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Centre for  
Metrological Traceability  
in Laboratory Medicine  
(CIRME)

Director: Prof. Mauro Panteghini

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



## Global harmonization in laboratory medicine

*Mauro Panteghini*

# Drivers for global harmonization in laboratory medicine

- Patient safety, empowerment and public confusion
- Clinical governance and guidelines
- Laboratory accreditation, consolidation and networking
- Advances in IT and electronic health records

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Adapted from Plebani M, Clin Chem Lab Med 2013;51:741  
and Tate J et al., Clin Chim Acta 2014;432:4

# Clinical-laboratory interface



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# Lab-related causes of diagnostic error

- Inappropriate test ordered (20%)
- Appropriate test not ordered (45%)
- Appropriate test result inaccurate
- Appropriate test result not used properly
  - Knowledge deficit
  - Failure of synthesis (no results integration)
  - Misleading result (unaware of test limitations)
- Appropriate test result delayed/missed

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Adapted from Epner PL et al. BMJ Qual Saf 2013;22:ii6  
and Zhi M et al. PLoS ONE 2013;8:e78962.



Promoting clinical and laboratory interaction by harmonization

Mario Plebani <sup>a,\*</sup>, Mauro Panteghini <sup>b</sup>

## Harmonization at the clinical-laboratory interface

### Harmonization of test demand (pre-pre-analytical phase)

- Practice guidelines and their local implementation
- Common laboratory test profiles
- Periodicity of (re)testing
- Reflex testing and algorithms
- Policy of introducing new tests and discontinuing obsolete tests

### Harmonization of result interpretation (post-post-analytical phase)

- Information on quality of laboratory tests
- Traceable reference intervals and decision thresholds
- Critical value definition and communication
- Interpretative comments: when and how to interpret

*Harmonization of consultant advisory services (both on demand and interpretation)*

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# NHS Atlas of Diagnostic Variation

- Large variations in clinician requesting that cannot easily be explained by differences in disease prevalence



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# Annual rate of use for CA125

From 0.11 to 9.0 per 1000 practice population

→ 80-fold variation

or

(after excluding 5 outliers)

from 0.92 to 8.4

→ **9-fold variation**

Contributory factors?

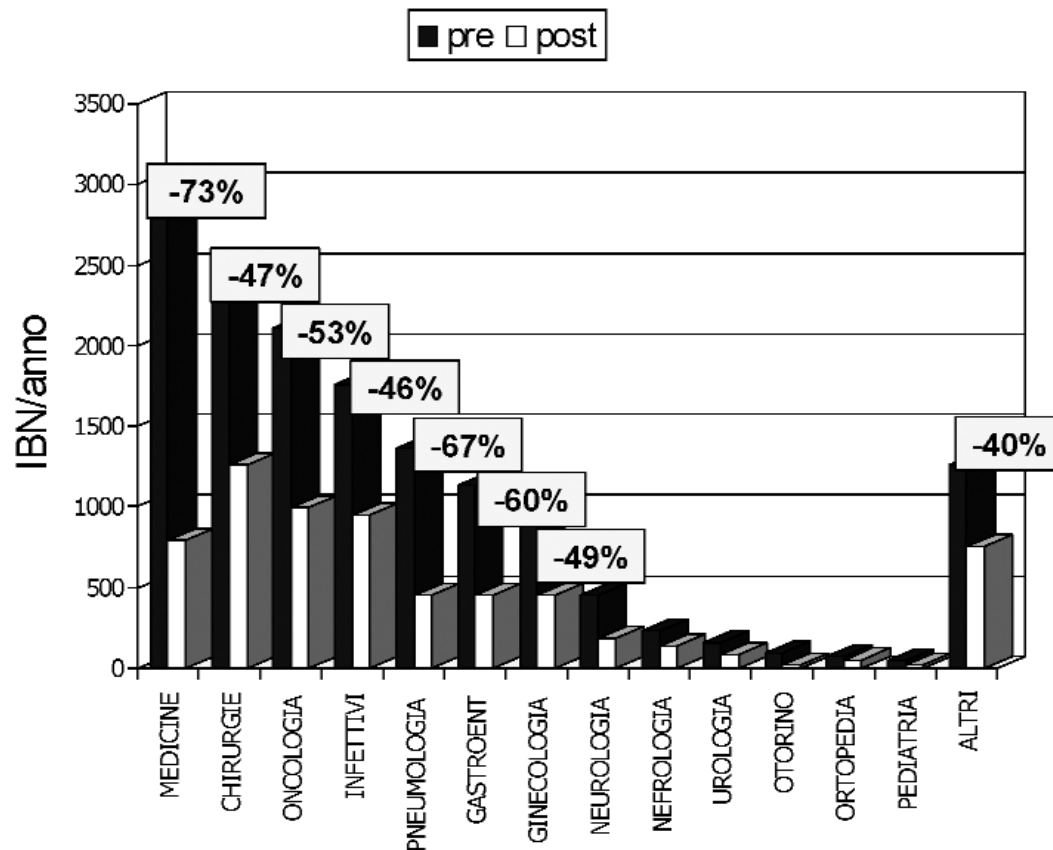
- Differences in professional practice
- Differences in uptake of innovation post-NICE guidelines

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Implementing practice guidelines on correct use of tumor marker largely decrease the number of ordered tests and reagent costs, without any impact on marker clinical role



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**Ospedale Luigi Sacco**  
AZIENDA OSPEDALIERA - POLO UNIVERSITARIO

# Removal from the test menu of obsolete and useless tests

- Removing tests that offer little incremental information would save money, avoid additional investigations arising from incidental and clinically irrelevant abnormalities, and improve the risk to benefit ratio.

Plebani M & Panteghini M, Clin Chim Acta 2014;432:15

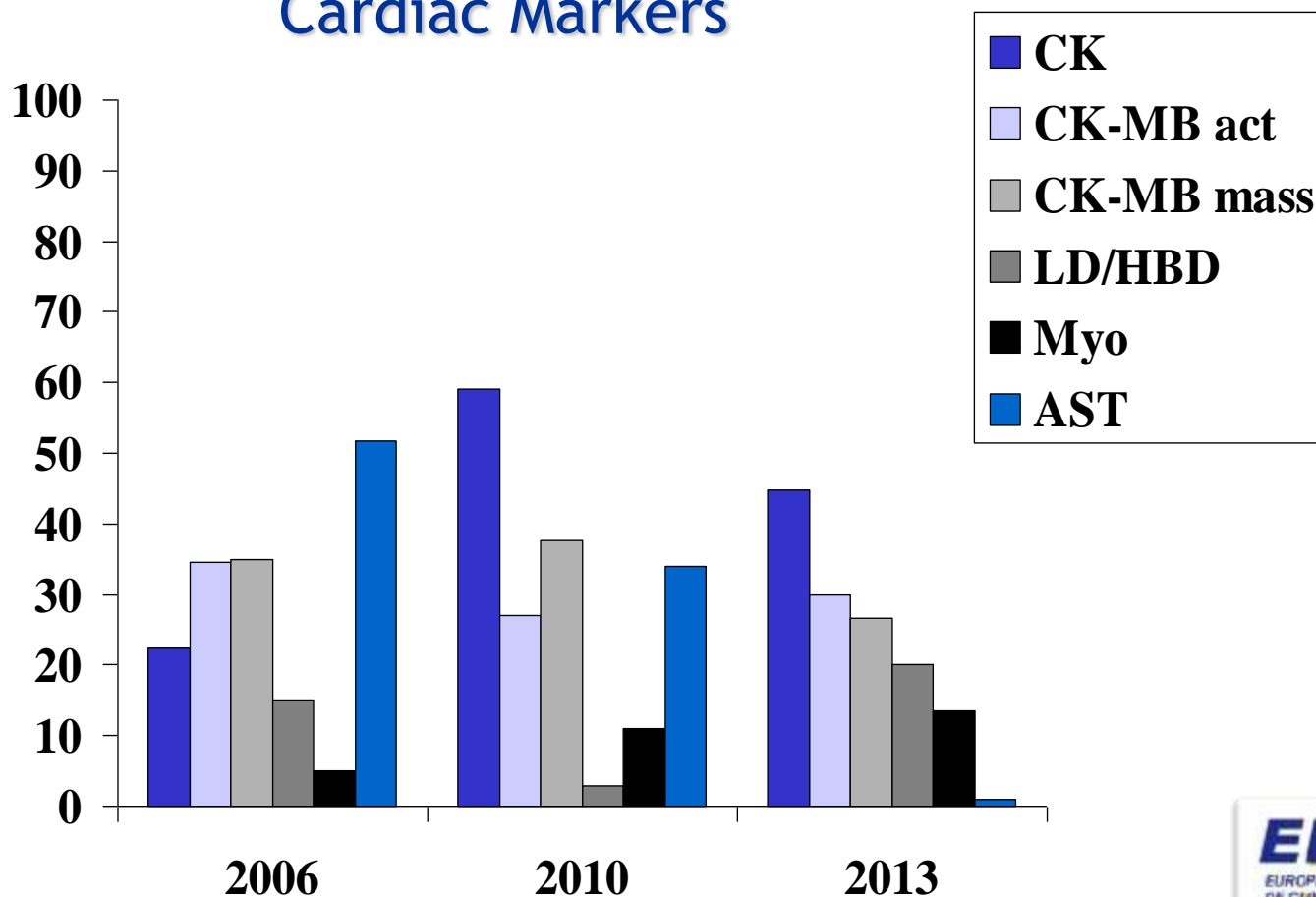
- For instance, deleting myoglobin, total creatine kinase (CK) and CK MB isoenzyme determinations from laboratory order forms in patients admitted to ED leads to significant cost saving and reduces possible confusion in data interpretation and patient management → Overall testing costs were reduced by € 104,871 per annum.

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# Markers still used for the diagnosis of AMI in addition to troponin

The Cardiac Marker Guideline Uptake in  
Europe (CARMAGUE) Study of the EFLM WG  
Cardiac Markers



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# The "famous pairs" in Laboratory Medicine

- Serum creatinine and urea
- ESR and C-reactive protein
- AST and ALT
- Amylase and lipase
- PT and aPTT
- fT3 and fT4
- Ferritin and transferrin saturation



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# Periodicity of (re)testing: How often should tests be requested

- As often as necessary (very small group)
- Once in a lifetime (genetic test for hereditary disorders)
- Never ordered on inpatients (lipoproteins as CV risk factors)
- Never ordered again once a positive result has been obtained (TPPA)
- Not ordered more frequently than daily or longer (C-reactive protein)
- Not ordered more frequently than monthly (HB/HCV Abs)
- Not ordered more frequently than every 3 months (HbA1c)
- Ordered no more frequently than annually (renal function in diabetics)
- C • Never be ordered (vitamin D screening)



**The Association for  
Clinical Biochemistry &  
Laboratory Medicine**



The Royal College of Pathologists  
Pathology: the science behind the cure

## **National Minimum Re-testing Interval Project:**

A final report detailing consensus recommendations for  
minimum re-testing intervals for use in Clinical Biochemistry

**Prepared for the Clinical Practice Group of the  
Association for Clinical Biochemistry and Laboratory Medicine and  
supported by the Royal College of Pathologists.**

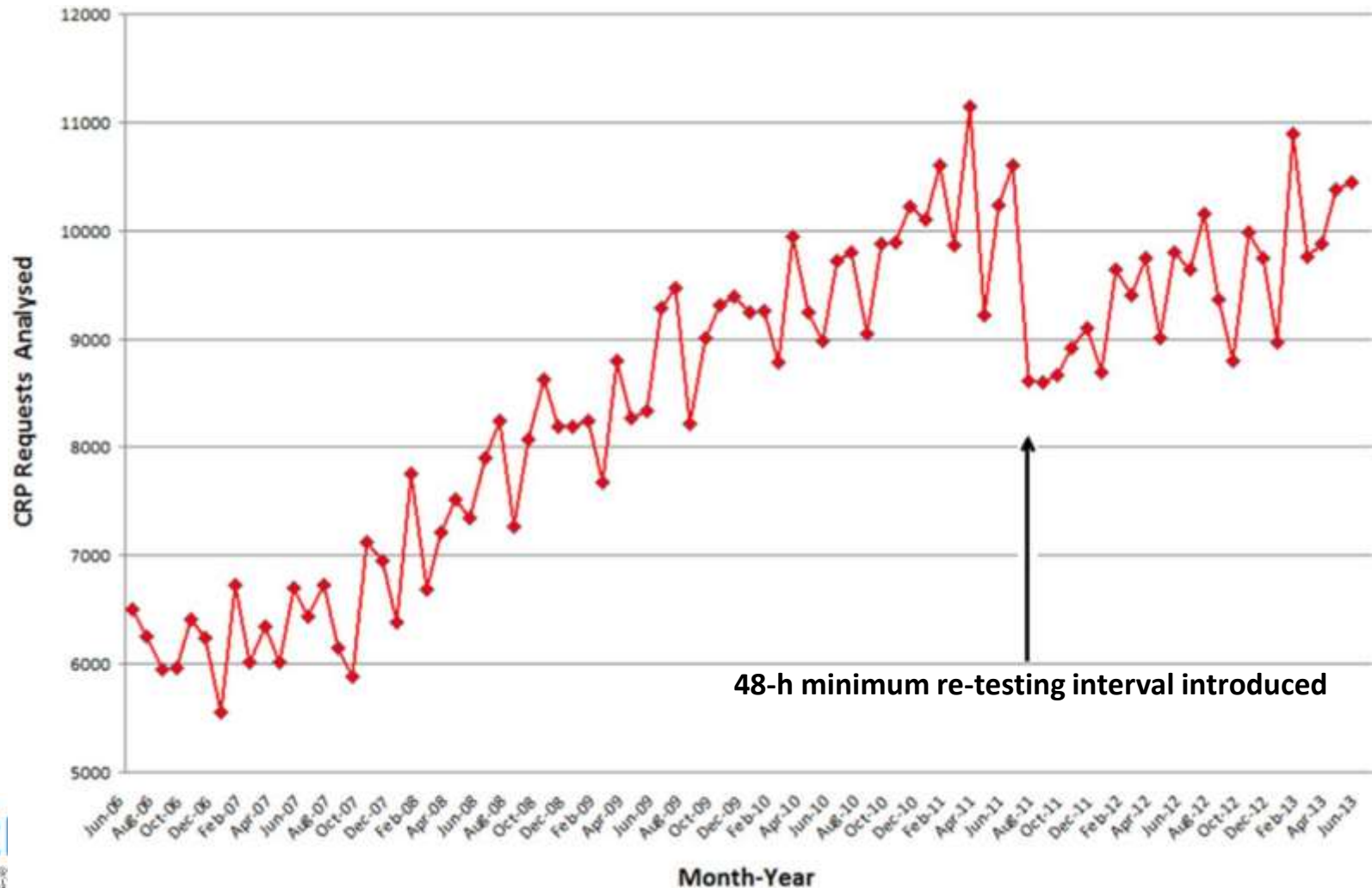
**Report Author: Dr Tim Lang – Project Lead**

