CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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

CIRME CELEBRATING 10 Years

CIRME: ten years after

Prof Mauro Panteghini

CIRME Scientific Coordinator

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

Research Centre for Metrological Traceability in Laboratory Medicine (CIRME)

created on 2006 with the scope to join in a sole entity scientists and activities of various Departments of the University of Milan interested in the development of reference methods and calibration materials of high metrological order in the field of biomedical diagnostics.

CIRME CELEBRATING 10 Years

ACCREDIA
L'ENTE ITALIANO DI ACCREDITAMENTO
Membro degli Accordi di Mutuo Riconoscimento EA, IAF e ILAC
Signatory of EA, IAF and ILAC Mutual Recognition Agreements

ilac-MRA

Tabella allegata al Certificato: 217 rev. 01
Responsabile: prof. Mauro PANTEGHINI
Sostituto: prof. Andrea MOSCA
Settori accreditati: 3

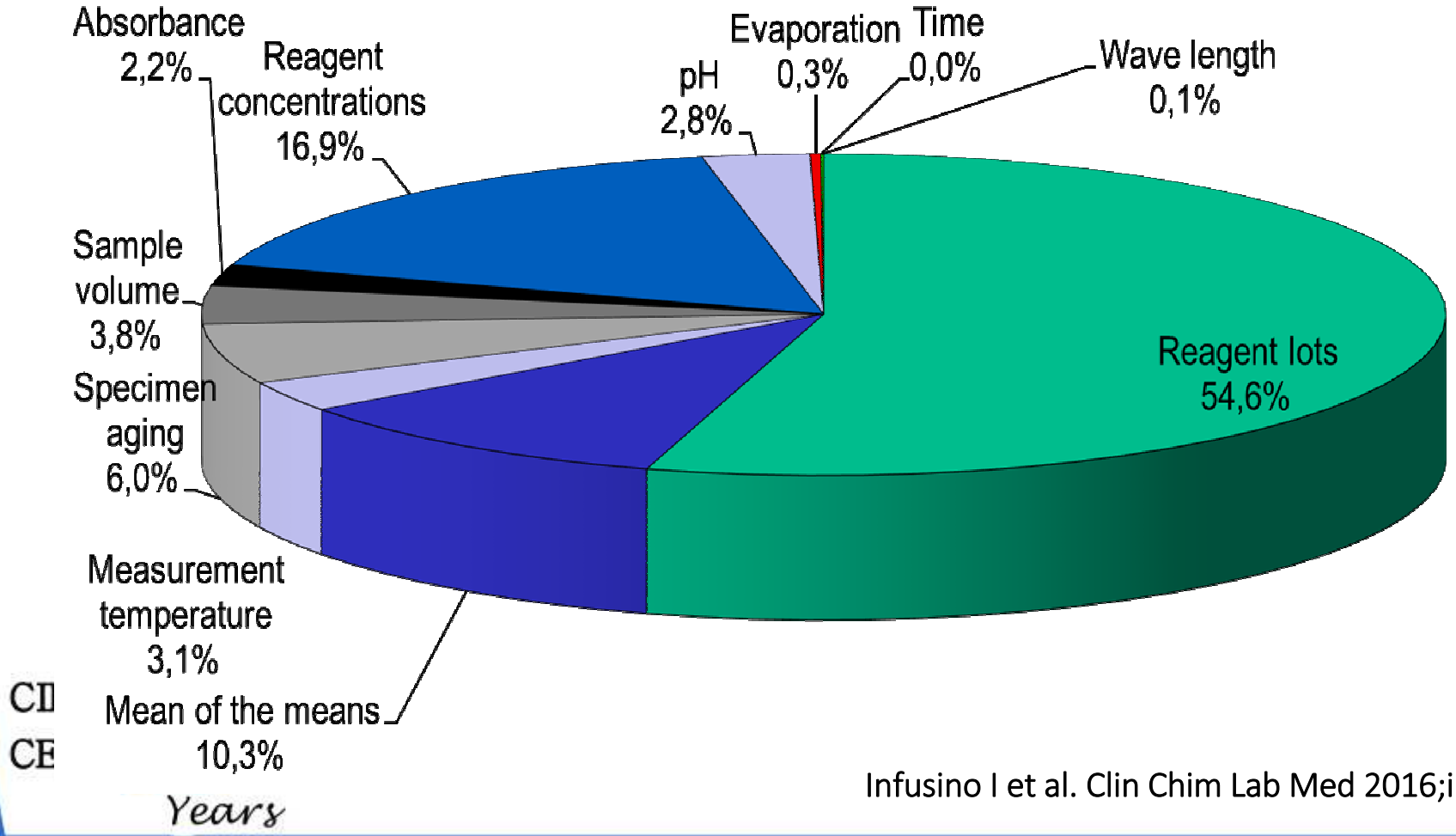
Laboratorio permanente

TABELLA DI ACCREDITAMENTO

Grandezza	Strumento in taratura	Campo di misura		Incertezza relativa (*)	Note
		Intervallo di concentrazione			
		da	a		
Attività catalitica	Alanina aminotransferasi (ALT)	0,063 µkat/L (3,8 U/L)	4,17 µkat/L (250 U/L)	2,3 %	
Attività catalitica	Fosfatasi alcalina (ALP)	0,067 µkat/L (4,0 U/L)	10,83 µkat/L (650 U/L)	2,5 %	
Attività catalitica	Aspartato aminotransferasi (AST)	0,063 µkat/L (3,8 U/L)	4,17 µkat/L (250 U/L)	2,5 %	
Attività catalitica	Creatina chinasi (CK)	0,083 µkat/L (5,0 U/L)	10,00 µkat/L (600 U/L)	2,5 %	
Attività catalitica	Gamma-glutamiltransferasi (GGT)	0,023 µkat/L (1,4 U/L)	4,58 µkat/L (275 U/L)	2,5 %	
Attività catalitica	Lattato deidrogenasi (LDH)	0,060 µkat/L (3,6 U/L)	10,00 µkat/L (600 U/L)	2,3 %	
Frazione di quantità di sostanza	Emoglobina glicata (HbA1c) con metodo HPLC-elettroforesi capillare	4 mmol/mol	150 mmol/mol	3,0 %	
Concentrazione di quantità di sostanza	Glucosio con metodo spettrofotometrico	0,28 mmol/l (5 mg/dl)	22,4 mmol/l (400 mg/dl)	1,80 %	

(*) L'incertezza di misura è espressa al livello di fiducia del 95%.

Example of uncertainty budget for ALT reference measurement procedure



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

JCTLM

List of reference measurement services

This file was created on 04 November 2010 from the JCTLM-DB website (http://www.bipm.org/jctlm/)
Your search criteria: Reference measurement services; Analyte: ALT; Analyte category: Enzymes; Matrix category: Blood serum

CIRME, Italy

Phone : +39 02 3904 2806
Fax : +39 02 5031 9835
Contact person : Prof. Mauro Panteghini
Email : mauro.panteghini@unimi.it

Analyte	alanine aminotransferase (ALT)
Material or matrix	blood serum, blood plasma
Applicable material or matrix	human serum or plasma (heparin); lyophilized, fresh, or frozen
Quantity	Catalytic activity concentration
Service measurement range	0.063 µkat/l to 4.17 µkat/l The conversion factor for enzyme catalytic activity concentrations: 1 U/L = 0.01667 µkat/L
Expanded uncertainty (level of confidence 95%)	(not available) to 2.3% The uncertainty of the lower limit of the measurement range is not available as this enzyme value is clinically unrelevant
Interlaboratory comparison results	RELA - IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine at http://www.dgkl-rfb.de:81/index.shtml Siekmann et al., *Clin. Chem. Lab. Med.*, 2002, **40**, 739-745
Measurement principle	Kinetic spectrophotometry
JCTLM reference measurement method/procedure	IFCC reference measurement procedure (37 °C) for ALT

Reference Materials, Measurement Methods and Services for *In Vitro* Diagnostics

JCTLM

Accurate results
for patient care

CIRME is a
JCTLM
Member
Organization

www.bipm.org/jctlm

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ONE OF 12 REFERENCE CENTERS LISTED IN THE JCTLM DATABASE

ACCREDIA ACCREDITATION ACCORDING TO ISO/IEC 17025 AND ISO 15195 STANDARDS

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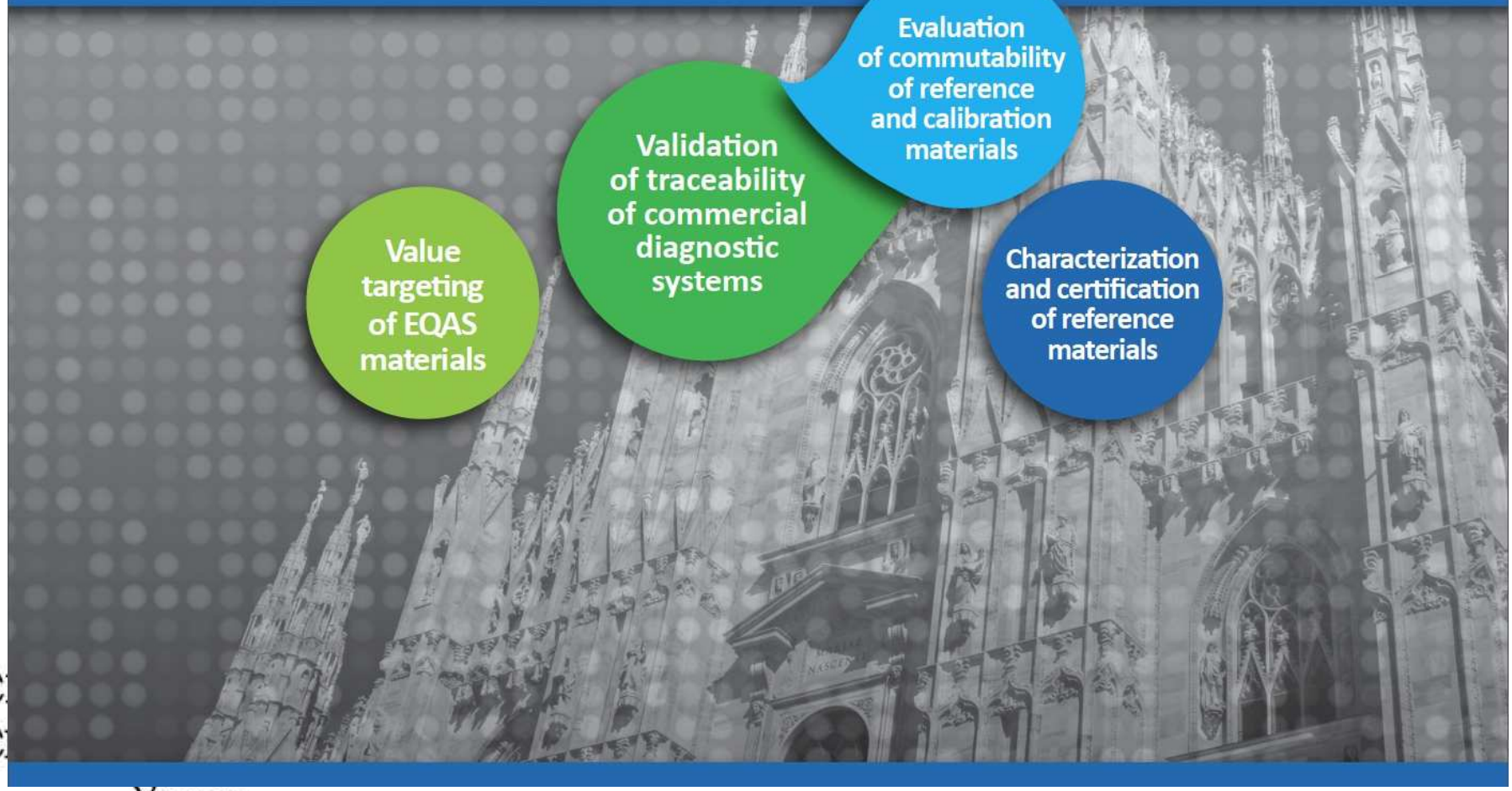

Years

In cooperation with

European Commission
Joint Research Centre
Institute for Reference Materials and Measurements

ERM
European Reference Materials

CERTIFICATE OF ANALYSIS

ERM®- DA470k/IFCC

HUMAN SERUM		
Proteins in the reconstituted material [1]	Mass concentration	
	Certified value [2] [g/L]	Uncertainty [3] [g/L]
α_2 macroglobulin (A2M)	1.43 [4]	0.06
α_1 acid glycoprotein (AAG)	0.617 [5]	0.013
α_1 antitrypsin (AAT)	1.12 [5]	0.03
albumin (ALB)	37.2 [4]	1.2
complement 3c (C3c)	1.00 [4]	0.04
complement 4 (C4)	0.162 [4]	0.007
haptoglobin (HPT)	0.889 [4]	0.021
immunoglobulin A (IgA)	1.80 [4]	0.05
immunoglobulin G (IgG)	9.17 [4]	0.18
immunoglobulin M (IgM)	0.723 [4]	0.027
transferrin (TRF)	2.35 [5]	0.08
transthyretin (TTR)	0.220 [5]	0.018

CERTIFICATE OF ANALYSIS

ERM®-AD453k/IFCC

ENZYME IN BUFFER		
	Catalytic activity concentration [1]	
	Certified value [2]	Uncertainty [3]
Lactate dehydrogenase isoenzyme 1 (LD1)	330 U/L 5.50 µkat/L	7 U/L 0.12 µkat/L

1) Catalytic activity concentration of lactate dehydrogenase isoenzyme 1 (LD1) in the reconstituted material, as obtained by the IFCC primary reference measurement procedure for the measurement of catalytic activity concentration of lactate dehydrogenase at 37 °C.

2) Certified values are values that fulfil the highest standards of accuracy and represent the unweighted mean value of the means of accepted sets of data, each set being obtained in a different laboratory. The certified value and its uncertainty are traceable to the International System of Units (SI). Values were converted from U/L into µkat/L by multiplication with the factor $f = 0.01667$.

3) The uncertainty is the expanded uncertainty of the certified value with a coverage factor $k = 2$ corresponding to a level of confidence of about 95 % estimated in accordance with ISO/IEC Guide 98-3, Guide to the Expression of Uncertainty in Measurement (GUM:1995), ISO, 2008.

