of international and national scientific activities in the field of Laboratory Medicine. He is currently Past-President of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). He has published more than 480 manuscripts (h-index: 46) and more than 440 abstracts. He presented over 130 invited lectures during international and national congresses.

Sverre Sandberg is director of the Norwegian quality improvement of primary care laboratories, NOKLUS (www.noklus.no and the Scandinavian evaluation of laboratory equipment for primary health care, SKUP (www.skup.nu), director of the Norwegian Porphyria Centre, NAPOS (www.napos.no), and is a professor at the University of Bergen.He has served in different positions in international organization as IFCC and EFLM and is currently the president of EFLM. He has published papers and given international lectures in his fields of interest: porphyria, photobiology, evidence based laboratory medicine, point of care instruments, biological variation, quality assurance of the total testing process, diabetes and has also been active in some other non-laboratory areas.

EFLM SYMPOSIUM

Performance specifications in laboratory medicine - Part 2

CHAIR: *Sverre Sandberg (NO)* CO-CHAIR: *TBA*

14.30 - 16.30

ROOM: LAMBRAKIS HALL

COOPERATION WITH: *European Federation of Clinical Chemistry & Laboratory Medicine (EFLM)*

3 LECTURES

LECTURES

Wytze Oosterhuis (NL)
Are total error and uncertainty of measurement two sides of the same coin?
(35 min + 5 min discussion)

Graham Jones (AU)
Performance specifications in EQAS
(35 min + 5 min discussion)

Mario Plebani (IT)
Performance specifications in extra-analytical phases
(35 min + 5 min discussion)

SESSION OVERVIEW

The session will provide an overview of different models to set performance specifications in laboratory medicine; 1) based on clinical outcome, on 2) biological variation, and 3) state of the art. In addition, it will address the total error concept, and performance specifications in external quality assessment schemes and in the extra-analytical phases.

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1. Understand the different principles for setting performance specifications.
2. Achieve practical skills in selecting performance specifications for different measurands (analytes).
3. Understand the total error and uncertainty concepts and their role in judging analytical performance.
4. Understand how to set performance specifications and quality indicators in the extra-analytical phases.

ABOUT THE CHAIRS & SPEAKERS

Graham Jones has been senior staff specialist in Chemical Pathology at St Vincent's Hospital in Sydney since 1997 and also conjoint associate professor and the University of New South Wales. He holds fellowships from the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists. He is active professionally both nationally and internationally with special interests in kidney disease, diabetes, quality control, external quality assurance traceability of results and uniform reporting of pathology results.

Wytze Oosterhuis works as a laboratory physician in Zuyderland Medical Center in Heerlen, The Netherlands. He is member of the EFLM Working Group on Guidelines, a joint activity of EFLM and European Union of Medical Specialists (UEMS). He is member of the EFLM Working Group on Patient Focused Laboratory Medicine, and the chair of the Task and Finish Group on Total Error. Since 1997 he collaborates for the IFCC Committee on Evidence Based Laboratory Medicine (EBLM). He is lecturer in the IFCC-Abbott visiting lecturer program. He is the delegate for the Dutch laboratory physicians in the UEMS Section of Laboratory Medicine – Medical Biopathology and chair of the Clinical Chemistry division. At national level – within the Netherlands Society of Clinical Chemistry and Laboratory Medicine – he is an active member of several working groups (e.g. Clinical Decision Making), and committees (Quality, Guidelines).

Mario Plebani is Professor of Clinical Biochemistry and Clinical Molecular Biology at the School of Medicine, University of Padova. He is Chief of the Dpt. of Laboratory Medicine at the University-Hospital of Padova, Chief of the Center of Biomedical Research (a specialized Center for quality in laboratory medicine for the Veneto Region). He is member of the Board of Management of the University of Padova as Director of the Post-graduate School in Clinical Biochemistry at the Medical School from 2006 to 2012, and President of the Course for Medical Technologists from 2008 to 2012. He served as President of the International Society of Enzymology for four years, as President of the Italian Society of Clinical Biochemistry and Molecular Clinical Biology for five years and President of the federation of Italian Societies of Laboratory Medicine (FISMeLAB) from 2009 to 2012. He is a member of the Study Group on Biomarkers in Cardiology of the European Society of Cardiology (ESC) Working Group on Acute Cardiac Care and, more recently of the TC - Study group on Biomarkers of the Acute Cardiovascular Care Association (ACCA). Prof. Plebani is Editor-in-Chief of Clinical Chemistry and Laboratory Medicine, and co-Editor in Chief of Diagnosis and Associate editor of the International Journal of Biological Markers. He has published 880 full papers, more than 900 abstracts and several books and book chapters, HI 64 and an Impact Factor of 877.495 in the last three year. His main areas of research are quality in laboratory medicine, diagnostic and laboratory errors, biomarkers in cancer and cardiovascular diseases, and in vitro allergy diagnostics.