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# C-reactive protein requests analysed for June 2006-June 2013



48-h minimum re-testing interval introduced

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## Original papers

### Low level of adherence to instructions for 24-hour urine collection among hospital outpatients

Marijana Miler\*, Ana-Maria Šimundić

University Department of Chemistry, Medical School University Hospital Sestre Milosrdnice, Zagreb, Croatia

Biochemia Medica 2013;23(3):316–20

- Patients are unaware of importance of proper collection of urine specimen and how this may affect test results



## Original papers

### Are patients well informed about the fasting requirements for laboratory blood testing?

Sanja Kackov<sup>1\*</sup>, Ana-Maria Simundić<sup>2</sup>, Ani Gatti-Drnić<sup>3</sup>

<sup>1</sup>Medical biochemistry laboratory, Polyclinic Bonifarm, Zagreb, Croatia

<sup>2</sup>University Department of Chemistry, Medical School University Hospital Sestre Milosrdnice, Zagreb, Croatia

<sup>3</sup>Medical biochemistry laboratory, Public Health Centre Zagreb-Centar, Zagreb, Croatia

Biochemia Medica 2013;23(3):326–31

- A substantial proportion of patients do not come properly prepared for lab testing and are not well informed about the fasting requirements

## Standardization of collection requirements for fasting samples For the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)

A.M. Simundic<sup>a,b,\*</sup>, M. Cornes<sup>b,c</sup>, K. Grankvist<sup>b,d</sup>, G. Lippi<sup>b,e</sup>, M. Nybo<sup>b,f</sup>

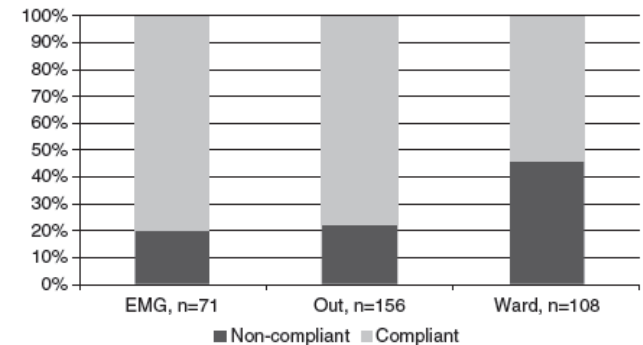
1. Existing guidelines for phlebotomy need revision. Revised recommendations should include the exact definition of requirements for patient preparation for laboratory testing. Blood for all blood tests should be drawn preferably in the morning from 7 to 9 a.m. [30]. Fasting should last for 12 h, during which water consumption is permitted. Alcohol should be avoided for 24 h before blood sampling. In the morning before blood sampling, patients should refrain from cigarette smoking and caffeine containing drinks (tea, coffee, etc.).
2. Professional associations (IFCC, EFLM and other) should support harmonization efforts by disseminating standardized recommendations for fasting.
3. Laboratories worldwide should implement standardized procedures for blood sampling and patient preparation.
4. Laboratories should have policies for sample acceptance criteria related to fasting samples. Blood samples for routine testing should not be taken if a patient has not been appropriately prepared for sample collection. 'No sample is better than a bad sample' should always be the leading principle.

# CLSI GP33-A Accuracy in Patient and Sample Identification

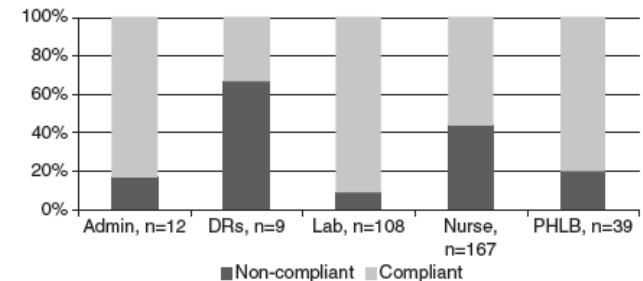
- to minimize the error risk:
  - generate labels at the time and site of collection
  - label the sample in the presence of the patient

An observational study by the EFLM Working Group for the preanalytical phase (WG-PRE)

**Question:** Were the tubes labelled in the presence of the patient?



**Figure 7** The level of compliance (for Q26) with recommended tube labelling procedure between different types of patient settings. EMG, emergency department; OUT, outpatient department; WARD, clinical wards.



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# Reasons for Rejecting Chemistry and Hematology Specimens

## ➤ CAP Q-Probe 95-02, Chemistry Specimen Acceptability (n=461 labs)

- 60% Hemolyzed
- 11% Insufficient quantity
- 7% Inadequately labeled
- 3.5% Improper collection tube
- 2% Clotted

## ➤ CAP Q-Probe 92-05, Hematology Specimen Acceptability (n=604 labs)

- 65% Clotted
- 10% Insufficient quantity
- 5% Unacceptable variance (delta check)
- 5% Inadequately labeled
- 2% Platelet clumps
- 2% Hemolyzed

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# Evidence Review

## Straight Needle Venipuncture vs. IV Catheter Starts

### Conclusions and Recommendations



	Straight Needle Venipuncture vs. IV Catheter Start
<b><i>Strength of evidence rating</i></b>	<b>High:</b> A sufficient number of well-designed and well conducted studies with substantial effect size are available. These studies provide consistent evidence of improvement with respect to rates of hemolysis and associated healthcare problems as a result of this practice.
<b><i>LMBP Recommendation Statement</i></b>	Straight needle venipuncture must replace the use of intravenous catheters as the primary method of collecting blood samples in the Emergency Department in order to significantly reduce rates of hemolysis.

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Clinical Biochemistry 2012; 45:1012-32

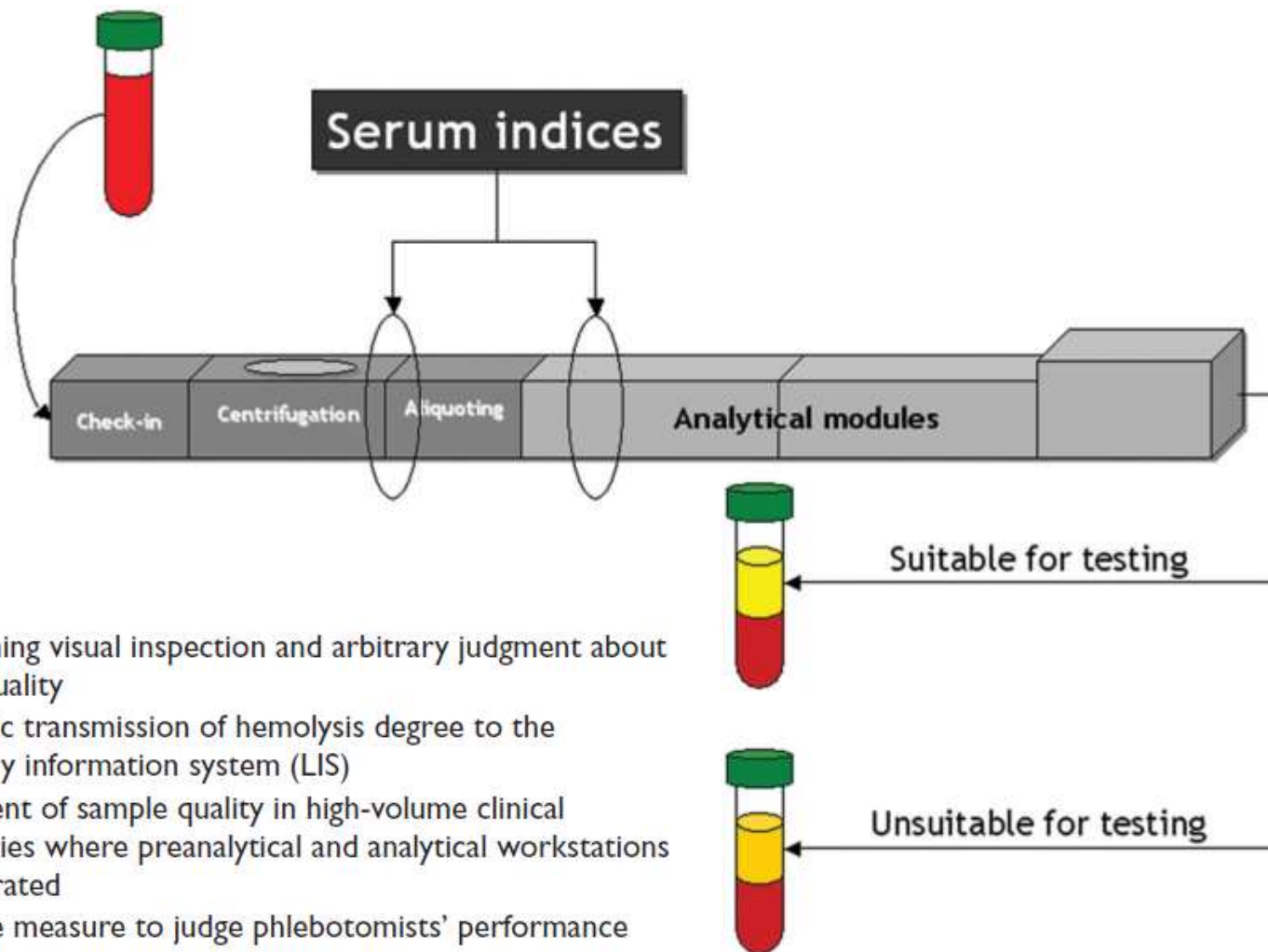
**LABORATORY MEDICINE** *Best Practices*



Visual handling of hemolyzed samples increases the risk of reporting inaccurate results for cTnT, K and bilirubin, possibly affecting the clinical decision and patient outcome.

Occurrence probability ↑	Severity of harm →				
	S1	S2	S3	S4	S5 Life-threatening
	O5				cTnT
	O4	AST, LDH		Bilirubin	K
	O3				
	O2	ALT	Ca, Cl	CRP, Na, Creat	
	O1	ALP, GGT	P, Mg, PROT	Lact, LIP, ALB, CK	Glucose

ISO14971:2012 Medical devices: application of risk management to medical devices.



#### Advantages

- Overcoming visual inspection and arbitrary judgment about sample quality
- Automatic transmission of hemolysis degree to the laboratory information system (LIS)
- Assessment of sample quality in high-volume clinical laboratories where preanalytical and analytical workstations are integrated
- Surrogate measure to judge phlebotomists' performance

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Giuseppe Lippi & Mario Plebani  
Journal of Laboratory Automation 2012;18:184-188



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Pilar Fernandez, María Antonia Llopis, Carmen Perich\*, Maria Jesús Alsina, Virtudes Alvarez, Carmen Biosca, Gloria Busquets, Maria Vicenta Domenech, Rubén Gómez, Isabel Llovet, Joana Minchinela, Rosa Pastor, Rosa Ruiz, Ester Tarrés, Mercè Ibarz, Margarita Simón and Mercè Montesinos

## Harmonization in hemolysis detection and prevention. A working group of the Catalan Health Institute (ICS) experience

Good agreement was obtained between hemoglobin concentrations measured using the reference method and HI, for the most of studied analyzers, particularly those giving quantitative HI.

**Table 4**  $\kappa$  of Cohen index and coefficients of intra-class correlation.

	Beckman		Siemens		Siemens	Roche
	Synchron Lxi725 – DXC800	AU 5400	Vista	CCI	Advia	Cobas-Modular
$\kappa$	0.7895	0.8326	0.8209	CCI	0.982	0.973
CI 95%	0.6899–0.8891	0.7278–0.9374	0.6587–0.9831	CI 95%	0.910–0.996	0.863–0.995





## Harmonization of automated hemolysis index assessment and use: Is it possible?

Alberto Dolci <sup>a,\*</sup>, Mauro Panteghini <sup>a,b</sup>

<sup>a</sup> Clinical Chemistry Laboratory, University Hospital "Luigi Sacco", Milan, Italy

<sup>b</sup> Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

**Table 1**

Characteristics of hemolysis index [HI] test parameters on different commercial platforms.