The following value for B2M was assigned:

Protein in the reconstituted material (see section 9.3)	Mass concentration	
	Certified value [2] [mg/L]	Uncertainty [3] [mg/L]
Beta-2-microglobulin (B2M) [1]	2.17	0.07

1) B2M as measured by immunonephelometry, immunoturbidimetry, fluorometric enzyme immunoassay and chemiluminescent immunoassay using a pure protein solution as calibrant.

2) The value is the unweighted mean of 13 accepted mean values, independently obtained by 13 laboratories. The certified mass concentration is traceable to the SI, via calibration with a pure protein solution of B2M.

3) Expanded uncertainty U with a coverage factor $k = 2$, corresponding to a level of confidence of approxiamtely 95 %, estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM), ISO, 1995.

ERM®-AD454k/IFCC

ENZYME IN BUFFER		
	Catalytic activity concentration [1]	
	Certified value [2]	Uncertainty [3]
Alanine aminotransferase (ALT)	103.8 U/L 1.73 µkat/L	2.6 U/L 0.05 µkat/L

1) Catalytic activity concentration of alanine aminotransferase (ALT) in the reconstituted material, as obtained by the IFCC primary reference measurement procedure for the measurement of catalytic activity concentration of alanine aminotransferase at 37 °C.

2) Certified values are values that fulfil the highest standards of accuracy and represent the unweighted mean value of the means of accepted sets of data, each set being obtained in a different laboratory. The certified value and its uncertainty are traceable to the International System of units (SI). Values were converted from U/L into µkat/L by multiplication with the factor $f = 0.01667$.

3) The uncertainty is the expanded uncertainty of the certified value with a coverage factor $k = 2$ corresponding to a level of confidence of about 95 % estimated in accordance with ISO/IEC Guide 98-3, Guide to the Expression of Uncertainty in Measurement (GUM:1995), ISO, 2008.

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ENZYME IN BUFFER		
	Catalytic activity concentration [1]	
	Certified value [2]	Uncertainty [3]
Creatine kinase isoenzyme MM (CK-MM)	314 U/L 5.23 µkat/L	6 U/L 0.10 µkat/L

1) Catalytic activity concentration of creatine kinase isoenzyme MM (CK-MM) in the reconstituted material, as obtained by the IFCC primary reference measurement procedure for the measurement of the catalytic activity concentration of creatine kinase at 37 °C.

2) Certified values are values that fulfil the highest standards of accuracy and represent the unweighted mean value of the means of accepted sets of data, each set being obtained in a different laboratory. The certified value and its uncertainty are traceable to the International System of Units (SI). Values were converted from U/L into µkat/L by multiplication with the factor $f = 0.01667$.

3) The uncertainty is the expanded uncertainty of the certified value with a coverage factor $k = 2$ corresponding to a level of confidence of about 95 % estimated in accordance with ISO/IEC Guide 98-3, Guide to the Expression of Uncertainty in Measurement (GUM:1995), ISO, 2008.

Clin Chem Lab Med 2010;48(6):795–803 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.146

Traceability of values for catalytic activity concentration of enzymes: a Certified Reference Material for aspartate transaminase

Brigitte Toussaint[1,*], Hendrik Emons[1], Heinz G. Schimmel[1], Steffen Bossert-Reuther[2], Francesca Canalias[3], Ferruccio Ceriotti[4], Georges Férard[5], Carlo A. Ferrero[4], Paul F.H. Franck[6], F. Javier Gella[7], Joseph Henny[8], Poul J. Jørgensen[9], Rainer Klauke[10], Jean-Marc Lessinger[11], Daniel Mazziotta[12], Mauro Panteghini[13], Shigeru Ueda[14] and Gerhard Schumann[10] on behalf of the IFCC Committee on Reference Systems for Enzymes

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10th Inte

COMMUTABILITY STUDY ON CANDIDATE MATERIALS FOR THREE NEW ENZYME CERTIFIED REFERENCE MATERIALS

B. Toussaint[4], F. Ceriotti[8], H. Schimmel[4], R. Rej[10], M. Besozzi[6], F.J. Gella[2], G. Giana[7], J. Lessinger[5], M. McCusker[1], M. Orth[9], M. Panteghini[3]

Study setup: 14 serum samples were analysed with existing CRMs and with the new candidate CRMs, using 8 different assays and 1 reference method. Results obtained by different methods were compared paire-wise and the proximity of candidate materials to patient samples in the plots, sign of similar behaviour, was investigated.

Existing CRMs to be replaced:

- CK: ERM-AD455/IFCC (CK-MB) Purified from human heart Lyophilised
- ALT: ERM-AD454/IFCC (cytosolic) Purified from pig heart Lyophilised
- LD: ERM-AD453/IFCC (LD1) Purified from human erythrocytes Lyophilised

New candidate CRMs:

2 candidates for CK ~300 U/L
2 candidates for ALT ~100 U/L
1 candidate for LD ~300 U/L
Material type:
Recombinant
Lyophilised or frozen

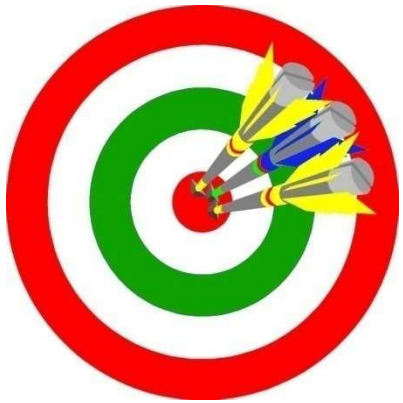
Measurements

- **Routine assays:**

Analytical systems
Abbott ci8200
Beckman Coulter Synchron DxC800
Ortho Clinical Diagnostics - Vitros 5600
Olympus AU480
Roche Modular Analytics
Roche cobas c501
Siemens - Advia 2400
Siemens - Dimension Vista_1500

- **IFCC Reference Measurement Procedure at 37 °C**

Creatinine



Expanded uncertainty goals

9.0% minimum

6.0% desirable

3.0% optimum

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Pasqualetti S et al. CCA 2015;450:125

Letter to the Editor

The calibrator value assignment protocol of the Abbott enzymatic creatinine assay is inadequate for ensuring suitable quality of serum measurements

Table 1

Uncertainties for each contributing factor in determination of serum creatinine with Abbott enzymatic assay on Architect *c*16000 platform after calibration with two different lot of system calibrator. Data obtained by measurements of NIST SRM 967a reference material (certified value ± expanded uncertainty: L1, 0.847 mg/dL ± 0.018 mg/dL and L2, 3.877 mg/dL ± 0.082 mg/dL).

	SRM 967a level 1	SRM 967a level 2
Multigent Clin Chem Calibrator lot no. 40043Y600		
Imprecision (u_{Rw})	0.47%	0.40%
Bias (u_{bias})	3.57%	7.05%
Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$]	3.60%	7.06%
Expanded uncertainty ($U = k \times u_c$)	7.20%	14.12%
Multigent Clin Chem Calibrator lot no. 40496Y600		
Imprecision (u_{Rw})	0.53%	0.42%
Bias (u_{bias})	4.02%	1.71%
Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$]	4.05%	1.76%
Expanded uncertainty ($U = k \times u_c$)	8.10%	3.52%

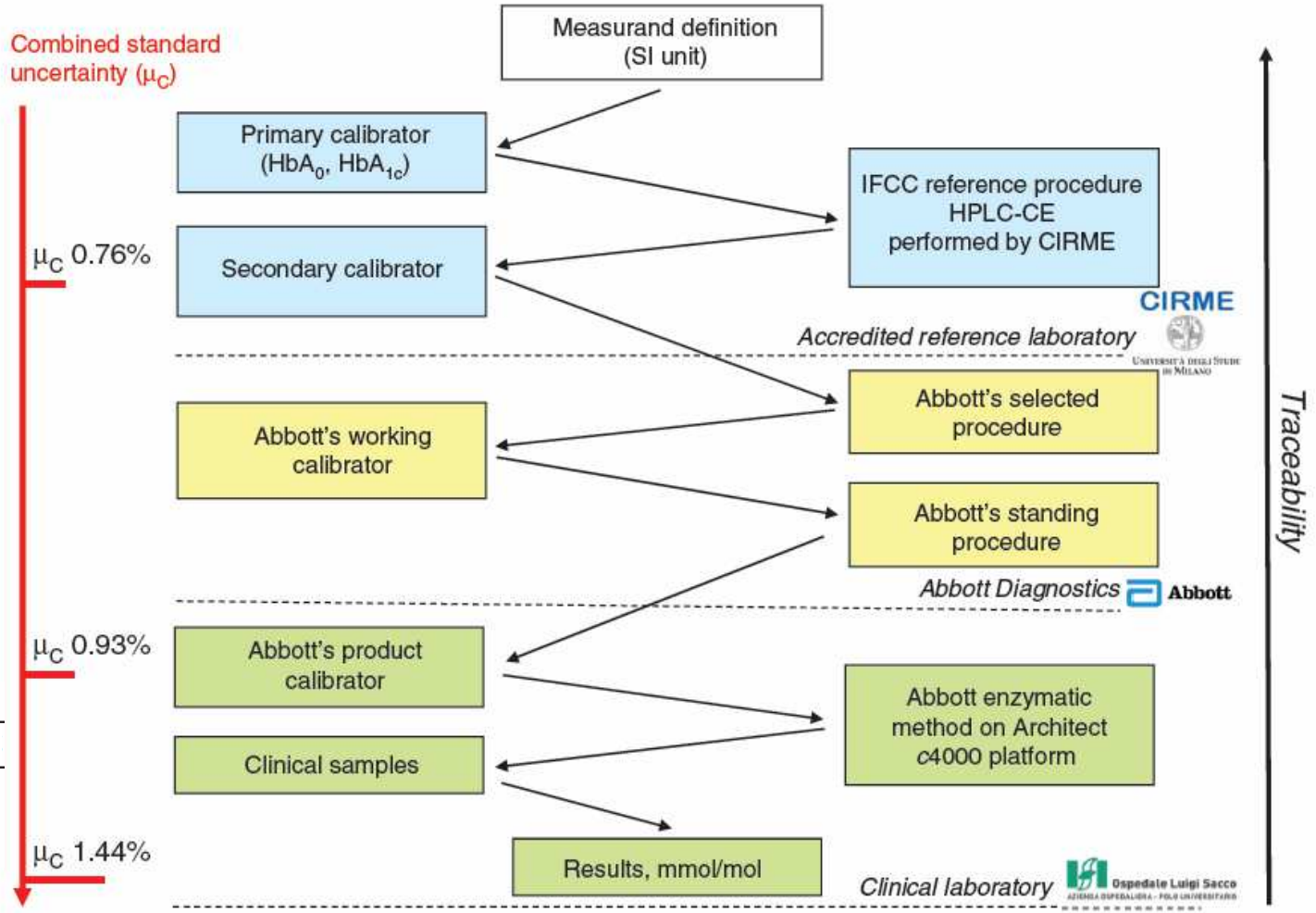
DE GRUYTER

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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Analytical goals for HbA_{1c} measurement

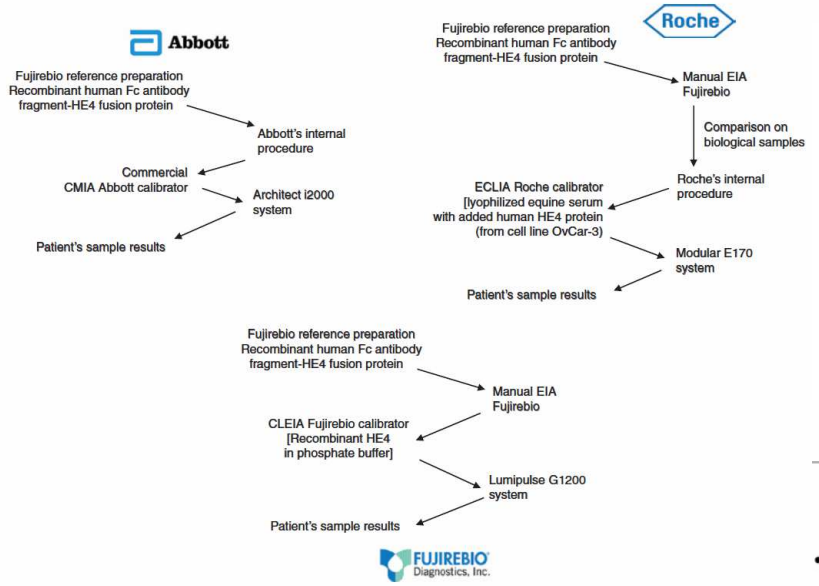
Quality level	*uC*
Optimal	≤0.6
Desirable	≤1.3
Minimal	≤1.9

10th

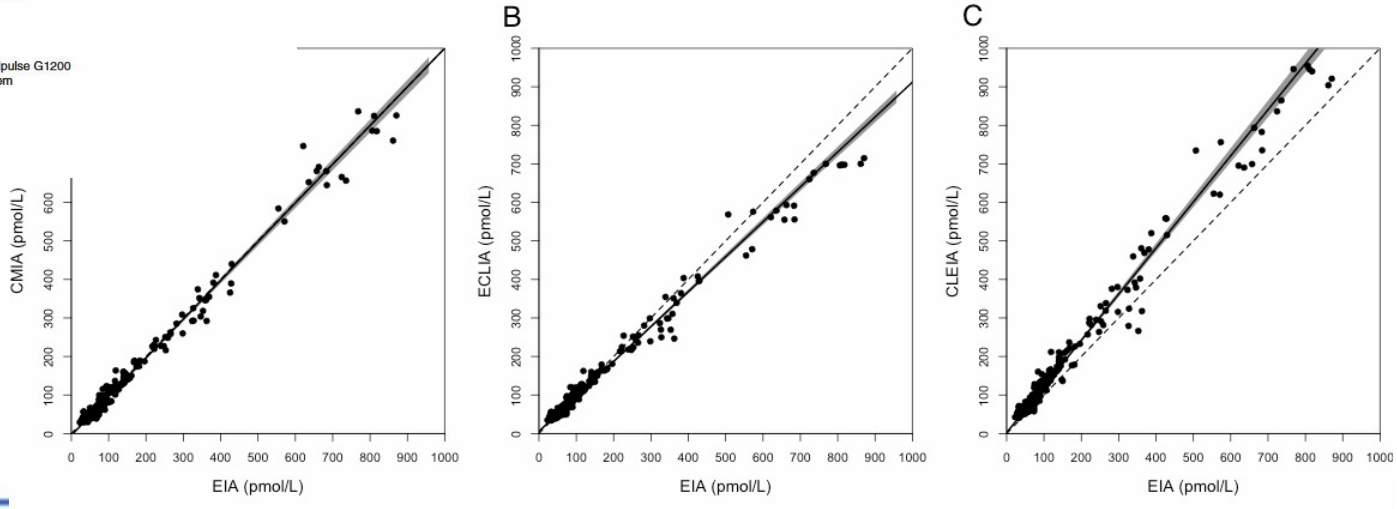
DE GRUYTER Clin Chem Lab Med 2016; 54(10): 1635–1643

Simona Ferraro*, Simona Borille, Assunta Carnevale, Erika Frusciante, Niccolò Bassani and Mauro Panteghini

Verification of the harmonization of human epididymis protein 4 assays



Conclusions: Abbott and Roche assays exhibited a good comparability in the range of HE4 values around the previously recommended 140 pmol/L cut-off. For patient monitoring, however, the assay used for determining serial HE4 must not be changed as results from different systems in lower and higher concentration ranges can markedly differ.



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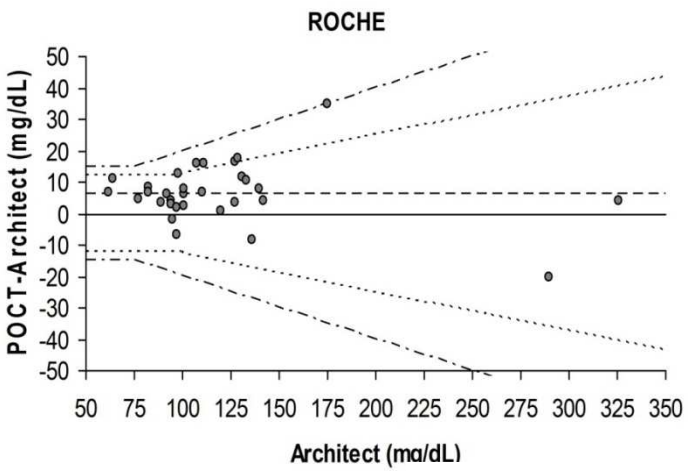
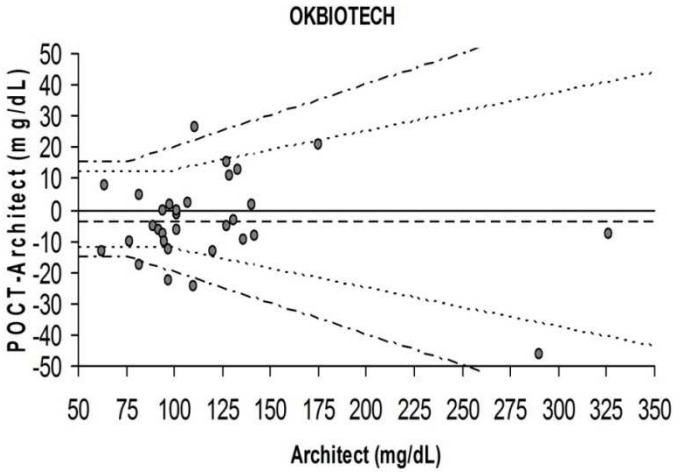
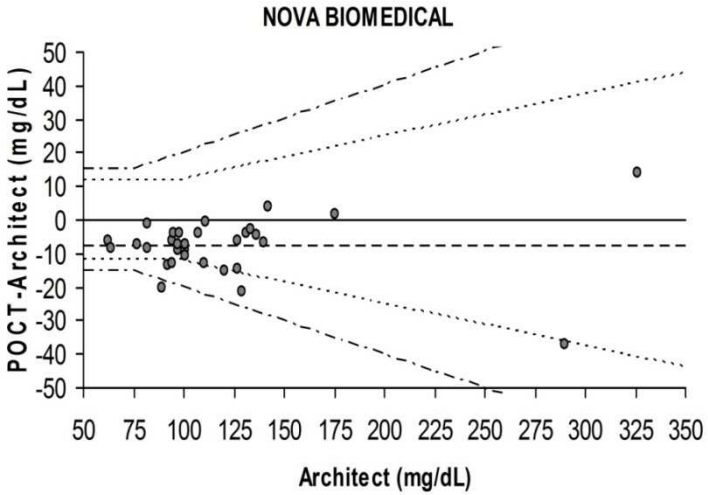
10th International Scientific Meeting. November 17-18, 2016

Verification of the accuracy of three glucose point-of-care testing (poct) devices for their use in a hospital setting

Elena Aloisio, Erika Frusciante, Alberto Dolci, Mauro Panteghini
Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Italy







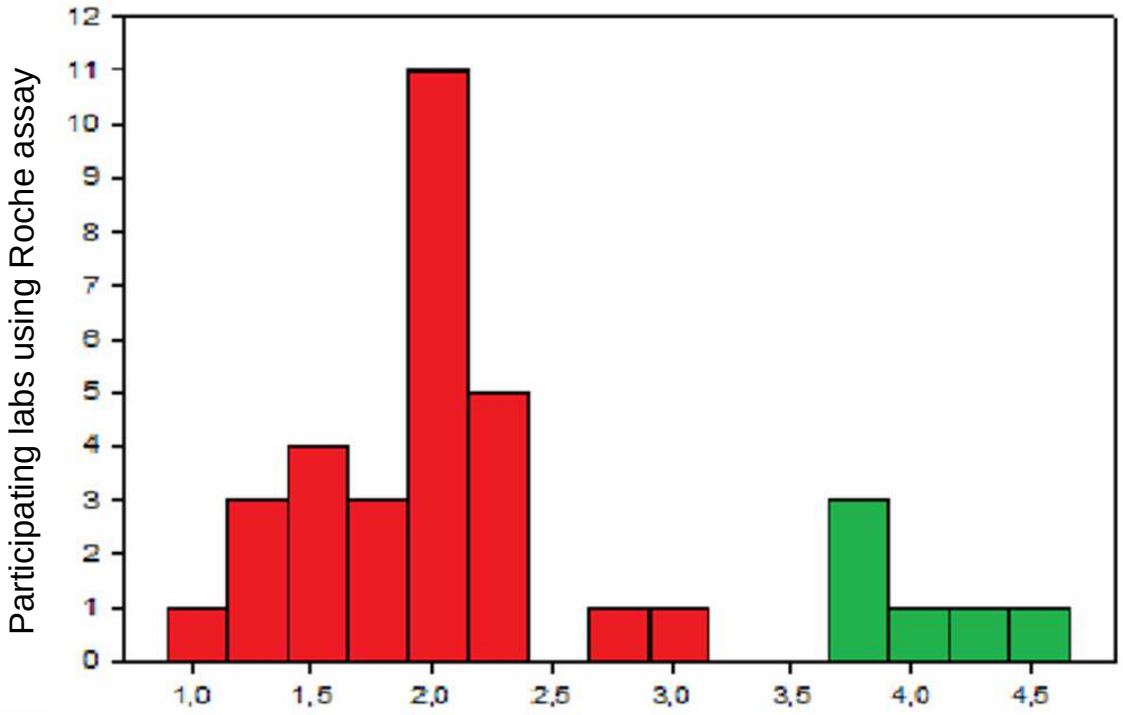
CIRME CELEBRATING 10 Years

Estimating folate deficiency and need to predict the effect of assay recalibration

- To improve assay harmonization, some commercial folate methods have recently undergone recalibration to the WHO NIBSC 03/178 International Standard
- After recalibration, a significant change in the average folate measured values was recorded

At a folate concentration around the lower reference limit of the old Roche assay, a positive bias of 50% vs. the new Roche assay can be observed

Regional EQAS exercise no. 4/2016



Roche Folate III assay
code 07559992190
(traceable to NIBSC 03/178 IS)

Roche Folate III assay
code 04476433190
(home-made
calibration)

CIRME CELEBRATING 10 Years

Taking into account the ~50% difference experimentally found at the lower reference limit (LRL) level, the shift from 4.6 µg/L (Roche recommended LRL for old calibration) to 3.9 µg/L (Roche recommended LRL for recalibrated assay) appears to be inconsistent.

Consequently, a misleading overestimate of the prevalence of folate deficiency is expected if the recalibrated Roche assay will be used together the manufacturer's newly recommended LRL.

New experimental data from healthy individuals have, therefore, to be quickly obtained with the recalibrated assay in order to accurately define the traceable reference interval and derive correct decisional strategies for folic acid supplementation.

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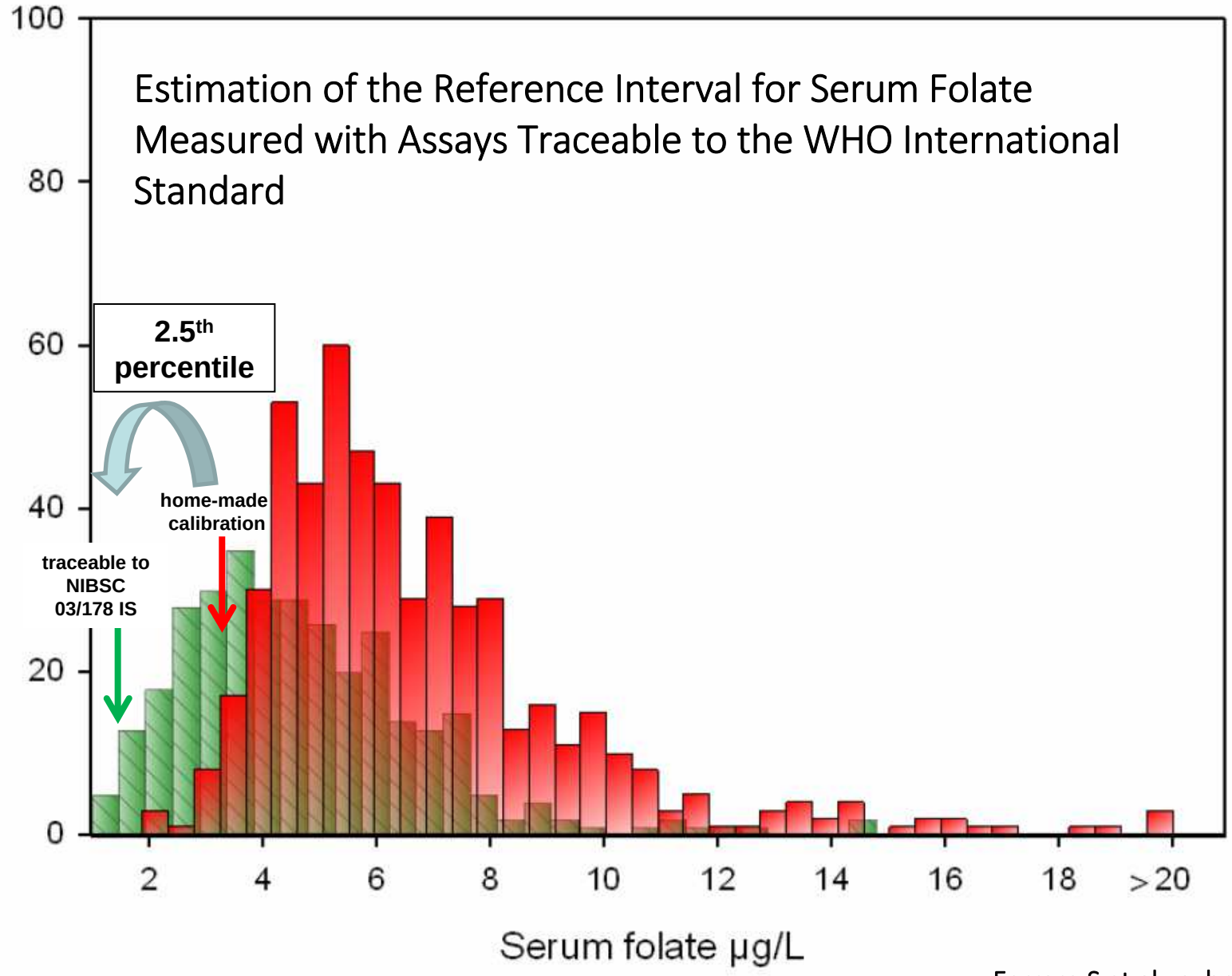
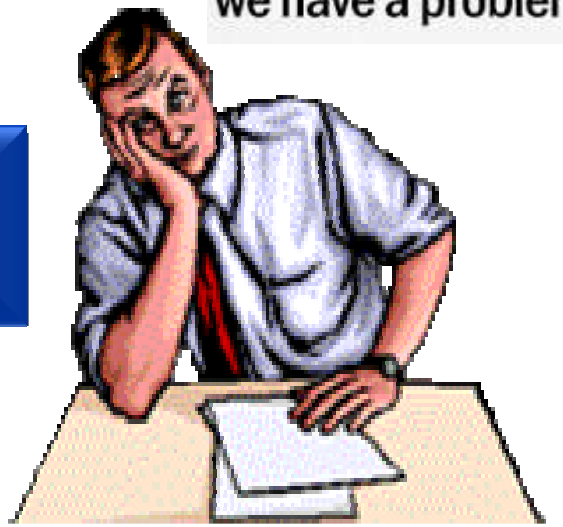
Years

Ferraro S et al., Clin Chem Lab Med 2016: in press



Ferraro S et al., submitted

Currently, the full information about calibration is usually not available



Manufacturers only provide the name of higher order reference material or procedure to which the assay calibration is traceable, without any description of implementation steps and their corresponding uncertainty.