Company/platform	Interferent material used	Maximum concentration of hemoglobin tested [g/l]	Sample volume for HI testing [μl]	Diluent type [volume] [μl]	Read wavelengths [nm]	HI report
Abbott Architect	Fresh erythrocyte hemolysate	20	5.3	Saline [200]	572/604; 628/660	5 levels
Beckman Coulter AU	Fresh erythrocyte hemolysate	5	2.0–1.6	Saline [150]	410/480; 600/800	6 levels
Beckman Coulter Synchron	Fresh erythrocyte hemolysate	5	14	Tris buffer pH 7.6 [200]	340, 410, 470, 600, 670	11 levels
Ortho Vitros	Fresh erythrocyte hemolysate	5–10	35 <sup>a</sup>	Undiluted	522/750	Concentration units
Roche Cobas & Integra	Fresh erythrocyte hemolysate	10	6	Saline [150]	570/600	Absolute numbers [range: 1–1000]
Siemens Advia	Fresh erythrocyte hemolysate	5.25	5	Saline [100]	571/596	5 levels
Siemens Dimension	Fresh erythrocyte hemolysate	10	10	Water [150]	405/700	8 levels
Recommended <sup>b</sup>	Fresh erythrocyte hemolysate	10	The lowest yielding an accurate measurement	Not giving rise to paraprotein precipitation	Detection methods should account for the absorbance spectrum overlap of hemoglobin, bilirubin and lipemia/turbidity	Concentration unit or absolute number

<sup>a</sup> HI analysis does not consume the sample.

<sup>b</sup> According to the Clinical and Laboratory Standards Institute document C56-A [5].

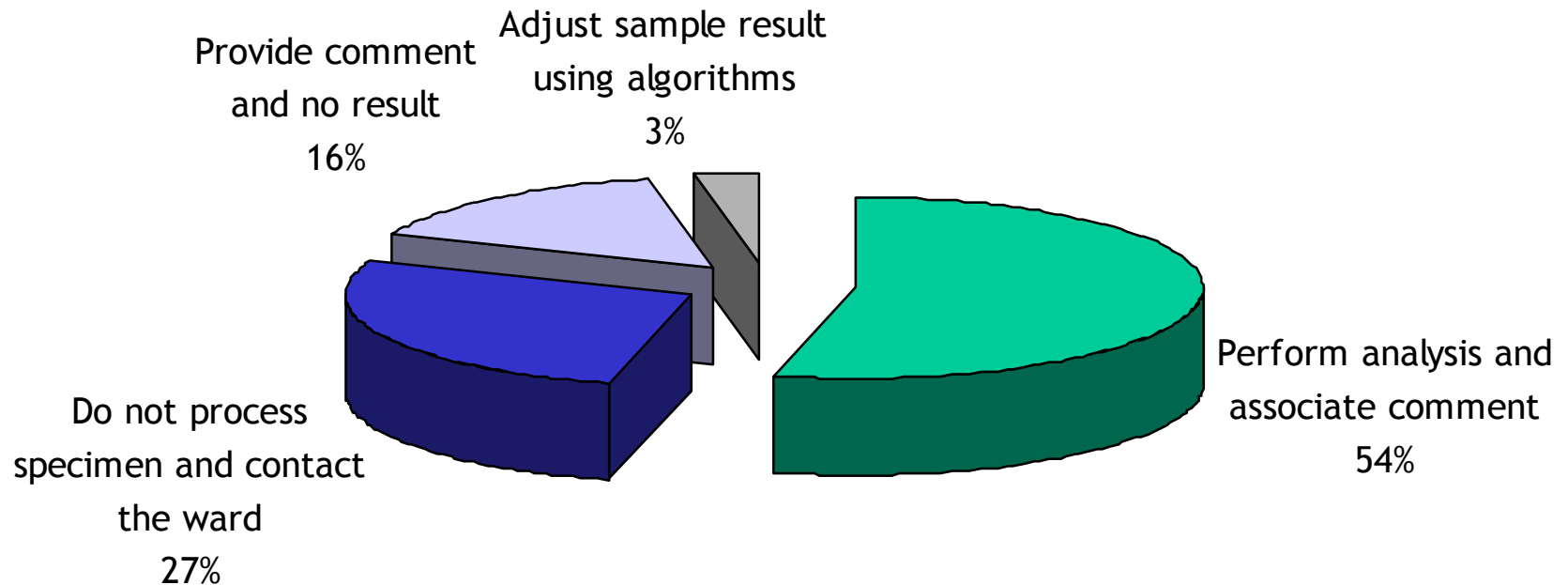
# Hemolysis limits based on biological variation (A) vs. manufacturer's recommended (B)

Test	Hemolysis interference limit, g/L									
	Advia 2400 (Siemens)		Synchron LXi725–DXC 800 (Beckman)		AU 5400 (Beckman)		Cobas 711,6000 (Roche)		Vista (Siemens)	
	A	B	A	B	A	B	A	B	A	B
ALT <sup>a</sup>	2.4	5	1.7	0.5	2.4	5	2.4	2	4.8	>10
AST <sup>a</sup>	0.6	5	0.3	0.5	0.6	na	0.4	0.4	0.2	0.25–0.5
CK <sup>a</sup>	2.4	5	1.7	0.5	4.8	1	2.4	2	4.8	5–10
COL	>6.9	7.5	>6.9	5	2.4	5	>6.9	7	4.8	>10
P	2.4	5.25	3.6	1.5	2.4	3.5	2.4	3	2.4	5–10
FAL	2.4	5	4.8	5	2.4	4.5	4.8	2	4.8	>10
FE <sup>a</sup>	4.8	na	0.6	0.5	6.9	1	2.4	2	2.4	0.25–0.5
GLU <sup>a</sup>	2.4	5.25	>6.9	5	>6.9	na	>6.9	10	0.9	>10
GGT <sup>a</sup>	6.9	5	3.6	2.5	6.9	5	4.8	2	>6.9	5–10
K	0.6	na	0.6	0.5	0.6	na	0.6	na	1	0.25
LD <sup>a</sup>	0.16	na	0.16	0.5	0.16	na	0.16	0.15	0.16	0.1–0.25
PT <sup>a</sup>	6.9	5	3.6	5	2.4	3	2.4	10	0.9	>10
TG	6.9	5.25	3.6	5	6.9	5	4.8	7	>6.9	>10

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# Harmonize management of unreliable samples: the most challenging issue?

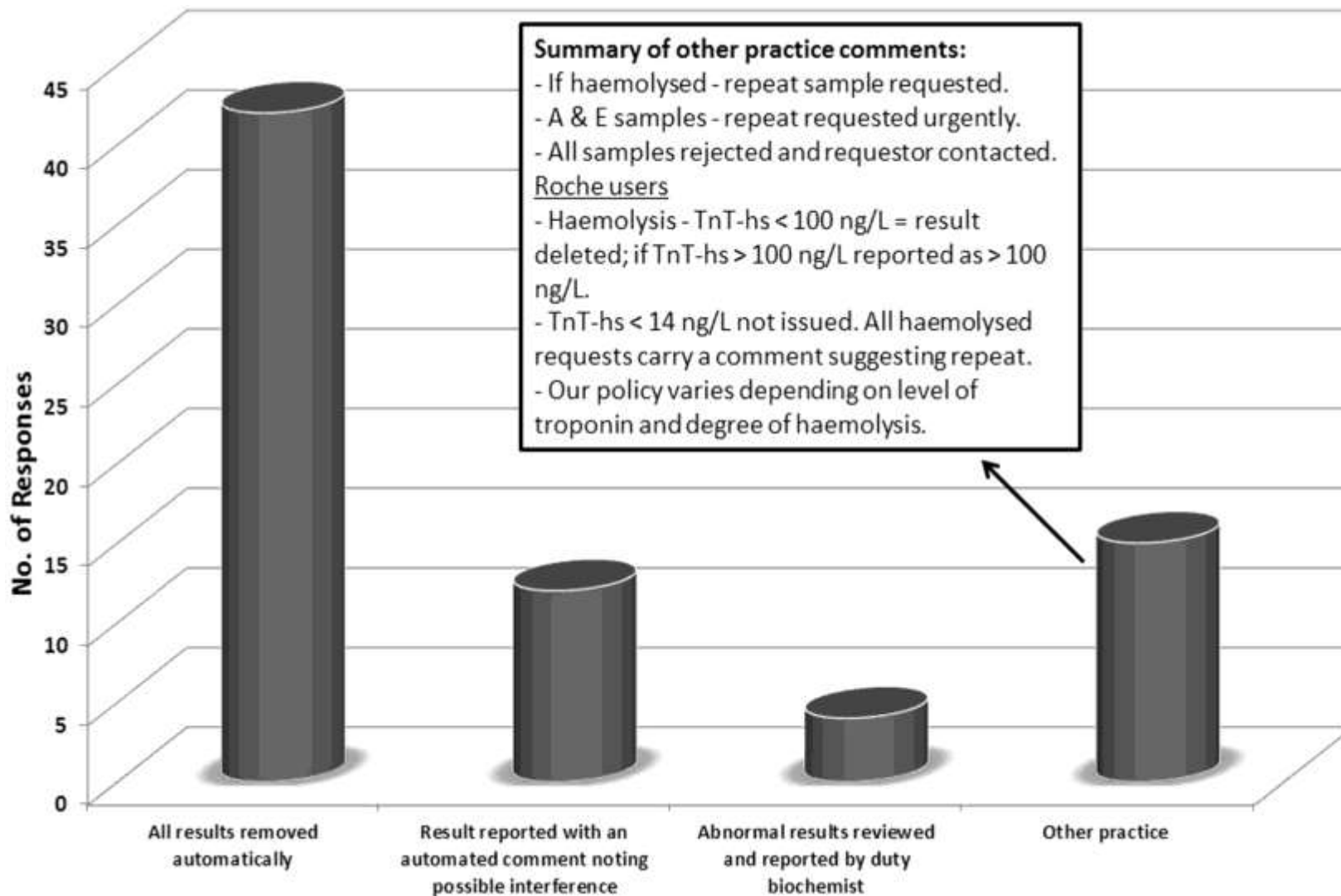


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The Association for  
**Clinical Biochemistry  
and Laboratory Medicine**

Annals of Clinical Biochemistry  
2015, Vol. 52(5) 527-542

## Heterogeneity of manufacturers' declarations for lipemia interference – An urgent call for standardization



Nora Nikolac <sup>a,\*</sup>, Ana-Maria Simundic <sup>a</sup>, Manuela Miksa <sup>a</sup>, Gabriel Lima-Oliveira <sup>b,1</sup>, Gian Luca Salvagno <sup>b</sup>, Beatrice Caruso <sup>c</sup>, Gian Cesare Guidi <sup>b,c</sup>

Comparison of declared and measured data on lipemia interference.

Parameter	Beckman Coulter AU 680	Cobas® 6000 < c501 >	Dimension Vista System
Sodium	✓	✓	✓
Potassium	✓	✓	✓
Chlorides	✓	✓	✓
Lipase	✓	✓*	✓*
Iron	✓	✓*	/
ALT	—	✓*	✓*
AST	—	✓*	—
Bilirubin, direct	✓	—	—
Urea	✓	✓	✓
Creatinine	+	+	—
Glucose	+	✓	✓
Phosphates	+	✓*	✓
Albumin	+	✓*	✓*
CK-MB	—	/	✓*
CK	—	✓	✓
LD	—	✓	✓*
AMY	—	✓*	✓
ALP	—	✓*	✓*
GGT	✓	✓*	—
Bilirubin	—	—	—
Magnesium	—	✓	✓*
Calcium	✓	✓	—
Total proteins	✓	✓*	✓*
CRP	✓	✓	/



Contents lists available at ScienceDirect

# Atherosclerosis

journal homepage: [www.elsevier.com/locate/atherosclerosis](http://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<sup>a,b,c,\*</sup>, Olivier S. Descamps<sup>d</sup>, Arnoud van der Laarse<sup>e</sup>, Cas Weykamp<sup>f</sup>, Hannsjörg Baum<sup>a,g</sup>, Kari Pulkki<sup>a,h</sup>, Arnold von Eckardstein<sup>i</sup>, Dirk De Bacquer<sup>j</sup>, Jan Borén<sup>k</sup>, Olov Wiklund<sup>k</sup>, Päivi Laitinen<sup>a</sup>, Wytze P. Oosterhuis<sup>b</sup>, Christa Cobbaert<sup>l</sup>, for the EAS-EFLM Collaborative Project

<sup>a</sup> European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group (WG) Cardiac Markers