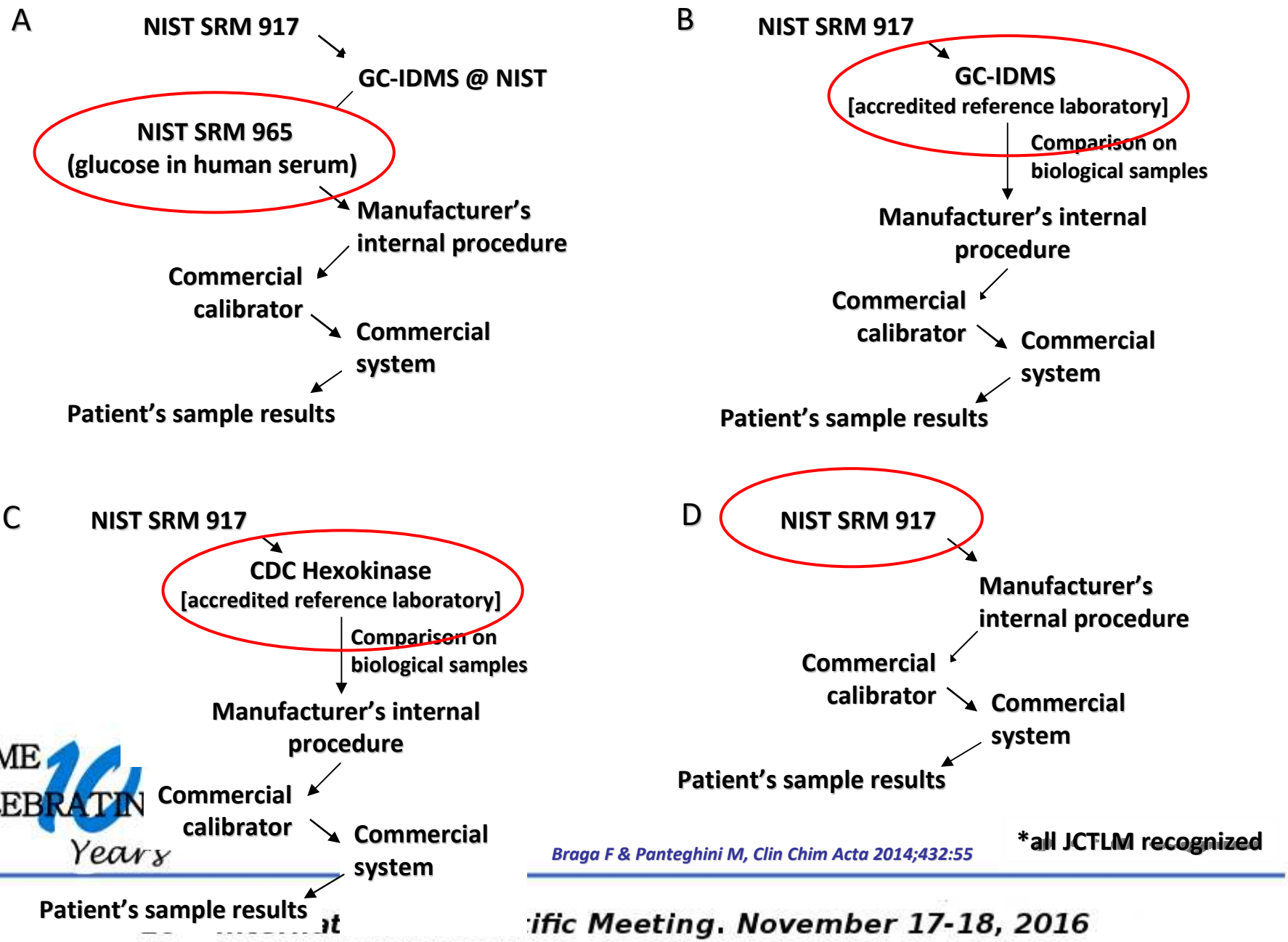
Opinion Paper

Federica Braga*, Ilenia Infusino and Mauro Panteghini

Table 2: The information that in vitro diagnostics manufacturers should provide to laboratory users about the implementation of metrological traceability of their commercial systems. Adapted from [7].

a) An indication of higher order references (materials and/or procedures) used to assign traceable values to calibrators;
b) Which internal calibration hierarchy has been applied by the manufacturer, and
c) A detailed description of each step;
d) The (expanded) combined uncertainty value of commercial calibrators, and
e) Which, if any, acceptable limits for uncertainty of calibrators were applied in the validation of the analytical system.

Types of metrological chains that can be used to implement the traceability of blood glucose results*



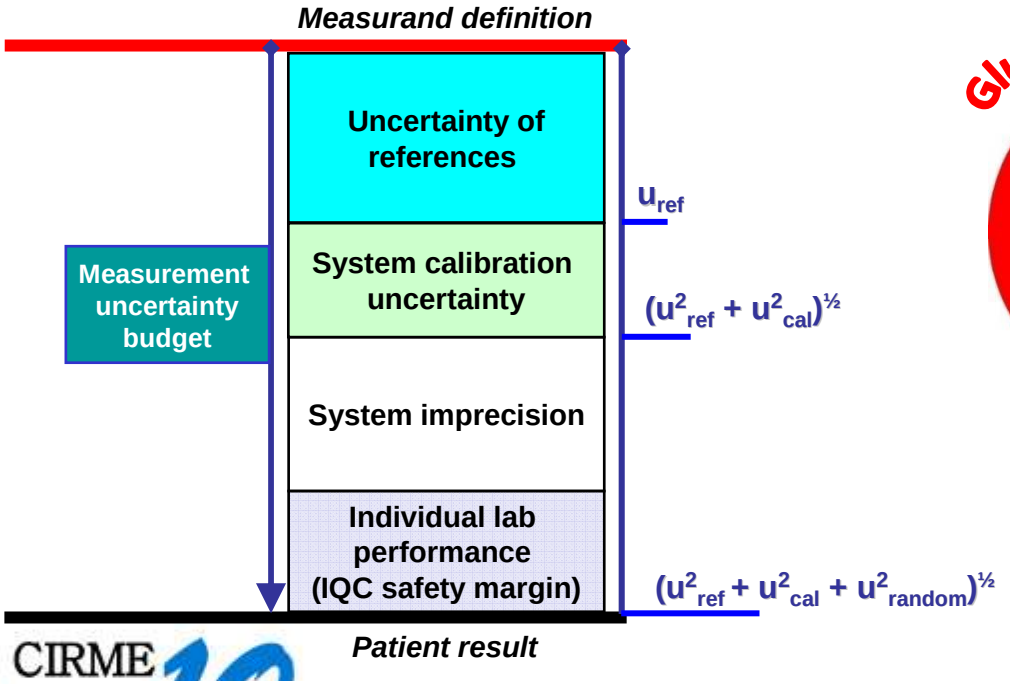
*all JCTLM recognized

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

ALLOWABLE UNCERTAINTY BUDGET FOR PLASMA GLUCOSE

Three main components of uncertainty:

1. *Uncertainty of references* - reference materials, reference procedures;
2. *Uncertainty of commercial system calibrators* - manufacturer 's calibrator values [transfer process];
3. *Uncertainty of random sources* – system imprecision, individual lab performance.



From BV MODEL

4.05% minimum

2.70% desirable

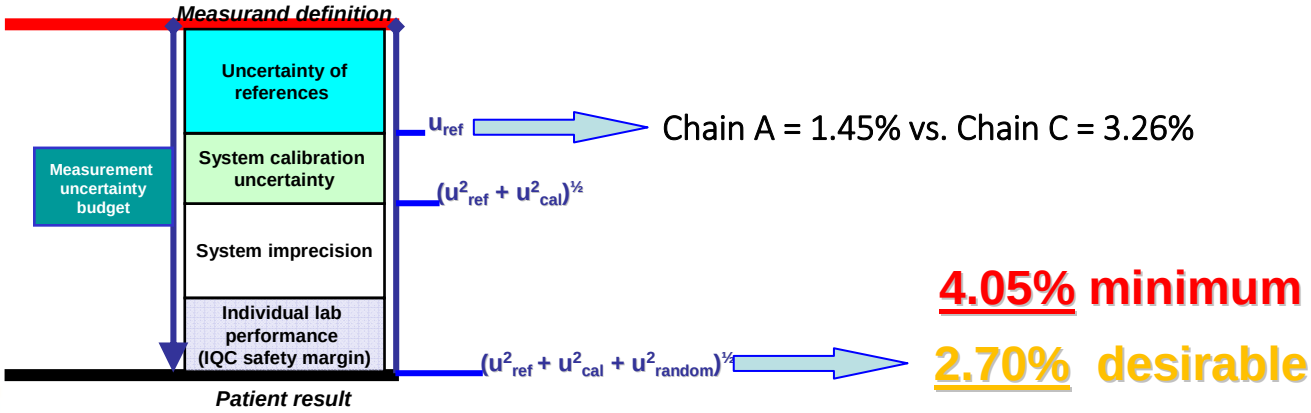
1.35% optimum

MEASUREMENT UNCERTAINTY GOAL
[for unbiased results]

Braga F et al. Clin Chem Lab Med 2015;53:905-12

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]



Chain A = 1.45% vs. Chain C = 3.26%

4.05% minimum

2.70% desirable

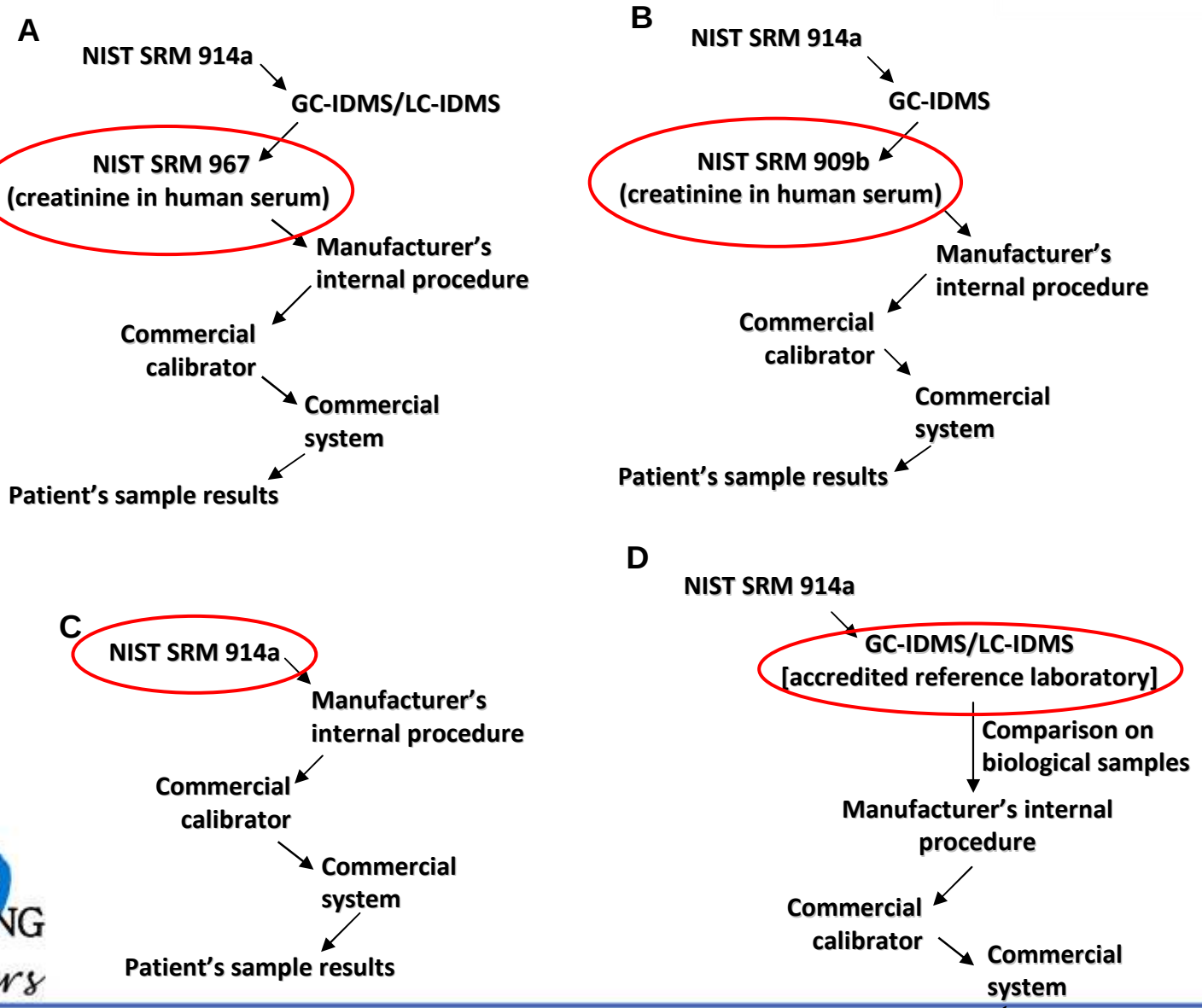
1.35% optimum

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

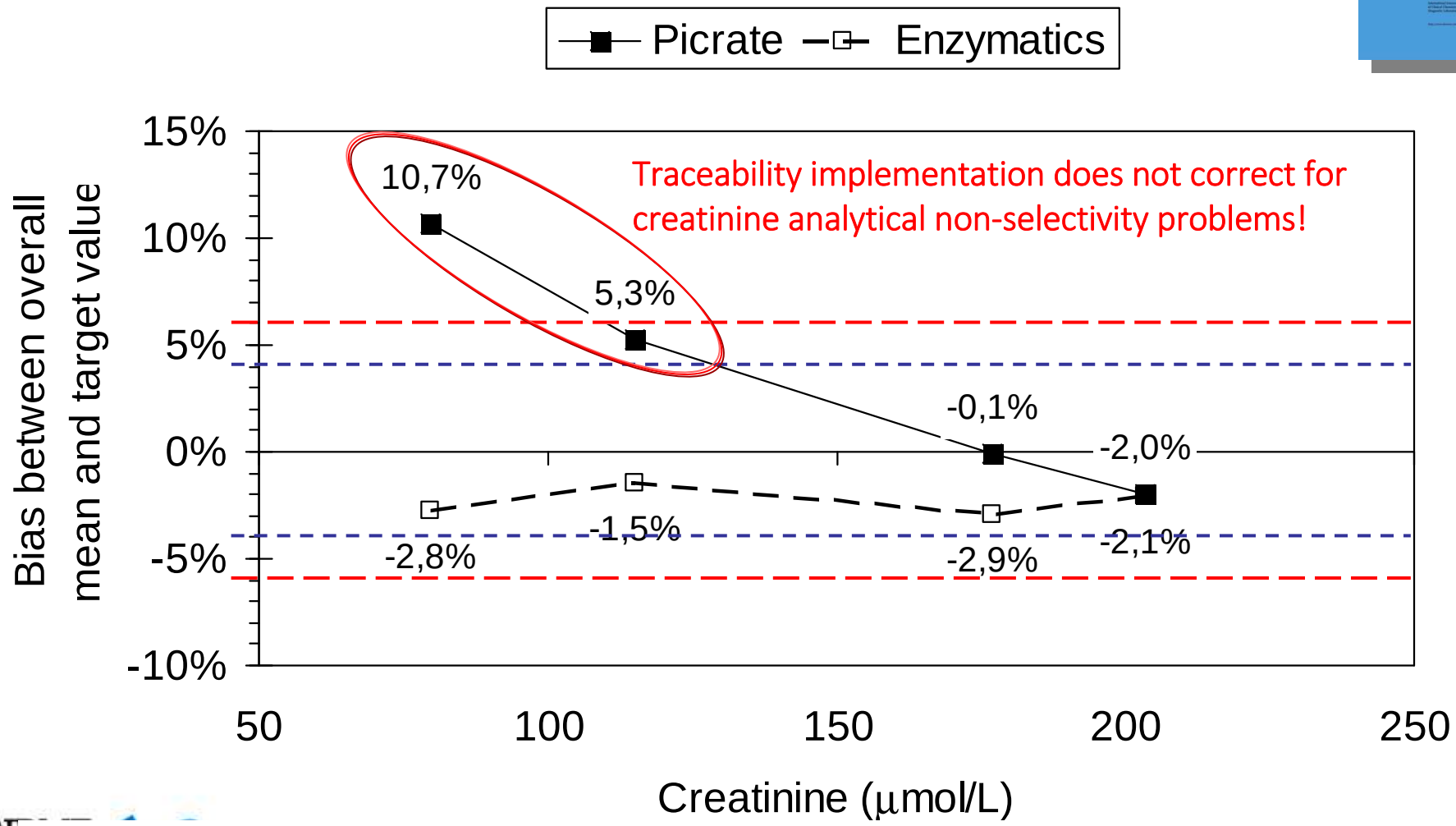
Types of metrological chains that can be used to implement the traceability of blood creatinine results*

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

***All JCTLM recognized**



Carobene A et al., Clin Chim Acta 2014;427:100



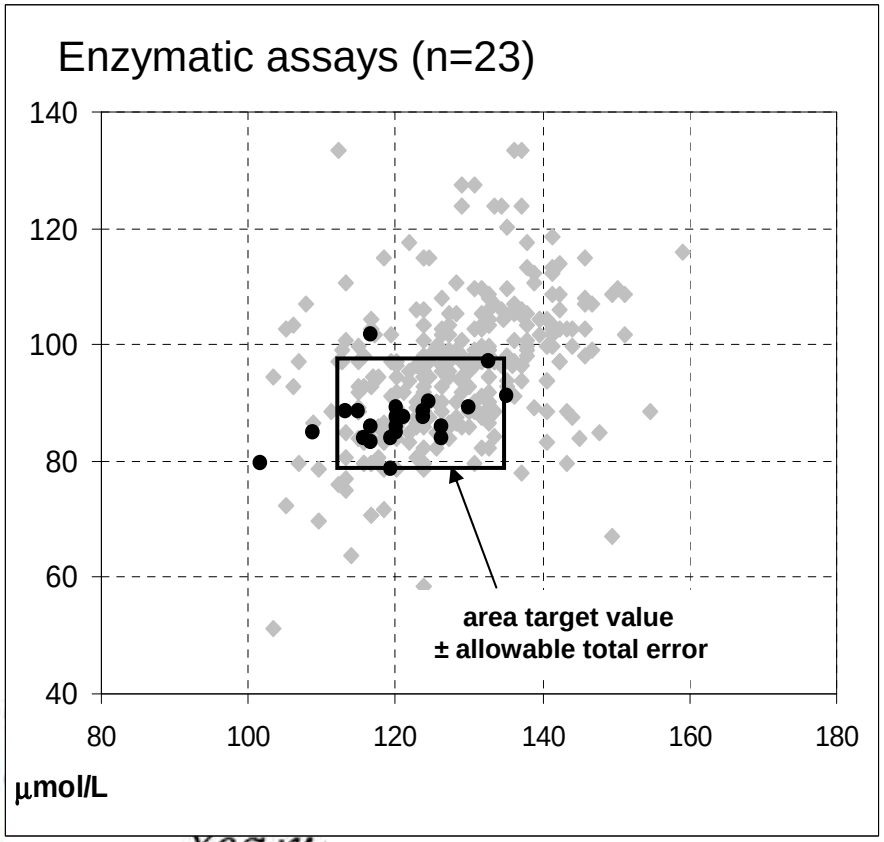
Percent bias of overall means for the two method macro-categories based on different analytic principle in post-standardization years (2010-2011). The dotted and the dashed line indicate the maximum acceptable bias at desirable (±4.0%) and at minimum quality level (±6.0%), respectively.

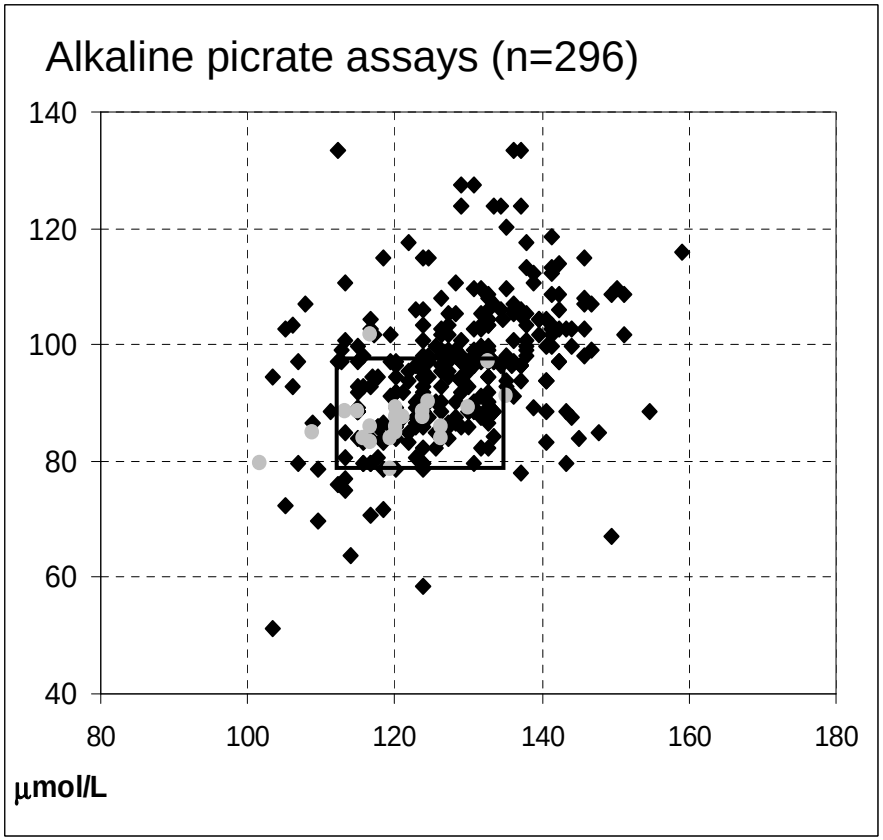
Table 3: Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring serum creatinine marketed by four in vitro diagnostics companies.

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	Enzymatic	Multigent clin chem calibrator	1.48%	IDMS	NIST SRM 967	A	2.12%–2.79%[d]
		ND	Multiconstituent calibrator	2.7%	IDMS	NIST SRM 967	A	2.12%–2.79%[d]
Beckman	AU	Enzymatic	System calibrator	ND	ND	NIST SRM 967	A	2.12%–2.79%[d]
		Alkaline picrate	System calibrator	ND	IDMS	NIST SRM 967	A	2.12%–2.79%[d]
		Uncompensated alkaline picrate	System calibrator	ND	ND	NIST SRM 909b L2	B	1.51%
	Synchron	ND	LX aqua calibrator	ND	IDMS	NIST SRM 914a	D	1.5%[e]
Roche	Cobas c	Enzymatic	C.f.a.s.	0.91%	IDMS	ND	D	1.5%[e]
		Alkaline picrate compensated	C.f.a.s.	1.62%	IDMS	ND	D	1.5%[e]
		Alkaline picrate rate–blanked and compensated	C.f.a.s.	1.42%	IDMS	ND	D	1.5%[e]
	Integra/Cobas c111	Enzymatic	C.f.a.s	1.06%	IDMS	ND	D	1.5%[e]
	Integra400/Cobas c111	Alkaline picrate compensated	C.f.a.s	0.30%	IDMS	ND	D	1.5%[e]
	Integra800	Alkaline picrate compensated	C.f.a.s	0.72%	IDMS	ND	D	1.5%[e]
	Modular	Enzymatic	C.f.a.s	0.91%	IDMS	ND	D	1.5%[e]
		Alkaline picrate compensated	C.f.a.s	1.38%	IDMS	ND	D	1.5%[e]
		Alkaline picrate rate-blanked and compensated	C.f.a.s	0.79%	IDMS	ND	D	1.5%[e]
Siemens	Dimension Vista	Enzymatic	ECREA calibrator A	5.08%[f]	ND	NIST SRM 914a	C	NA
			ECREA calibrator B	3.16%[f]	ND	NIST SRM 914a	C	NA
		Alkaline picrate	Chemistry calibrator	1.6%	GC-IDMS	NIST SRM 914a	D	1.5%[e]
	Advia	Enzymatic	Chemistry calibrator	0.45%	IDMS	NIST SRM 914a NIST SRM 967	A	2.12%–2.79%[d]
		Alkaline picrate rate-blanked and compensated	Chemistry calibrator	1.6%	IDMS	NIST SRM 967	A	2.12%–2.79%[d]

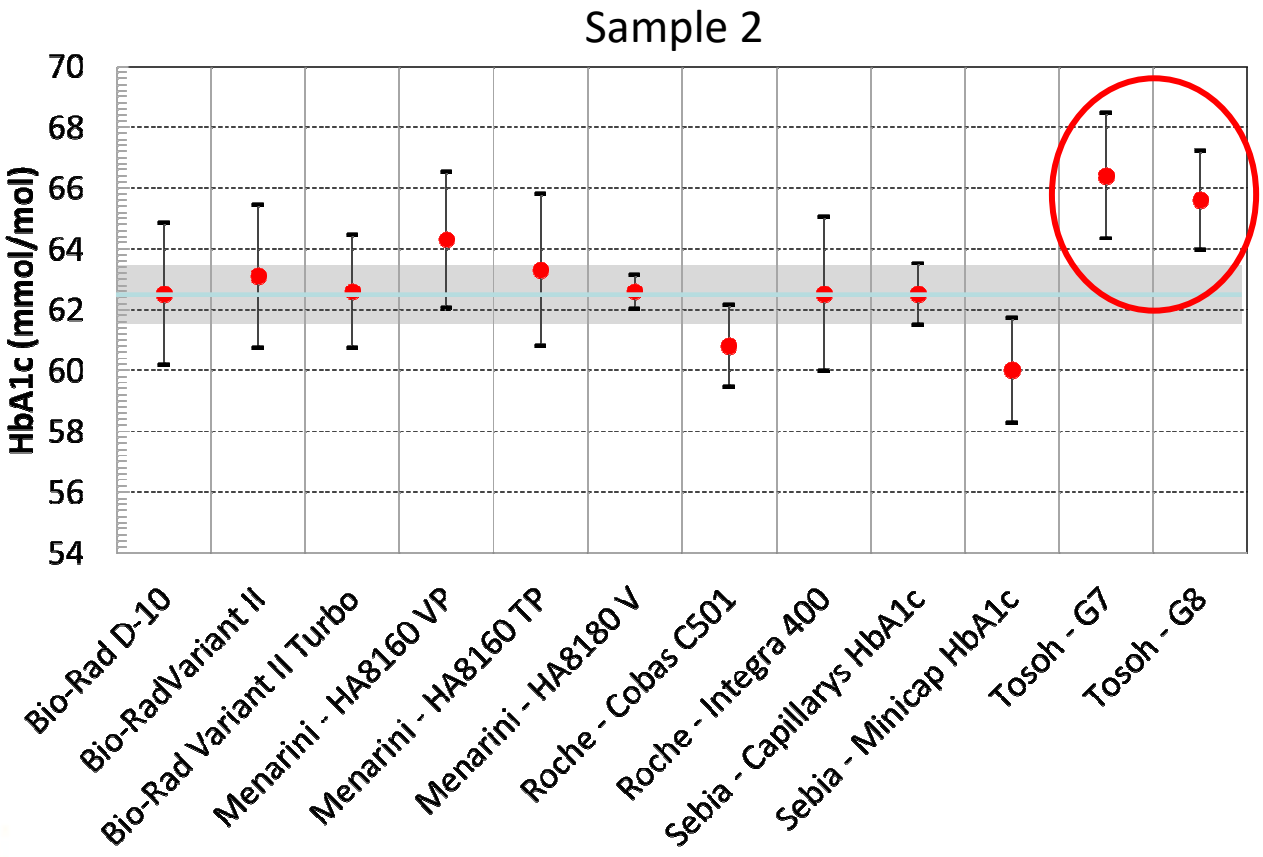
[Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905]

EQAS materials with physiologic (88.4 µmol/L) and borderline (123.8 µmol/L) creatinine concentrations vs. the desirable goal for TE (±8.9%). Notwithstanding the marked difference in size of two groups, it was evident that the vast majority (87%) of laboratories using systems employing enzymatic assays were able to fulfill the desirable performance, while only one third of laboratories using picrate-based systems were able to meet the target.