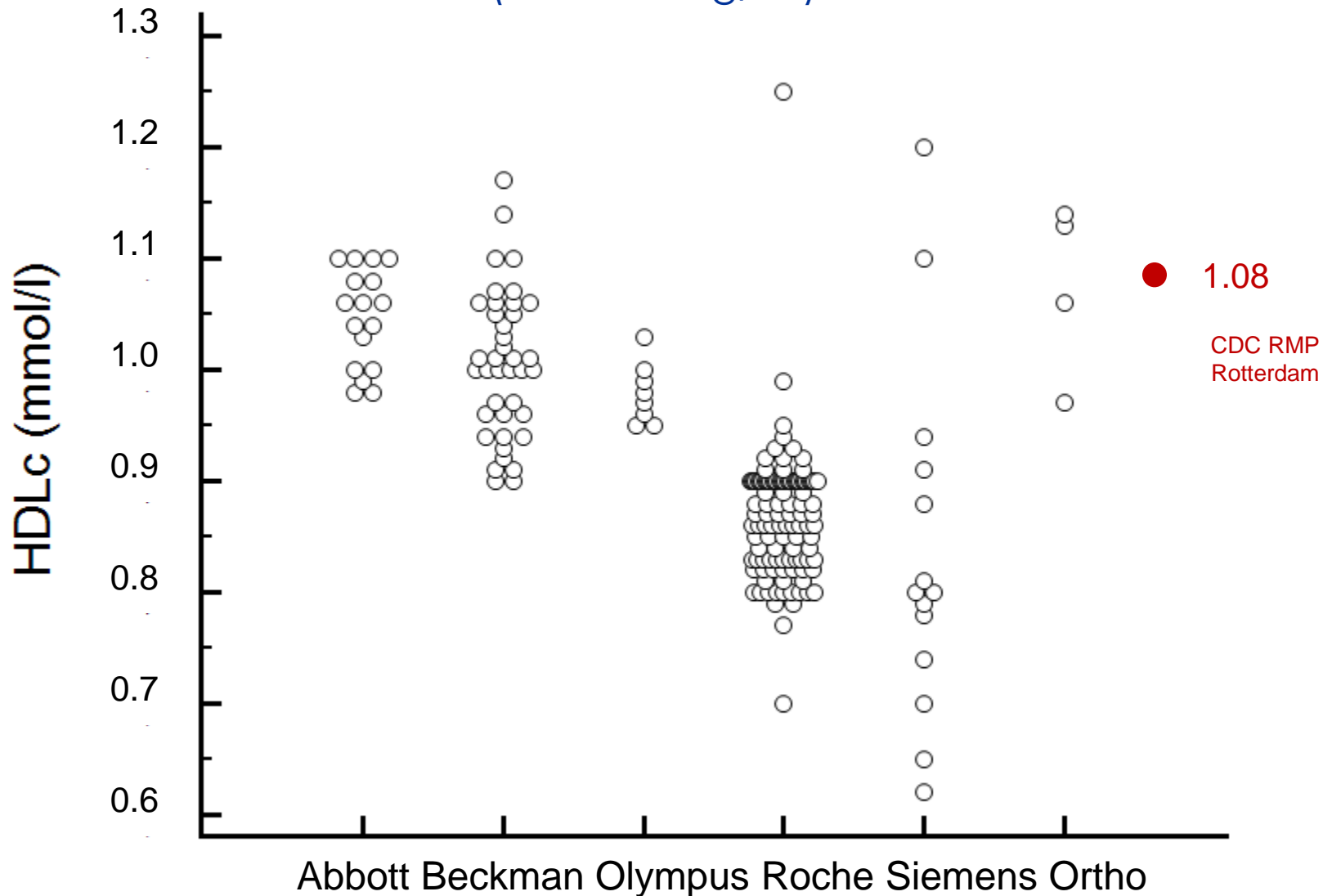
<sup>b</sup> WG Guidelines, EFLM

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



## 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%)

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# The choice of anticoagulant

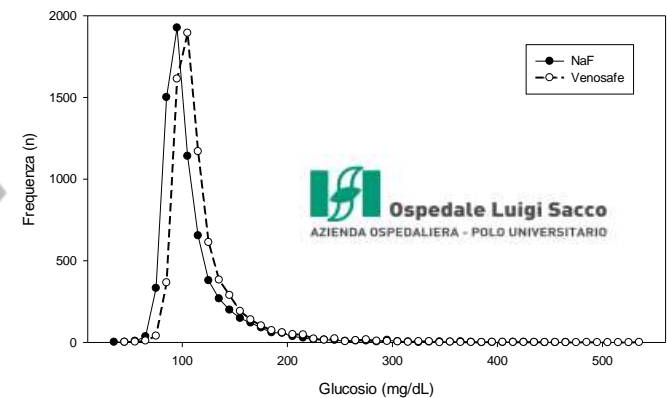
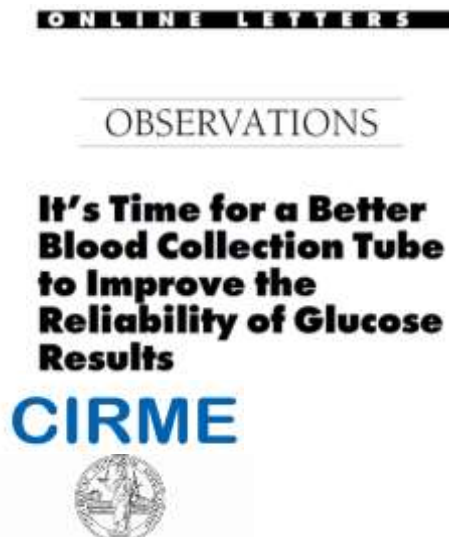
## PLASMA GLUCOSE DETERMINATION: GOLD STANDARD FOR SAMPLE COLLECTION

### NATIONAL ACADEMY OF CLINICAL BIOCHEMISTRY (NACB) GUIDELINES FOR LABORATORY ANALYSIS IN DIABETES

- tubes with only enolase inhibitors, such as NaF, should not be relied on to prevent glycolysis
- tube containing a rapidly effective glycolysis inhibitor, such as citrate buffer, should be used for collecting the sample

(Rating scale for the quality of evidence, B moderate)

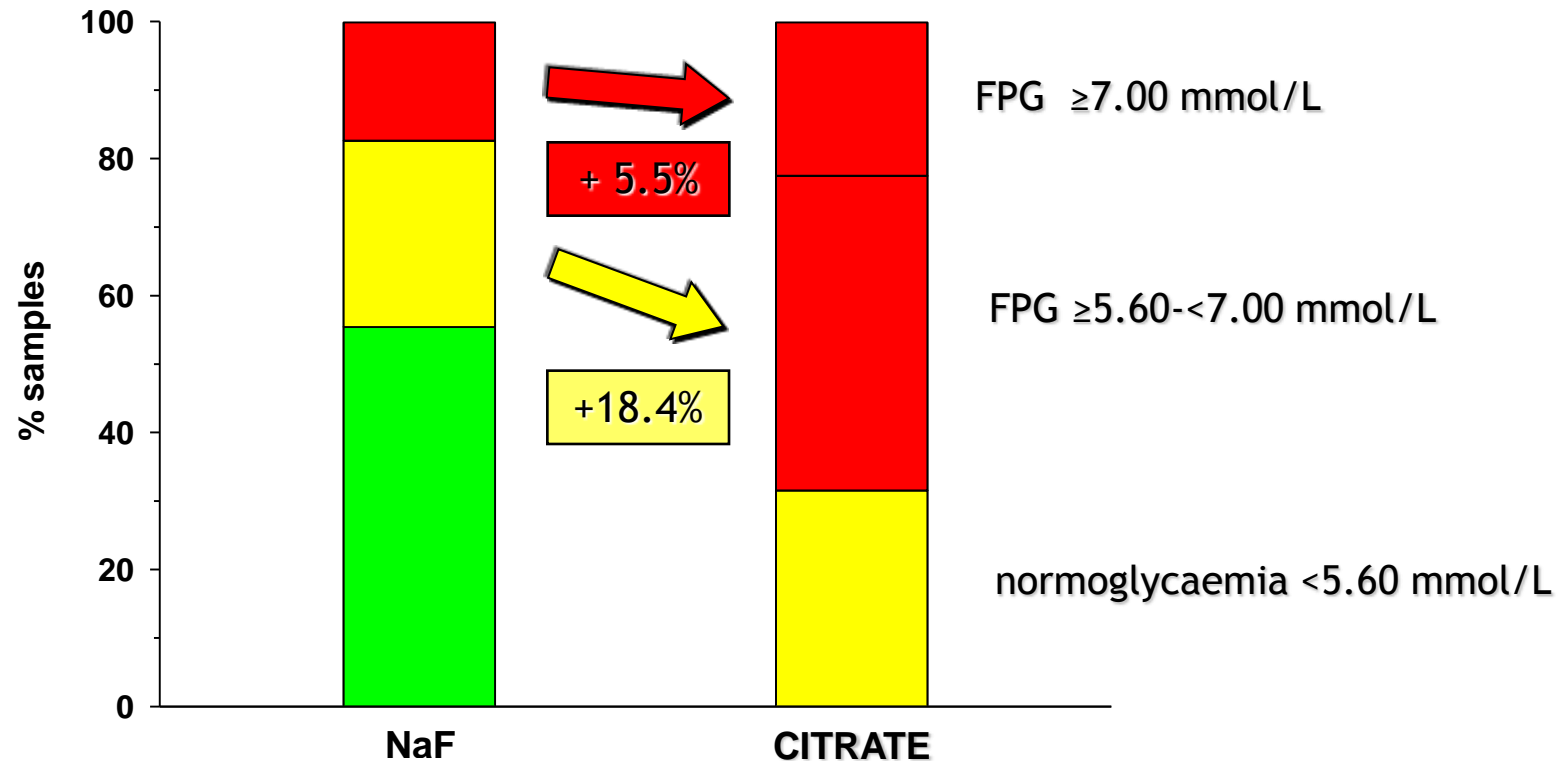
*Clin Chem 2011;57:e1-47*



↑ undesirable FPG from 26.8% to 45.2%  
↑ abnormal FPG from 17.8% to 23.3%

The shift from fluoride to citrate blood collection tubes for glucose testing: is the clinical impact carefully considered?

# CLINICAL CLASSIFICATION OF SUBJECTS UNDERWENT FPG TEST



DIABETOLOGIST ASSOCIATIONS SHOULD CLARIFY IF:

1. Decisional limits for FPG should be redefined with the use of tubes that promptly inhibit the in vitro glycolysis
2. Current cut-offs should be maintained, so that the “higher” FPG results could more effectively and early identify subjects at increased risk for diabetes

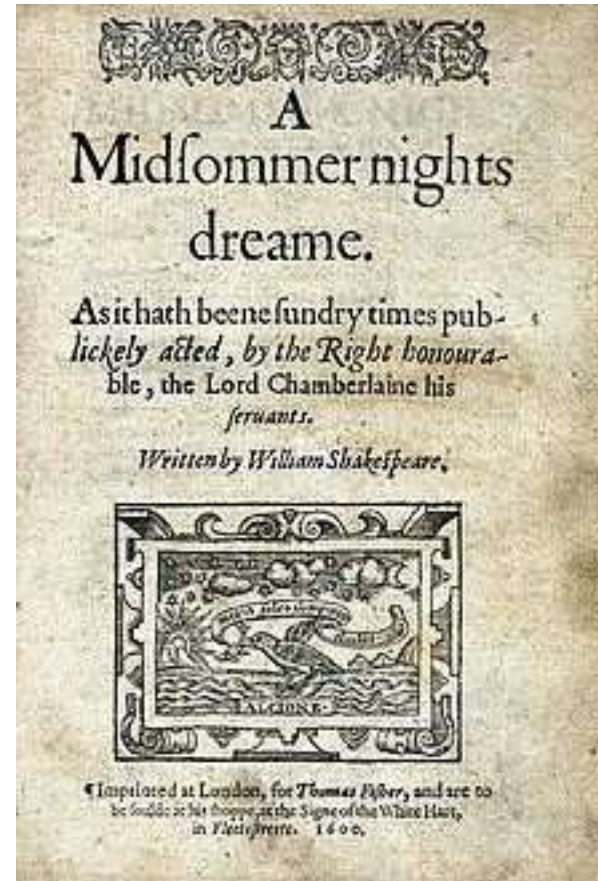


# The Report

The product that underpins the effectiveness of the laboratory product

A synthesis of:

- data
- knowledge
- information



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# Challenges reported by US primary care physicians when using lab test results

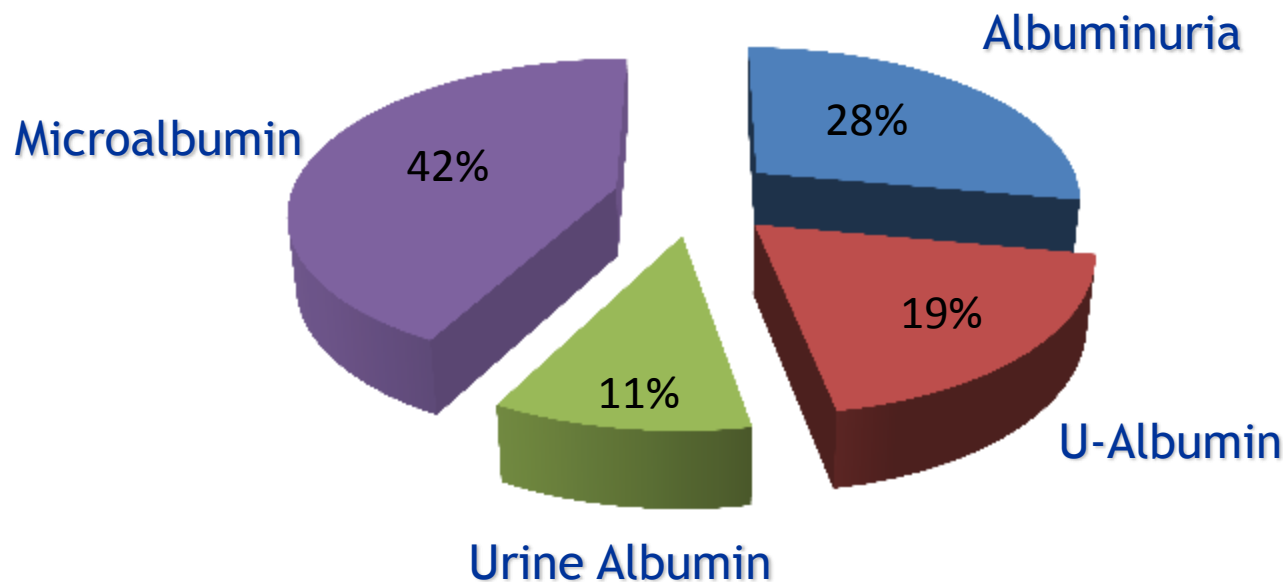
	% of respondents reporting factor is very or extremely problematic	
Receiving results		
Results not received in a timely manner	34	
Previous results are not easily available	32	
Errors in results are suspected	25	
Results are inconsistent with patient's symptoms	24	
Report format		
Lab-to-lab variation in normal range	22	Potentially affecting 13 million pts/yr, raising significant concerns about the safety and efficient use of lab tests
Lab-to-lab variation in report formats	21	
Lab report format is difficult to understand	18	
Not enough information in lab report	16	



# Urine Albumin Measurement

SIBioC Survey 2015: post-analytical phase

How do you define the analyte in the report?



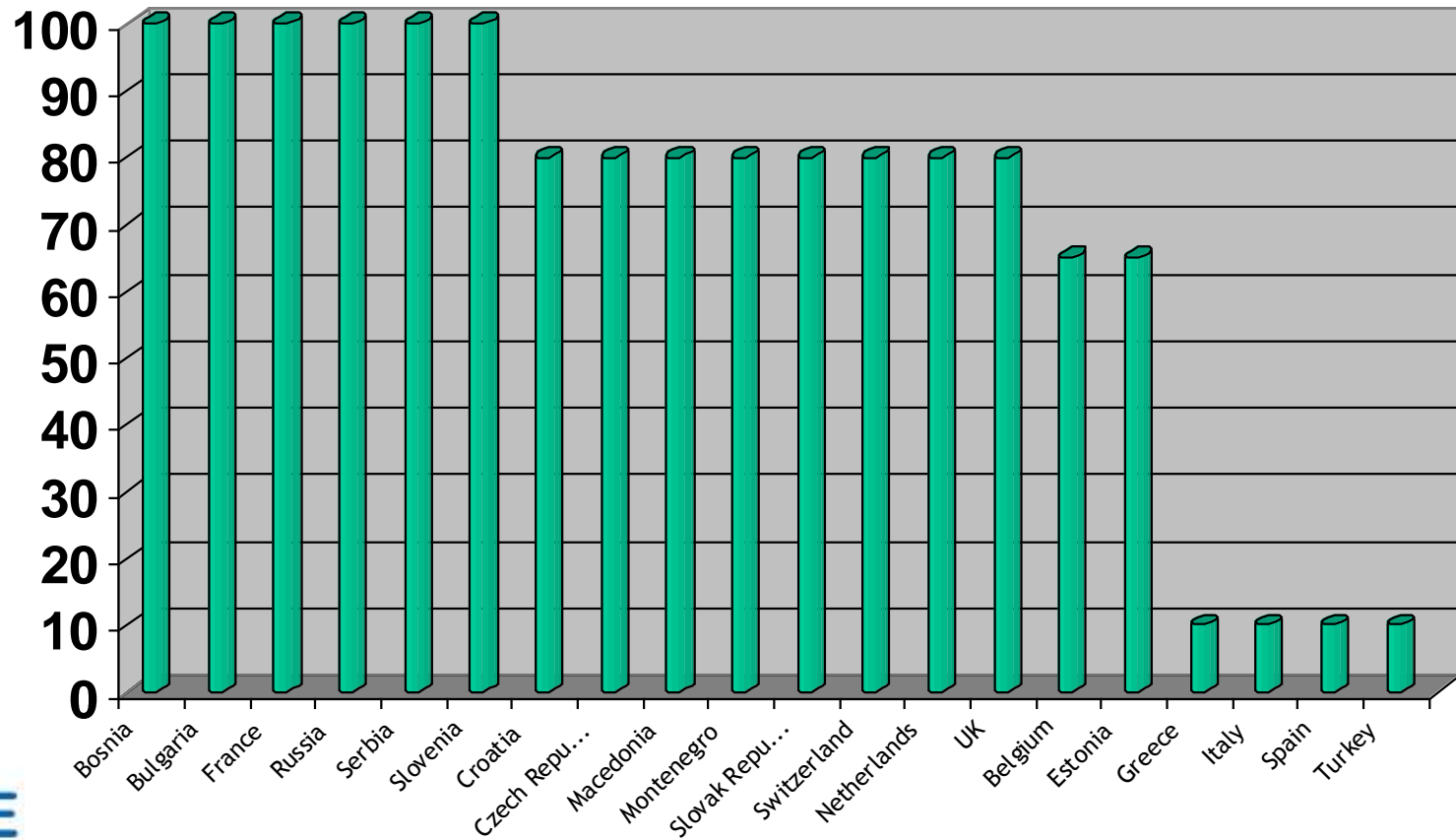
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# Adoption of SI units @ national level



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## Decimal numbers and safe interpretation of clinical pathology results

Michael Sinnott,<sup>1,2</sup> Robert Eley,<sup>1,2</sup> Vicki Steinle,<sup>3</sup> Mary Boyde,<sup>4</sup> Leanne Trenning,<sup>1</sup> Goce Dimeski<sup>5</sup>

### Take-home messages

- ▶ Poor comprehension of decimal numbers was illustrated by many laboratory and clinical staff.
- ▶ Resultant misinterpretation of test results is a potential source of medical errors.
- ▶ Whenever possible, pathology results should be presented as whole numbers.



→ To be interpreted results should be compared with:

- a population reference interval (transversal evaluation - biological level)
- a decision limit (transversal evaluation - nosological level)

Two fundamental issues drive improvement in defining and using reference intervals in clinical practice:

- 1) There is the need to link the analytical standardization based on the principles of metrological traceability with the identification of appropriate reference intervals.
- 2) The ISO 15189:2012 states that “biological reference intervals shall be periodically reviewed” and they should be verified every time a variation in analytical and/or pre-analytical procedures occurs.



# Lack of proper reference intervals may hamper the implementation of standardization

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

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Until today

From today

Method-dependent  
results



Method-dependent  
reference intervals

Standardized methods  
that provide traceable  
results



Traceable reference  
intervals

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

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

Age (gender) group	Percentile value, mg/dL <sup>a</sup>	
	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

<sup>a</sup>To express creatinine values in  $\mu\text{mol/L}$ , multiply the values by 88.4. d, days; m, months; y, years.

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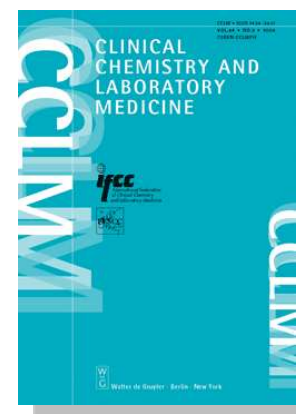
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## Research Article

# Common reference intervals for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and $\gamma$ -glutamyl transferase (GGT) in serum: results from an IFCC multicenter study

Ferruccio Ceriotti<sup>1,\*</sup>, Joseph Henny<sup>2</sup>, Josep Queraltó<sup>3</sup>, Shen Ziyu<sup>4</sup>, Yeşim Özarda<sup>5</sup>, Baorong Chen<sup>6</sup>, James C. Boyd<sup>7</sup> and Mauro Panteghini<sup>8</sup>  
on behalf of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL) and Committee on Reference Systems for Enzymes (C-RSE)



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# Validation of traceable reference intervals



→ The validation can be done according to the CLSI document C28-A3, paragraph 11.2, by examining 20 reference individuals from a laboratory's own subject population.

→ If no more than 2 (10%) of the 20 tested values fall outside the TRI, this can be adopted.

# Critical value definition and communication

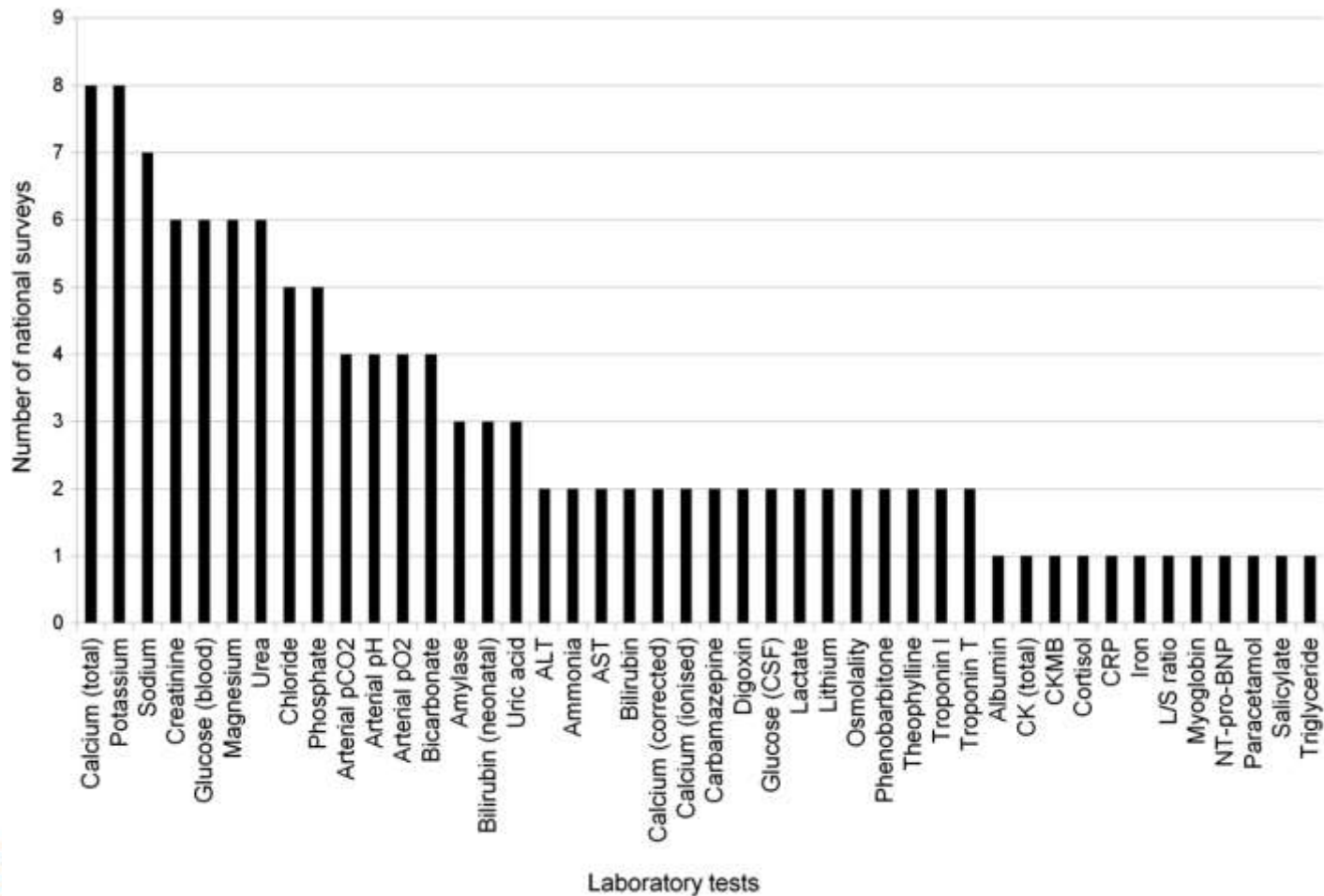
- Laboratories are responsible for communicating critical values, a key issue in maximizing patient safety
- However, the reported variations between procedures and policies used by different laboratories in the same country and by those in different countries emphasize the need for harmonization

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# Laboratory tests considered important in published surveys to be included in alert lists



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# Need for harmonized policies and procedures

- Definition of critical tests
- Identification of critical values
- Notification procedures of critical values:
  - data validation
  - timeliness of reporting
  - communication tools (phone, informatics, call centers)
  - personnel responsible for data transmission and receiving results
  - acknowledgment of results and feed-back
  - data recording
- Procedures for evaluating and monitoring outcomes of critical results management practices

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# The result standardization issue: an absolute priority for public health

Same language ?

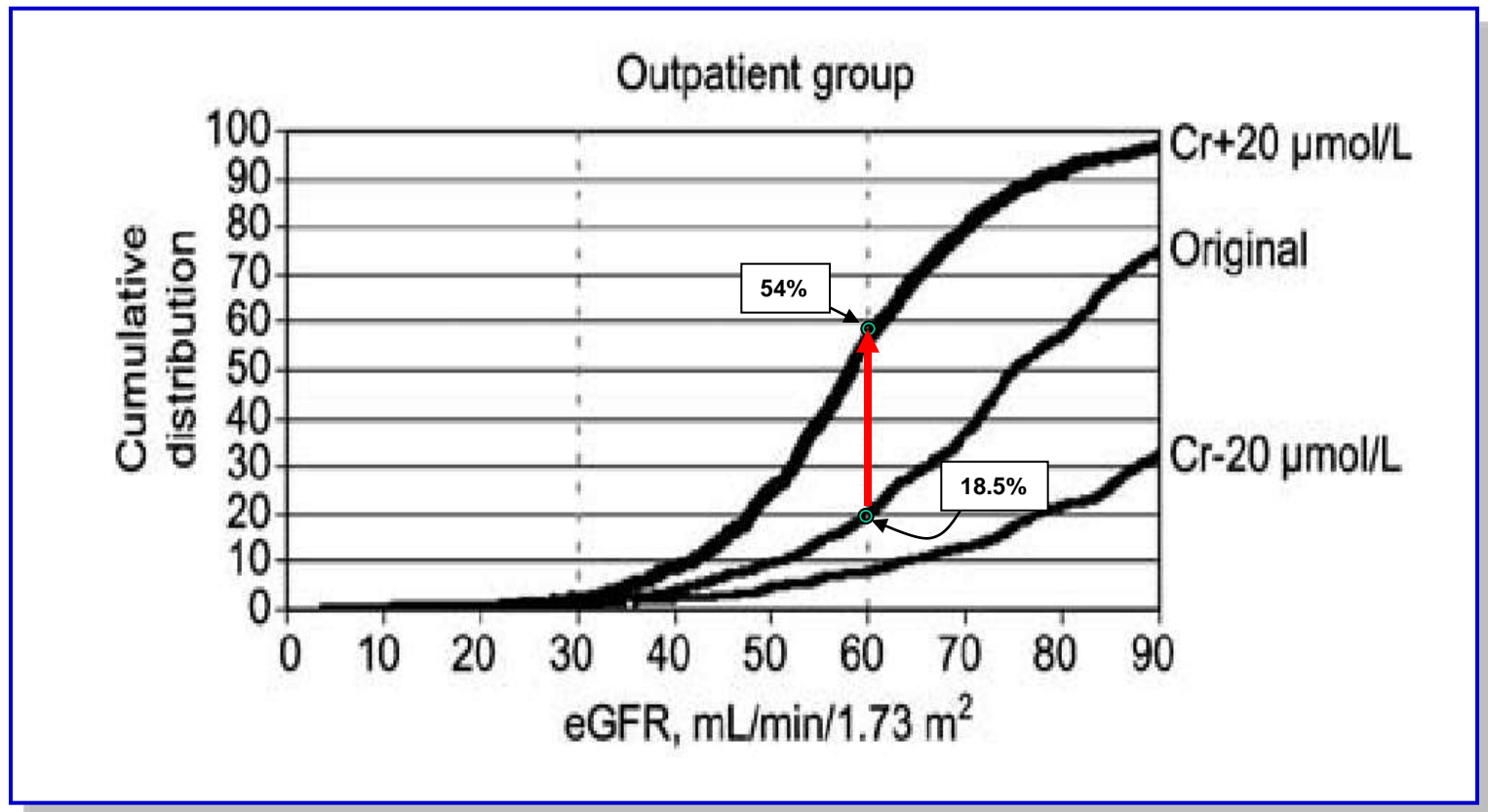
Same language ?