[Carobene A et al., Clin Chim Acta 2014;427:100]



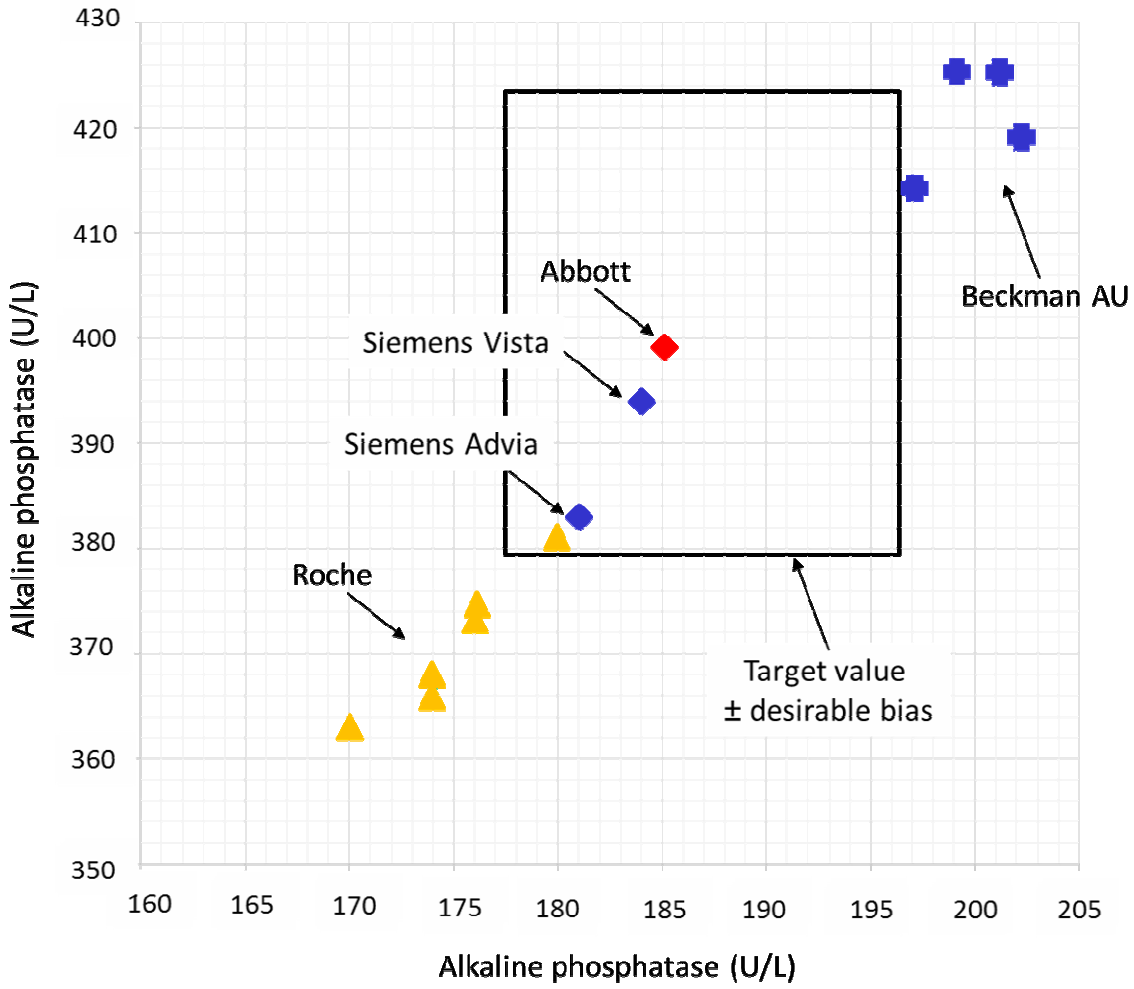
Mosca A et al., Clin Chim Acta 2015;451:305

DE GRUYTER Clin Chem Lab Med 2016; aop

Letter to the Editor

Federica Braga*, Erika Frusciante, Ilenia Infusino, Elena Aloisio, Elena Guerra, Ferruccio Ceriotti and Mauro Panteghini

Evaluation of the trueness of serum alkaline phosphatase measurement in a group of Italian laboratories



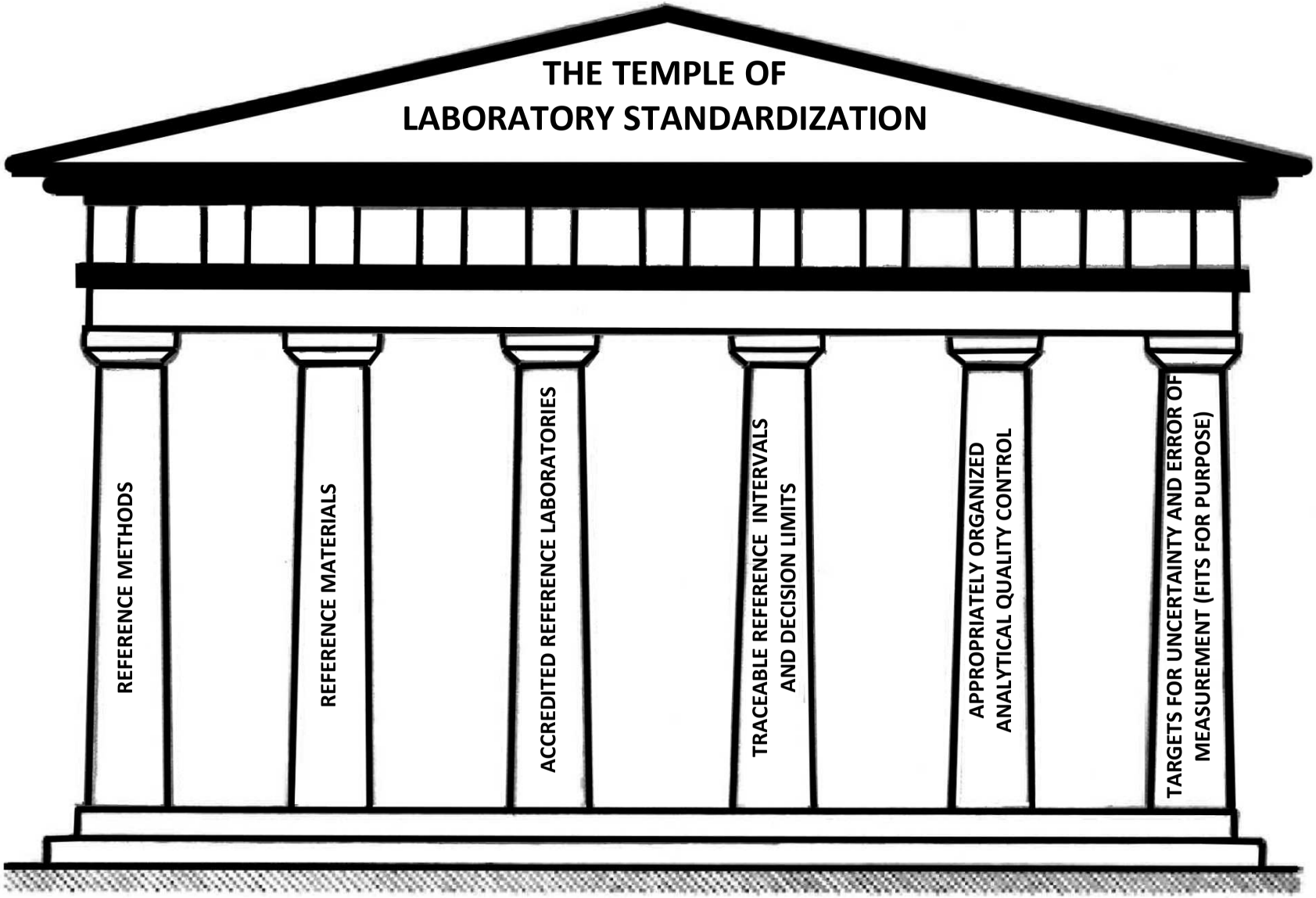
Research Centre for Metrological Traceability in Laboratory Medicine (CIRME) – Educational activities

CIRME organizes international and national conferences on the topic of Traceability and Standardization in Laboratory Medicine and works actively to promote postgraduate specialization courses

CIRME CELEBRATING 10 Years

CIRME CELEBRATING 10 Years

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



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

Lack of proper reference intervals/decision limits may hamper the implementation of standardization

- The implementation of standardization can modify the analyte results
- Without adequate R.I./D.L. this situation can impair the interpretation of the results and, paradoxically, worsen the patient's outcome
- The absence of reliable R.I./D.L. for the newly standardized commercial methods hampers their adoption

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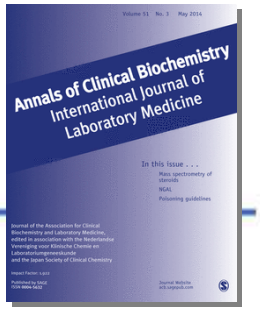
[Adapted from Ceriotti F, Hinzmann R, Panteghini M. Ann Clin Biochem 2009;46:8]



Traceable reference intervals as 4th pillar of the reference measurement system: how a problem becomes a solution

Historically

Method-dependent results

↓

Method-dependent reference intervals

Traceability era

Standardized methods that provide traceable results

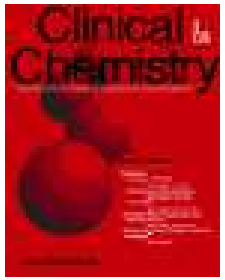
↓

Traceable reference intervals

Infusino I, Schumann G, Ceriotti F, Panteghini M. CCLM 2010;48:301
Ferraro S, Braga F, Panteghini M. CCLM 2016;54:523

Reference Intervals for Serum Creatinine Concentrations: Assessment of Available Data for Global Application

Ferruccio Ceriotti,[1*] James C. Boyd,[2] Gerhard Klein,[3] Joseph Henny,[4] Josep Queraltó,[5] Veli Kairisto,[6] and Mauro Panteghini,[7] on behalf of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL)



Age (gender) group	Percentile value, mg/dL[a]	
	2.5th	97.5th
Cord blood	0.52	0.97
Preterm neonates 0–21 d	0.32	0.98
Term neonates 0–14 d	0.31	0.92
2 m–<1 y	0.16	0.39
1 y–<3 y	0.17	0.35
3 y–<5 y	0.26	0.42
5 y–<7 y	0.29	0.48
7 y–<9 y	0.34	0.55
9 y–<11 y	0.32	0.64
11 y–<13 y	0.42	0.71
13 y–<15 y	0.46	0.81
Adult (males)	0.72	1.18
Adult (females)	0.55	1.02

[a]To express creatinine values in μmol/L, multiply the values by 88.4. d, days; m, months; y, years.

Table 1: Traceable reference intervals for enzymes with established reference measurement systems obtained in European and Asian adults.

Enzyme	European		Asian	
	Females	Males	Females	Males
AST	11–34		14–32	
ALT	8–41	9–59	11–31	14–54
GGT	6–40	12–68	15–43	15–68
LDH	125–220		138–235	
CK	34–145	46–171	40–152	58–261
AMY	31–107		47–136	
ALP	33–98	43–115	40–106	48–131

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

The implementation of standardization in clinical practice needs first the availability of the 3 main pillars:

- Reference measurement procedures
- Reference materials
- Accredited reference laboratories

Then, it needs to define a 4th pillar:

- Traceable reference intervals/decision limits

And, an appropriately organized analytical (internal and external) quality control should become the 5th pillar.

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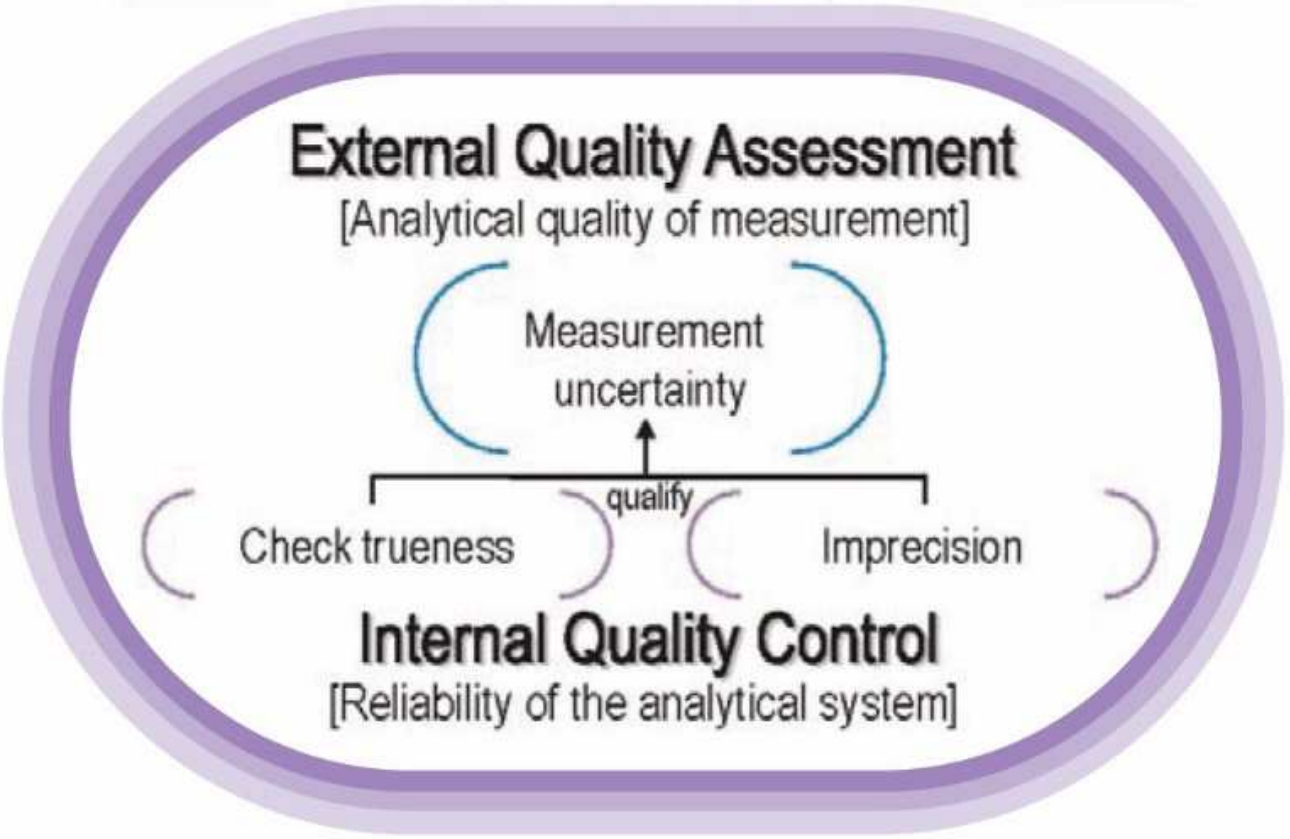