→ Our customers (i.e., clinicians and patients) expect laboratory results to be ***equivalent and interpreted in a reliable and consistent manner.***



## Effect of analytic bias in creatinine on the distribution of estimated GFR values

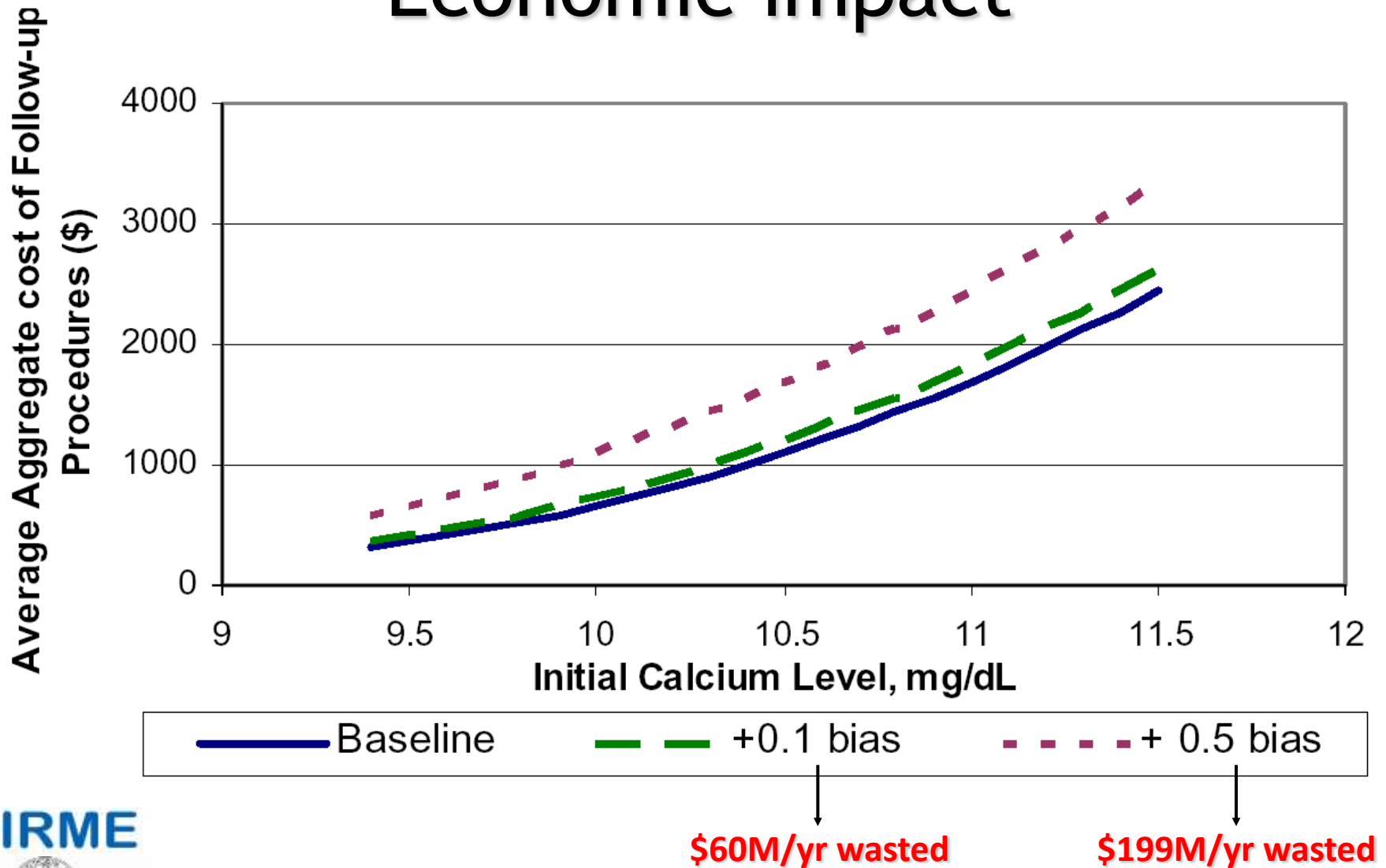


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# Economic impact



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Source: NIST Planning Report 04-1, 2004

In short: the lack of standardization  
may become an ethical issue

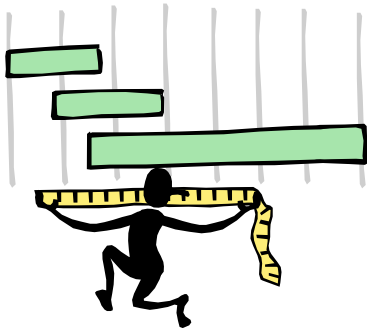
“Standardization of laboratory  
tests has an ethical dimension as  
it aims to affect the way  
diagnostic tests are used in order  
to guarantee optimal care for  
patients in a global world.”

Analytical improvements are matter of  
patient safety and key to future

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# Basic requirements to establish traceability

- Establishment of a calibration hierarchy
- Establishment of the metrological traceability for the measurement results (understand the measurements)
- Elimination of measurement bias
- Adequate estimation of measurement uncertainties

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# Role of IVD manufacturers

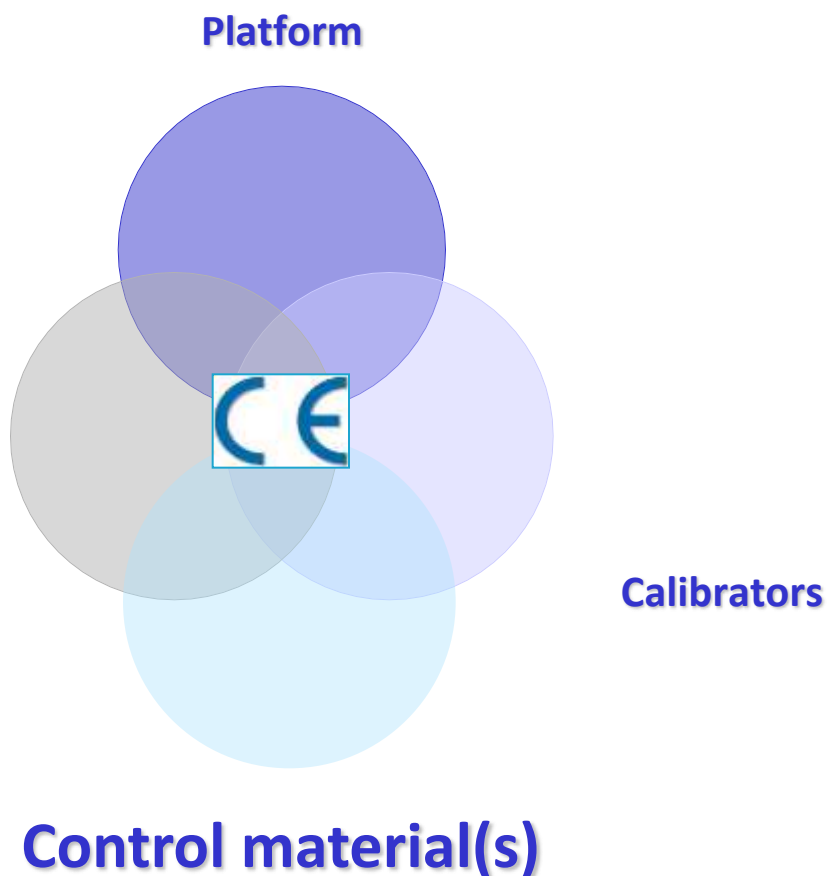
IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process uncertainty limits, which represent a proportion of the uncertainty budget allowed for clinical laboratory results.

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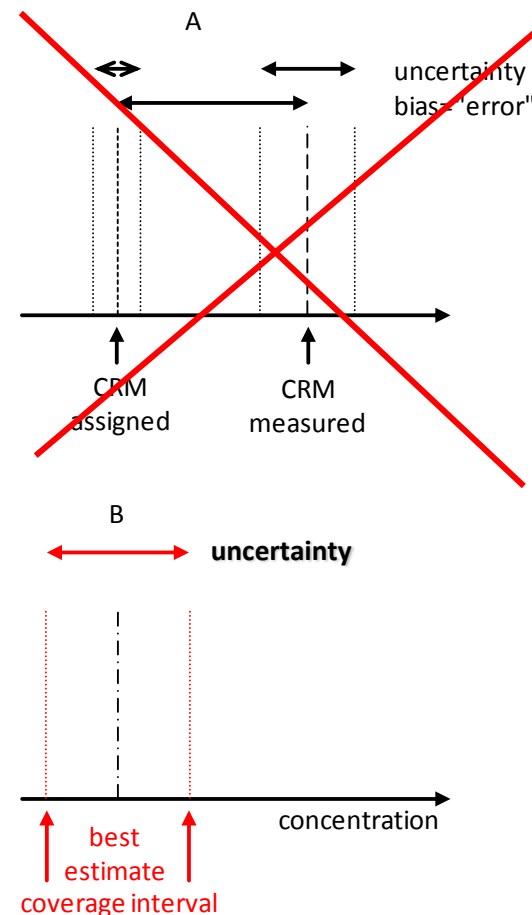


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Thus, clinical laboratories need to rely on the manufacturers who must ensure traceability of their analytical system to the highest available level



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



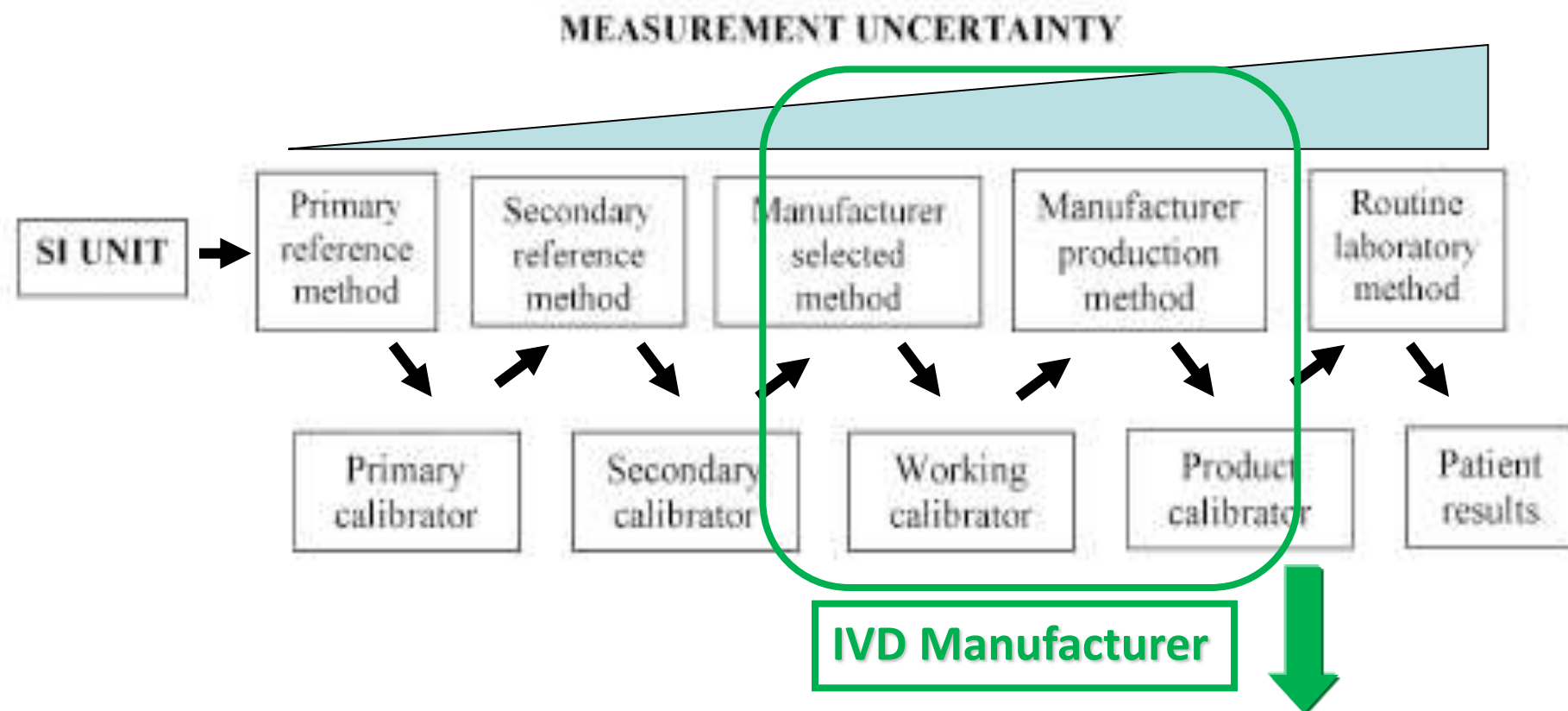
[Adapted from Kallner A,  
*Scand J Clin & Lab Invest* 2010; 70(Suppl 242): 34]