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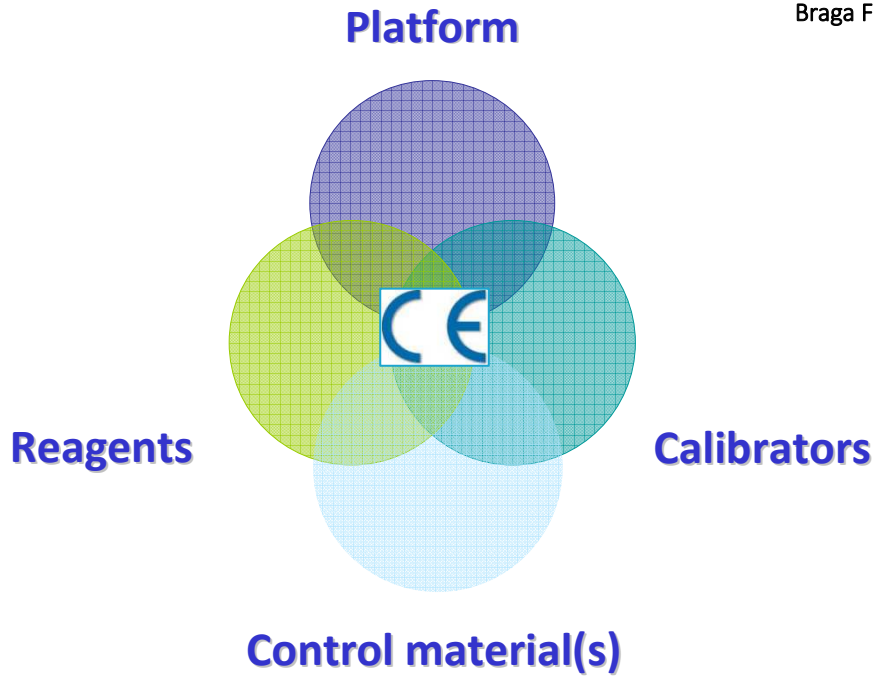
MILANO - *NOVEMBER 30th, 2010*

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

Monitoring the reliability of the analytical system through Internal Quality Control: Component I. Check alignment ("system traceability")

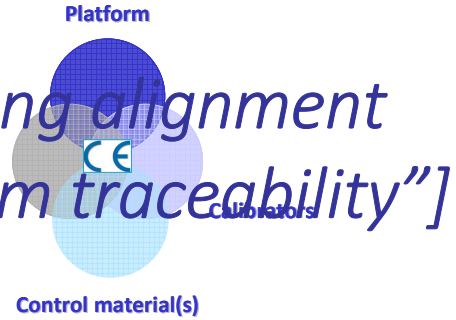
Braga F et al. J Med Biochem 2015;34:282
Braga F et al. Clin Chem Lab Med 2015;53:905



Clinical laboratories must verify the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions, by checking that values of control materials provided by the manufacturer as component of the analytical system are in the established range, with no clinically significant changes in the assumed traceable results.

Internal Quality Control (Component I)

Acceptance/rejection of the analytical run in "real time"



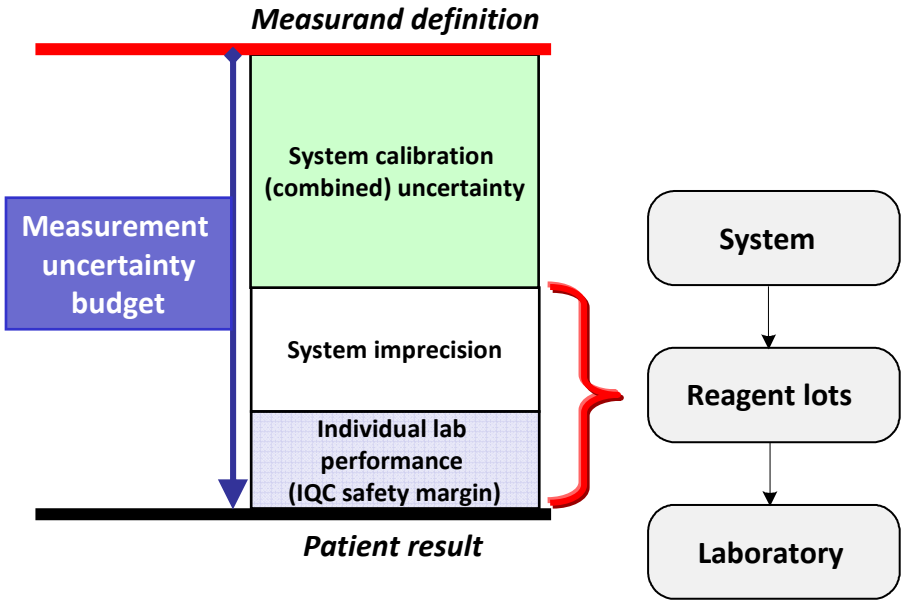
Testing alignment ["system traceability"]

Any "out of control" signal must be made available with sufficient time to allow immediate corrective actions to bring again the situation under control (virtually "unbiased") and before reports related to the samples analyzed in the affected analytical run are issued.

CIR
CEI
Years

Braga F, Panteghini M. Biochim Clin 2015;39:551

Monitoring the reliability of the analytical system through Intrnal Quality Control: Component II. Estimating the measurement uncertainty due to random effects ("imprecision")



Main characteristics for a control material to be used in the IQC component II program in order to derive the uncertainty of the analytical system due to the random effects.

Requirement	Comment
Material from a third-party independent source should be used	Material must be different from the system control material used for checking alignment (IQC component I)
Material should closely resemble authentic patient samples (fulfil commutability) (e.g., fresh-frozen pool)	Commercial non-commutable controls may provide a different impression of imprecision performance
Material concentration levels should be appropriate for the clinical application of the analyte measurement	When clinical decision cut-points are employed for a given analyte, materials around these concentrations should preferentially be selected

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Braga F et al. J Med Biochem 2015;34:282
Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905

6th pillar

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).

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

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

				Evaluation capability				
				Accuracy				
				Individual laboratory				
	Sample characteristics				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.

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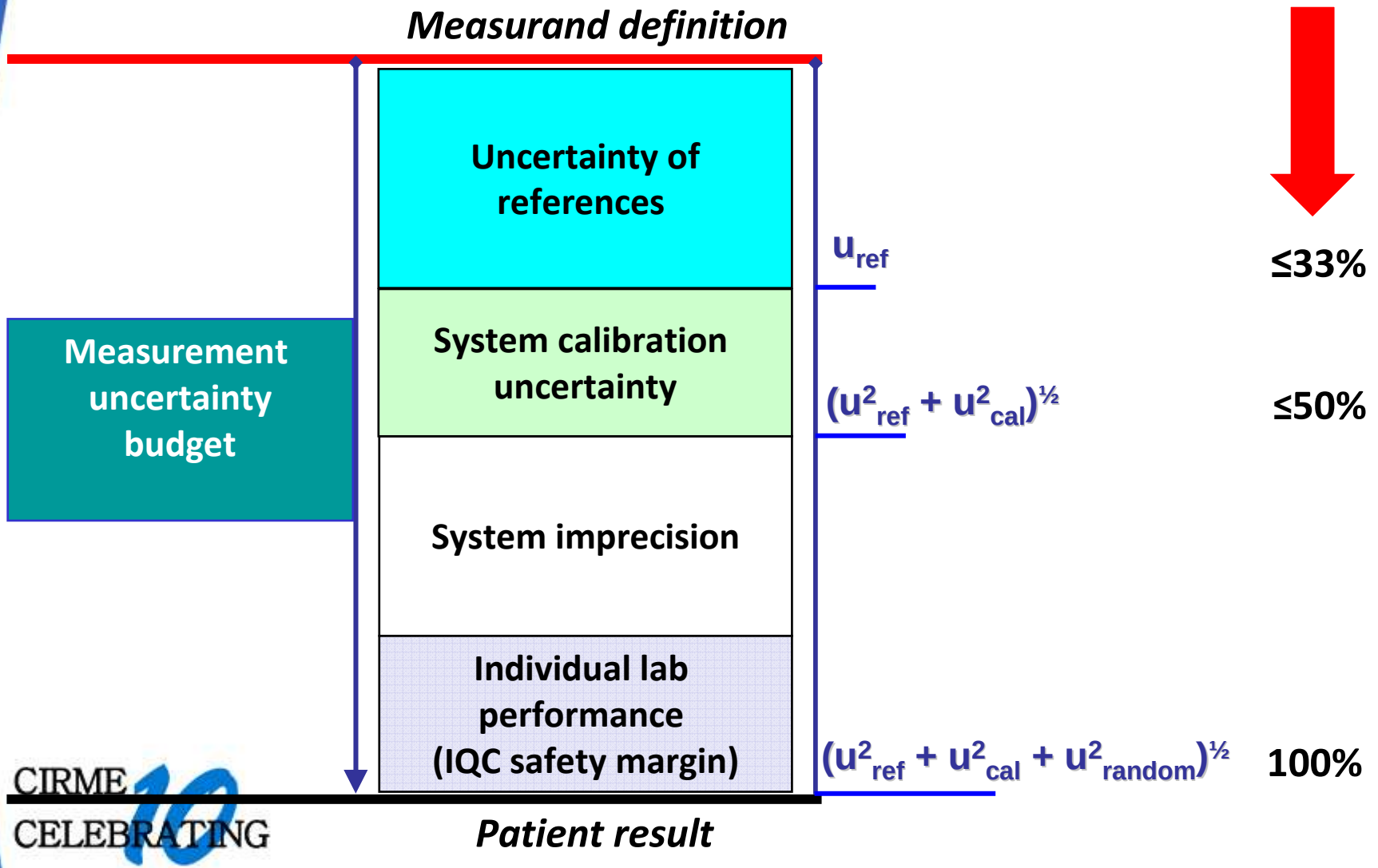
Recommended limits for combined uncertainty budget (expressed as percentage of total budget goal) in traceability implementation



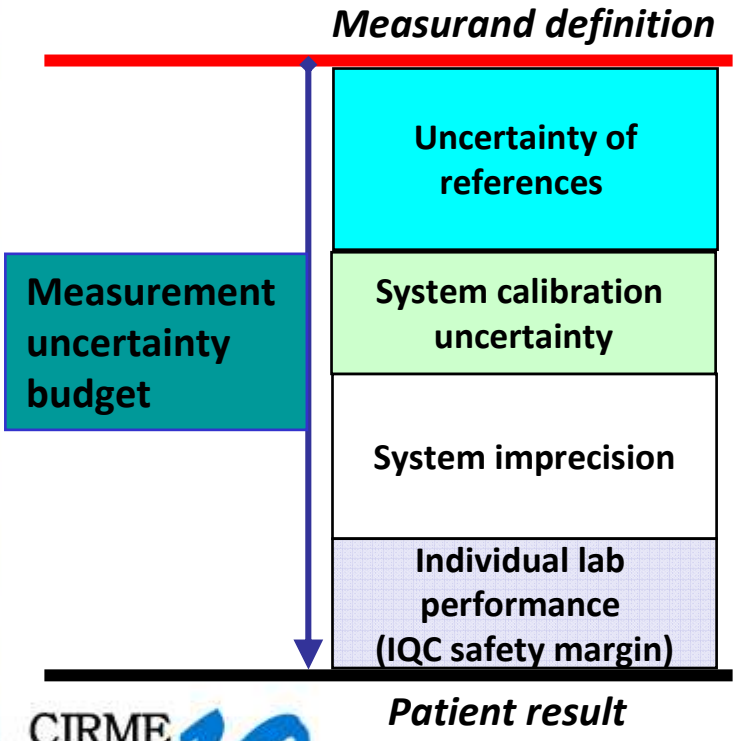
[Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905]

This approach should be applied to every analyte measured in the clinical laboratory in order to establish if the current status of the uncertainty budget of its measurement associated with the proposed metrological traceability chain is suitable for clinical application of the test.

[Panteghini M, Clin Chem Lab Med 2012;50:1237]

Turning the problem upside down
Focus first on the field assays

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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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 three most highly cited CIRME papers

The Scandinavian Journal of Clinical & Laboratory Investigation,
Vol. 68, No. S241, June 2008, 84–88

ORIGINAL ARTICLE

Enzymatic assays for creatinine: Time for action

Mauro Panteghini*

Centre for Metrological Traceability in Laboratory Medicine (CIRME)
University of Milan, Milan, Italy

Available online at www.sciencedirect.com
ScienceDirect
Clinical Biochemistry 42 (2009) 236–240
CLINICAL BIOCHEMISTRY

Traceability as a unique tool to improve standardization in laboratory medicine

Mauro Panteghini *

Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

REVIEWS **RASSEGNE**

biochimica clinica, 2007, vol. **31**, n. 4 247

Traceability, reference systems and result comparability

Mauro Panteghini
Centro per la Riferibilità Metrologica in Medicina di Laboratorio (CIRME), Università di Milano

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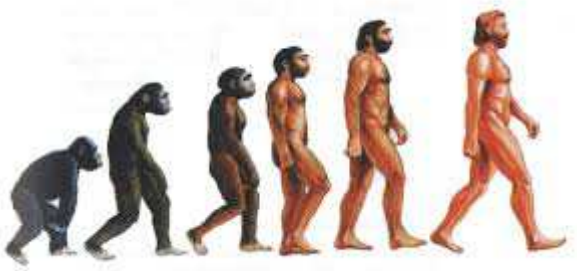
Clin Chem Lab Med 2001; 39(9):795–800 © 2001 by Walter de Gruyter · Berlin · New York

Opinion Paper

Establishing a Reference System in Clinical Enzymology

Mauro Panteghini[1], Ferruccio Ceriotti[2], Gerhard Schumann[3] and Lothar Siekmann[4]



Mini-Review

Clin Biochem Rev Vol 28 November 2007 | 155

Traceability in Clinical Enzymology

Ilenia Infusino, Roberto Bonora, *Mauro Panteghini
Enzyme Reference Laboratory, Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, 20157 Milano, Italy

Clin Chem Lab Med 2010;48(3):301–307 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.075

Minireview

Standardization in clinical enzymology: a challenge for the theory of metrological traceability

Ilenia Infusino[1], Gerhard Schumann[2], Ferruccio Ceriotti[3] and Mauro Panteghini[1,*]

[1] Enzyme Reference Laboratory, Center for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

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Clin Chem Lab Med 2016; ao

Mini Review

Ilenia Infusino*, Erika Frusciante, Federica Braga and Mauro Panteghini

Progress and impact of enzyme measurement standardization

DE GRUYTER Clin Chem Lab Med 2016; 54(1): 7–15

Review

Federica Braga*, Sara Pasqualetti, Simona Ferraro and Mauro Panteghini

Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis

Hematopathology / sTfR and sTfR/log Ferritin Index in Diagnosis of Iron-Deficiency Anemia

Review

Serum human epididymis protein 4 vs carbohydrate antigen 125 for ovarian cancer diagnosis: a systematic review

Simona Ferraro,[1] Federica Braga,[1] Monica Lanzoni,[2,3] Patrizia Boracchi,[2,3] Elia Mario Biganzoli,[2,3] Mauro Panteghini[1]

J Clin Pathol 2013;66:273.