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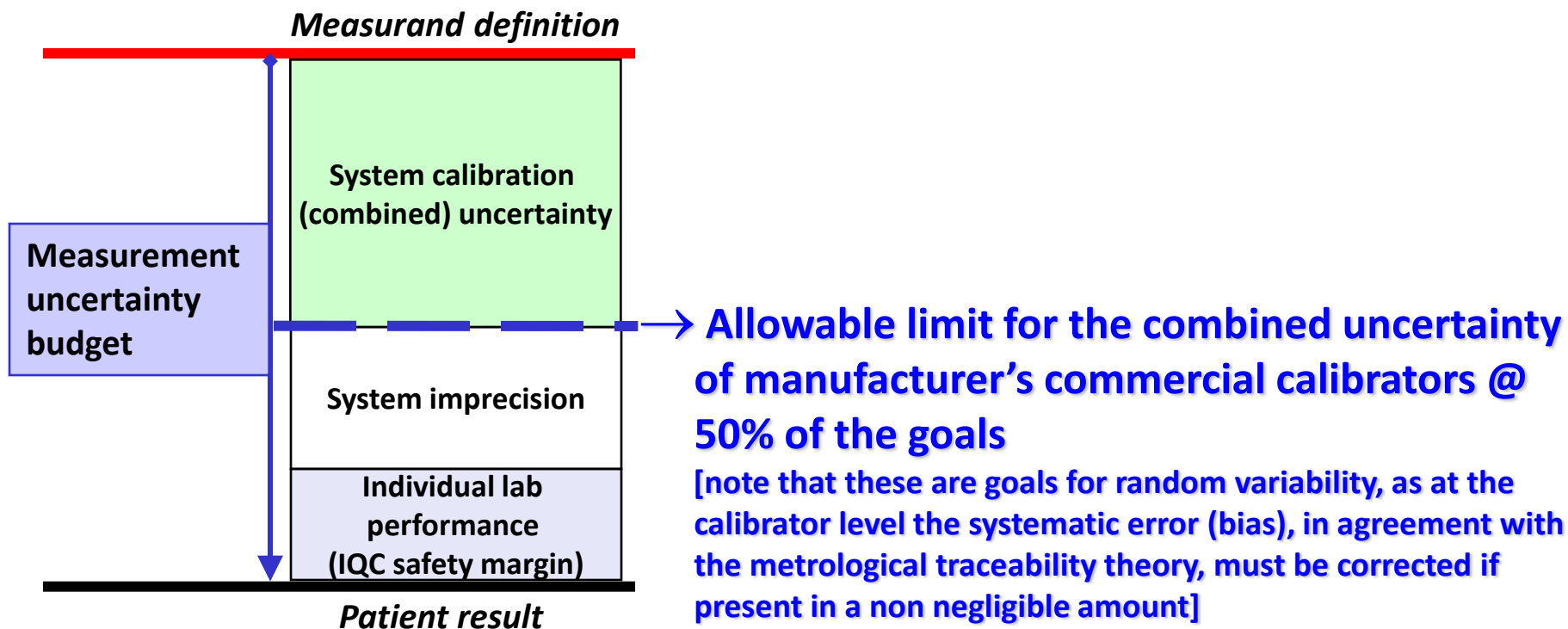
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# Measurement uncertainty budget



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 should include the uncertainty associated with higher levels of the metrological traceability chain.

# 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.





Contents lists available at ScienceDirect

# Clinica Chimica Acta

journal homepage: [www.elsevier.com/locate/clinchim](http://www.elsevier.com/locate/clinchim)

Letter to the editor

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

Note: For serum creatinine measurements on patient samples, the acceptable limits for expanded uncertainty derived from its  $CV_i$  are 6.0% (desiderable) and 9.0% (minimum quality level), respectively.

**Table 1**

Uncertainties for each contributing factor in determination of serum creatinine with Abbott enzymatic assay on Architect c16000 platform after calibration with two different lot of system calibrator. Data obtained by measurements of NIST SRM 967a reference material (certified value  $\pm$  expanded uncertainty: L1, 0.847 mg/dL  $\pm$  0.018 mg/dL and L2, 3.877 mg/dL  $\pm$  0.082 mg/dL).

	SRM 967a level 1	SRM 967a level 2
<i>Multigent Clin Chem Calibrator lot no. 40043Y600</i>		
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%
<i>Multigent Clin Chem Calibrator lot no. 40496Y600</i>		
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%

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**Ospedale Luigi Sacco**  
AZIENDA OSPEDALIERA - POLO UNIVERSITARIO

# The role of the Laboratory Profession: “check”



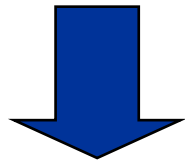
- Availability and quality of information about IVD metrological traceability and uncertainty
- Daily surveillance of IVD system traceability

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**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

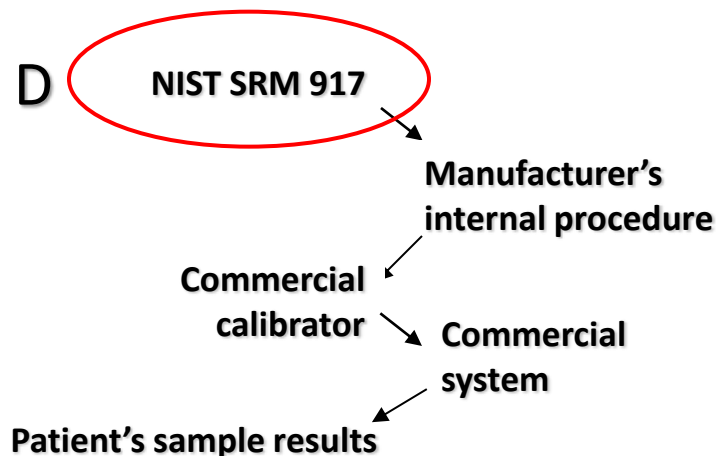
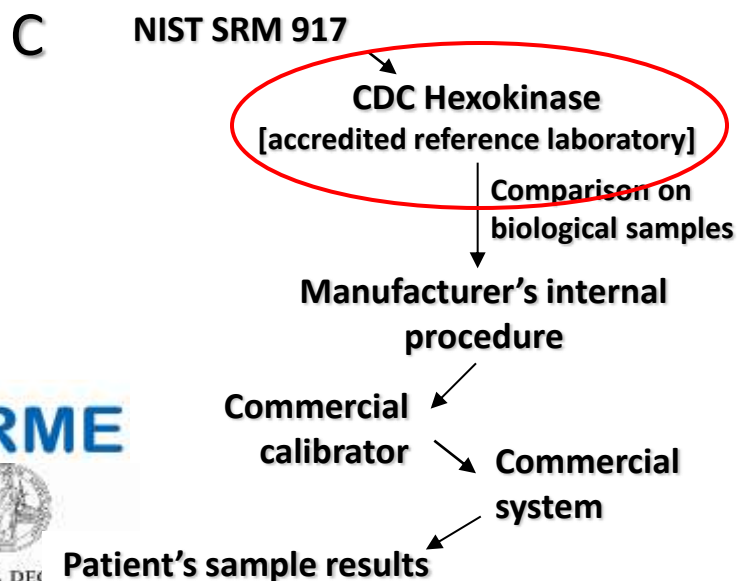
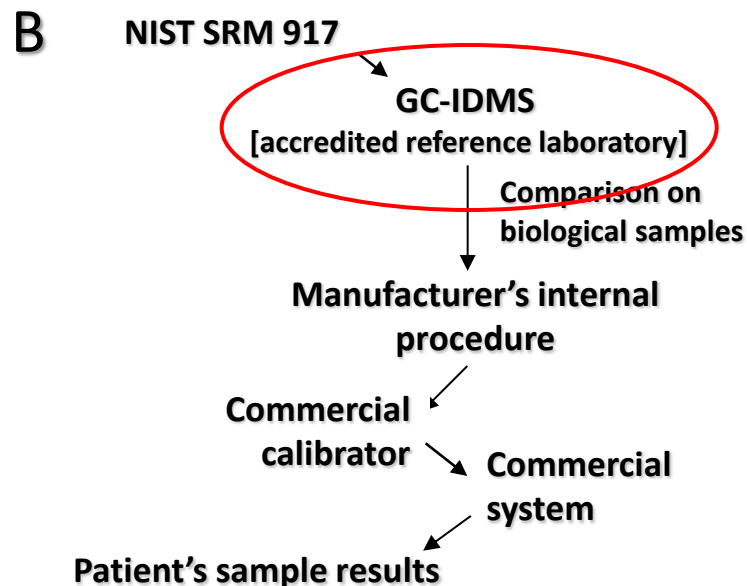
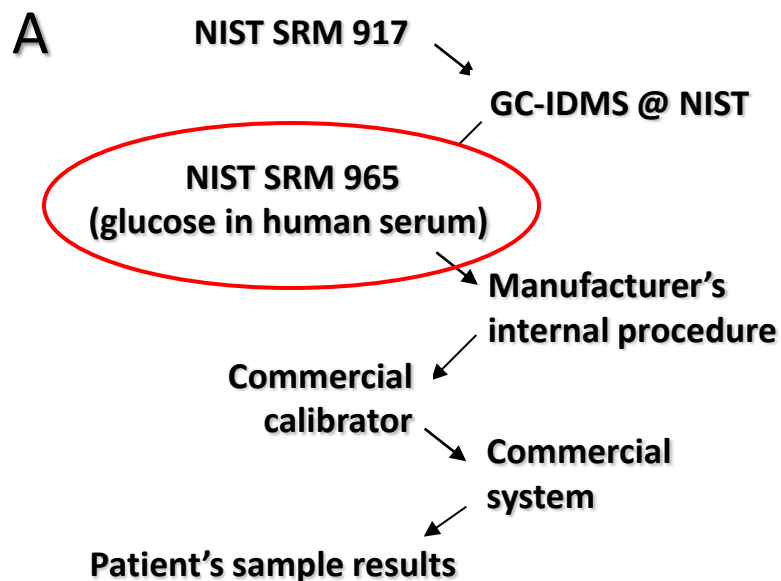
Federica Braga\*, Ilenia Infusino and Mauro Panteghini

# Performance criteria for combined uncertainty budget in the implementation of metrological traceability

**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

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## Verification of in vitro medical diagnostics (IVD) metrological traceability: Responsibilities and strategies

Federica Braga\*, Mauro Panteghini

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

**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 <sup>a</sup>	Higher-order reference employed		Type of traceability chain used <sup>b</sup>	Combined standard uncertainty associated with the used chain <sup>c</sup>
					Method	Material		
Abbott	Architect	ND	Multiconstituent calibrator	2.70%	IDMS	NIST SRM 965	A	1.22–1.45% <sup>d</sup>
Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22–1.45% <sup>d</sup>
	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60–3.00% <sup>e</sup>
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% <sup>f</sup>
		GOD		0.80%	Hexokinase	NIST SRM 917a	C	1.88–3.26% <sup>f</sup>

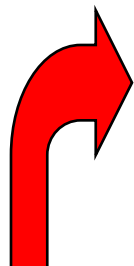
**Profession (e.g., JCTLM, EFLM):** Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)



**Diagnostic manufacturers:**

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

Post-marketing  
surveillance of IVD  
metrological traceability



**End users (clinical laboratories):**

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



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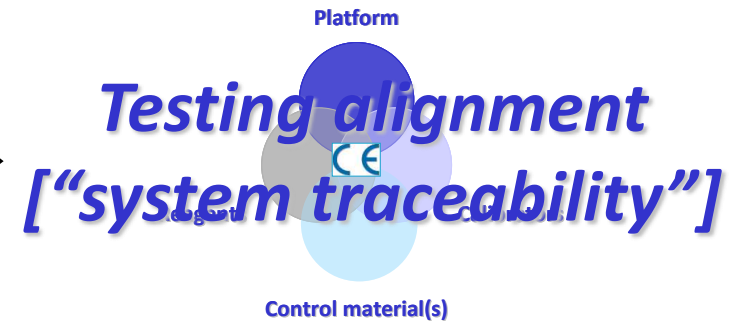
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Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7



# ***Internal Quality Control (Component I)***

**Acceptance/rejection of  
the analytical run in  
“real time”**



**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.**

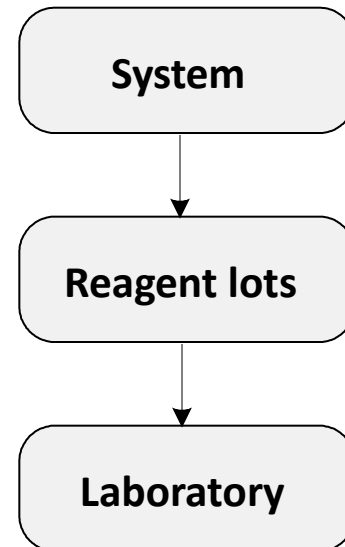
# ***Internal Quality Control (Component II)***