Soluble Transferrin Receptor (sTfR) and sTfR/log Ferritin Index for the Diagnosis of Iron-Deficiency Anemia

A Meta-Analysis

Ilenia Infusino,[1,2] Federica Braga,[1,2] Alberto Dolci, MD,[2] and Mauro Panteghini, MD,[1,2]

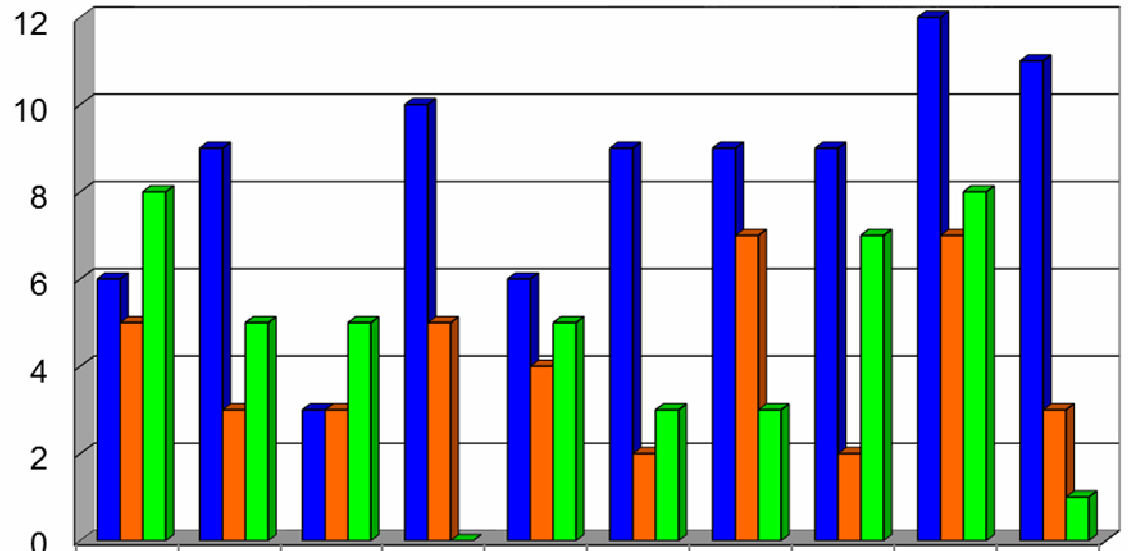
DE GRUYTER DOI 10.1515/cclm-2013-0738 — Clin Chem Lab Med 2014; 52(6): 767–777

Review

Simona Ferraro*, Roberta Mozzi and Mauro Panteghini

Tracing a roadmap for vitamin B_{12} testing using the health technology assessment approach

CIRME publications



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
PubMed	6	9	3	10	6	9	9	9	12	11
Altre	5	3	3	5	4	2	7	2	7	3
Abstracts	8	5	5	0	5	3	3	7	8	1

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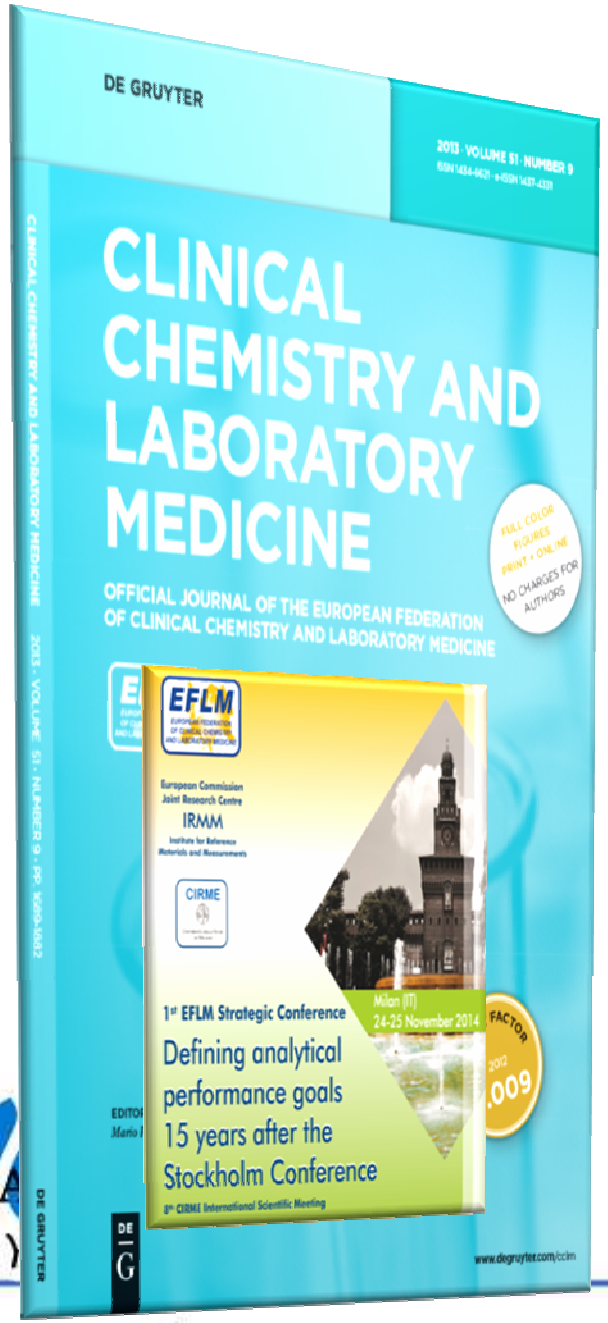

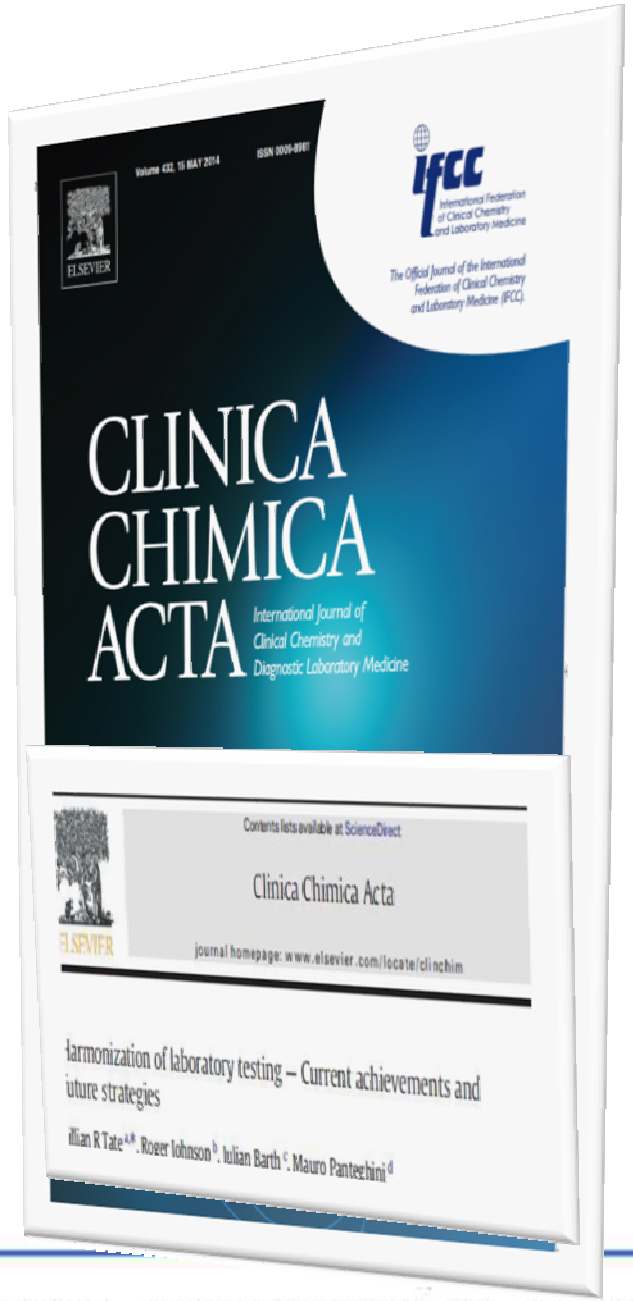

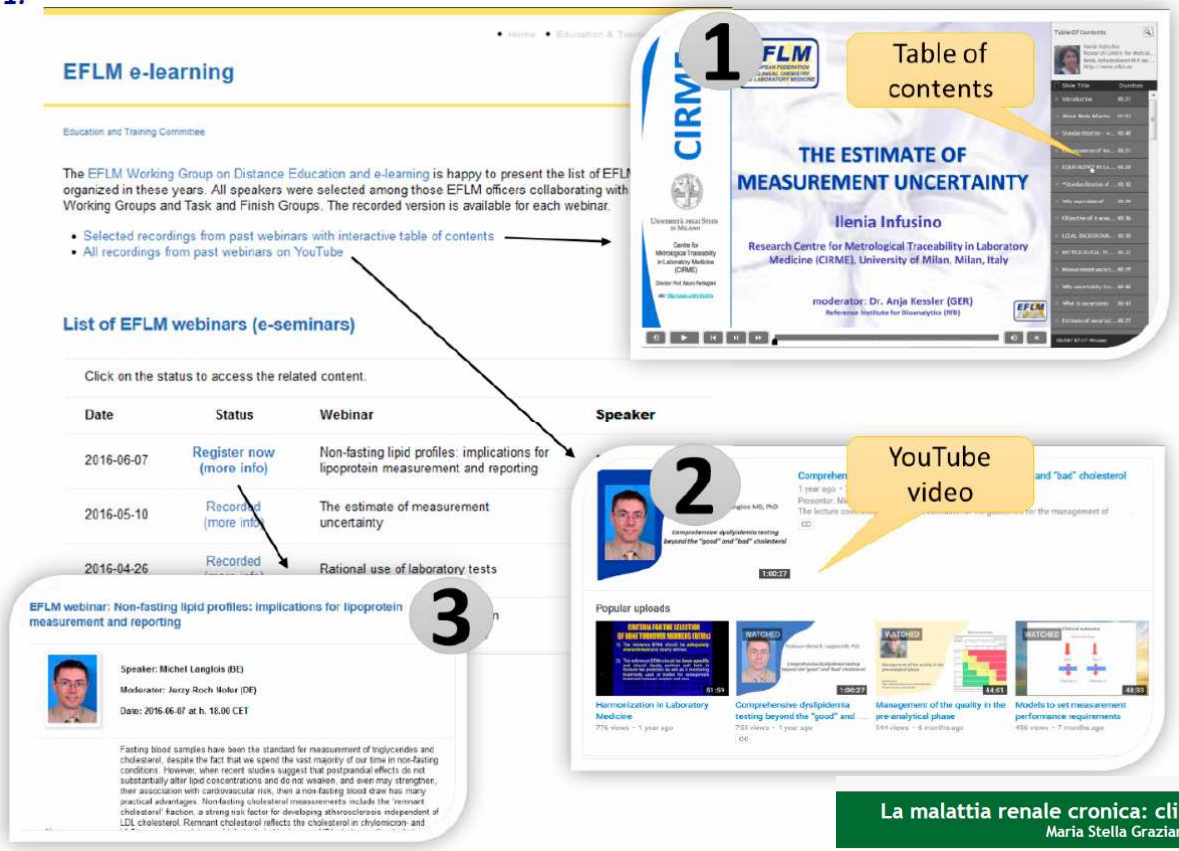

La malattia renale cronica: clinica e laboratorio
Maria Stella Graziani

Standardizzazione della misura della creatinina: risultati e problemi ancora aperti

Federica Braga
Centro di Ricerca per la Riferibilità Metrologica in Medicina di Laboratorio (CIRME), Università degli Studi, Milano

PROGETTO FORMATIVO SIBioC

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ISO normative standards related to metrological traceability of IVD MD

[ISO/TC 212 Working Group 2, Reference systems]

- IVD MD — Mea **Revised version under development** ical traceability of values assigned
- IVD MD — Measurement of quantities in biological samples — Metrological traceability of values for cata **To be incorporated into revised 17511** control materials (ISO 18153:20

- IVD MD — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures (ISO 15193:2009, 2nd ed.)
- IVD MD — Measurement of quantities in samples of biological origin — Requirements for certified reference materials and the content of supporting documentation (ISO 15194:2009, 2nd ed.)
- Laboratory medicine - Requirements for reference measurement laboratories (ISO 15195:2003)

- ISO/NP 20914 — Medical laboratories – Practical guide for the estimation of measurement uncertainty
- ISO/NP 21151 — IVD MD -- Measurement of quantities in samples of biological origin -- Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to product (end user) calibrators and patient samples

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