**System stability at  
medium/long term**

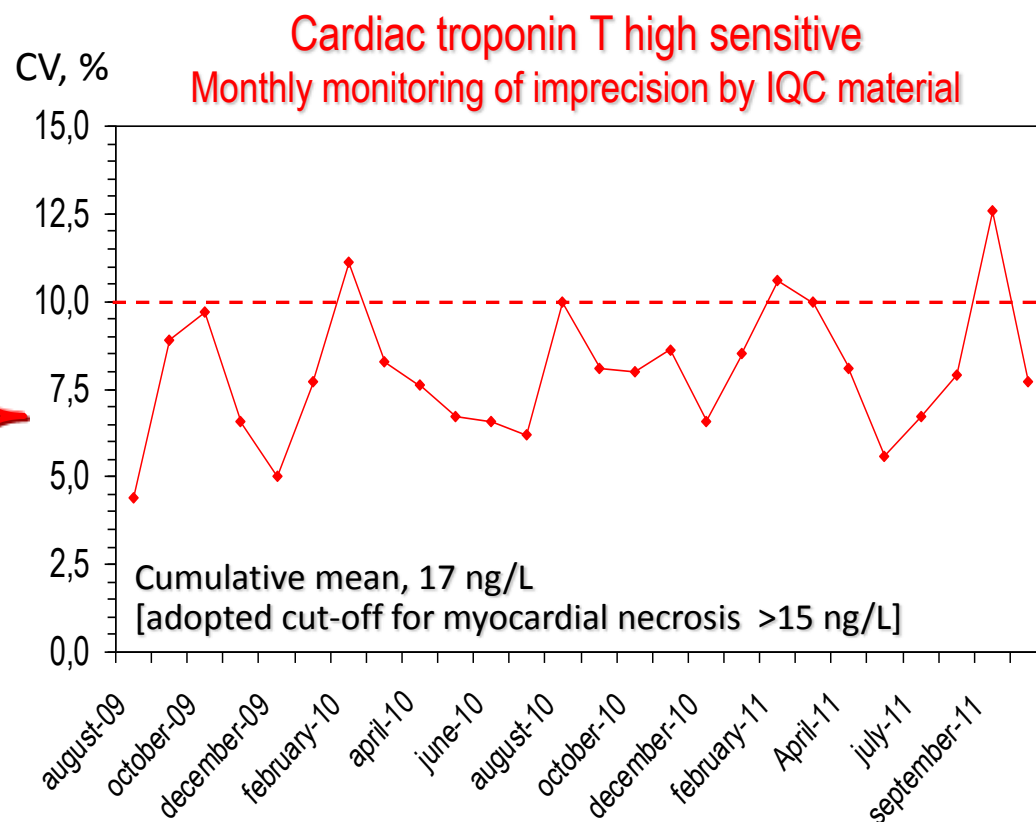
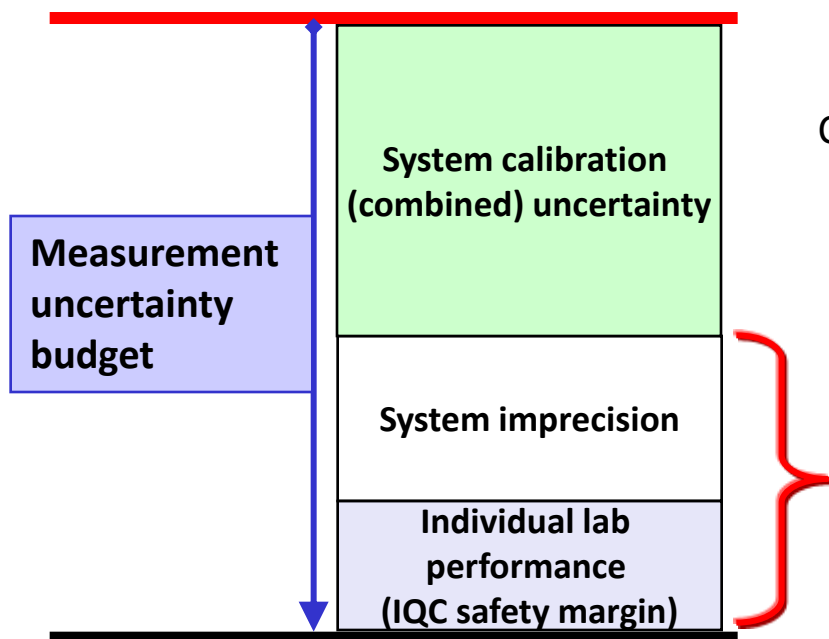


***Estimating the  
measurement uncertainty  
due to random effects  
("imprecision")***

**This program provides, through  
mechanisms of retrospective  
evaluation, data useful to the  
knowledge of variability of the  
analytical system and of its use by  
the individual laboratory.**



# Monitoring the reliability of the analytical system through IQC: Component II. Evaluate the system + individual lab imprecision



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# Requirements for the applicability of EQAS results in the evaluation of the performance of participating laboratories in terms of traceability of their measurements

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## Feature

## Aim

EQAS materials value-assigned with reference procedures by an accredited ref. laboratory

To check traceability of commercial system to reference systems

Proved commutability of EQAS materials

To allow transferability of participating laboratory performance to the measurement of patient samples

Definition and use of the clinically allowable measurement error

To verify the suitability of laboratory measurements in clinical setting

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*Panteghini M, CCLM 2010;48:7*  
*Infusino I et al., CCLM 2010;48:301*  
*Braga F & Panteghini M. CCLM 2013;51:1719*  
*Braga F & Panteghini M, Clin Chim Acta 2014;432:55*

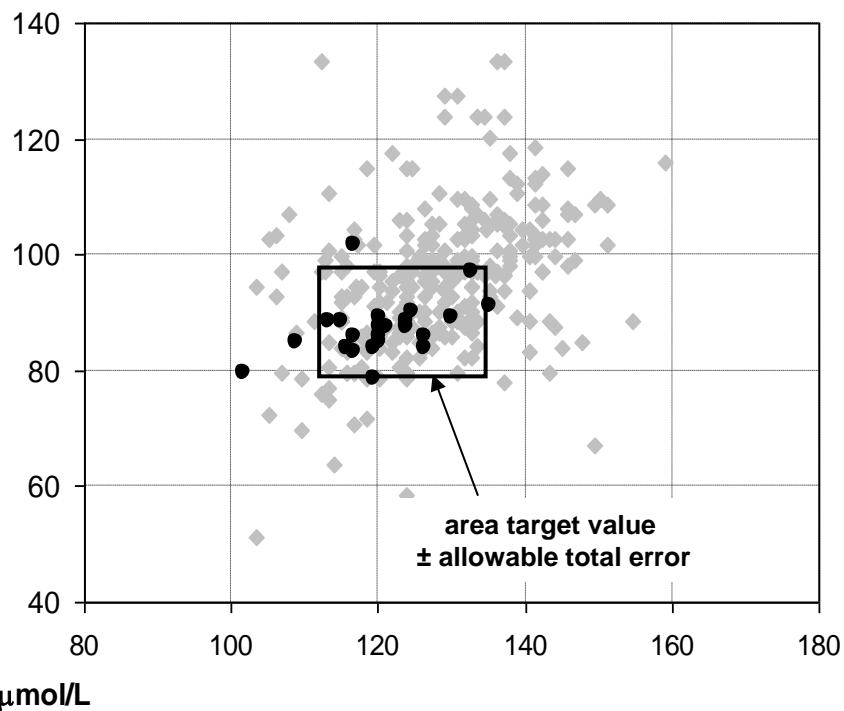
# Unique benefits of EQAS that meet metrological criteria

- Giving objective information about quality of individual laboratory performance
- Creating evidence about intrinsic standardization status/ equivalence of the examined assays
- Serving as management tool for the laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem
- Helping manufacturers that produce superior products and systems to demonstrate the superiority of those products
- Identifying analytes that need improved harmonization and stimulating and sustaining standardization initiatives that are needed to support clinical practice guidelines
- Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality

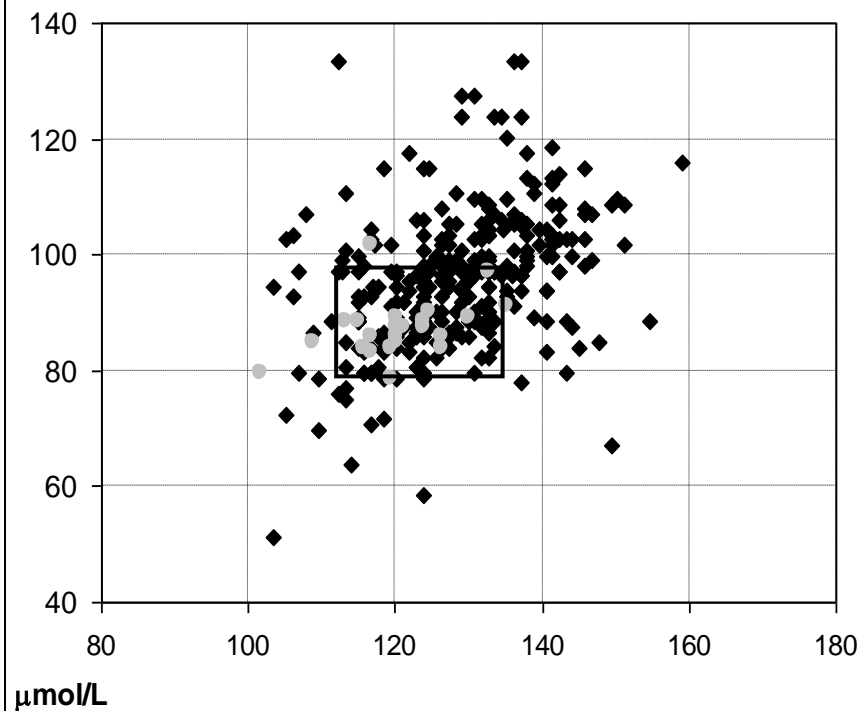
EQAS materials with physiologic (88.4  $\mu\text{mol/L}$ ) and borderline (123.8  $\mu\text{mol/L}$ ) creatinine concentrations vs. the desirable goal for TE ( $\pm 8.9\%$ ).

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.

Enzymatic assays (n=23)



Alkaline picrate assays (n=296)



<http://users.unimi.it/cirme/home/index.php>

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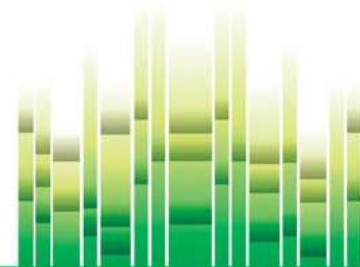
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Centro Interdipartimentale per la  
Riferibilità Metrologica in Medicina di  
Laboratorio (CIRME)

under the auspices of



The Joint Committee for Traceability in Laboratory Medicine



9th International Scientific Meeting  
**STRUCTURING EQAS FOR MEETING  
METROLOGICAL CRITERIA:  
READY FOR PRIME TIME**

MILANO, ITALY  
*November 27<sup>th</sup>, 2015*

AULA MAGNA - SETTORE DIDATTICO COLOMBO  
Università degli Studi  
Via L. Mangiagalli 25, Milano

## *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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# Analytical performance specifications: definition

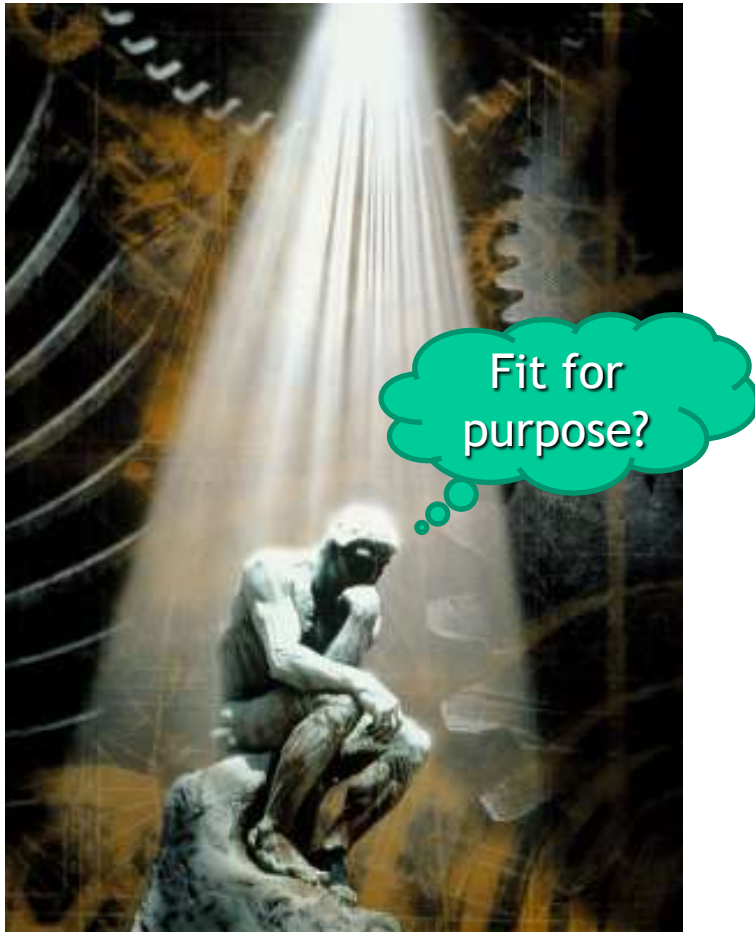
- Criteria that specify (in numerical terms) the quality required for analytical performance in order to deliver laboratory test information that would satisfy *clinical needs* for improving *health outcomes*.

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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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European Commission  
Joint Research Centre  
**IRMM**  
Institute for Reference  
Materials and Measurements



# 1<sup>st</sup> EFLM Strategic Conference Defining analytical performance goals 15 years after the Stockholm Conference

8<sup>th</sup> CIRME International Scientific Meeting

Milan (IT)  
24-25 November 2014



with the  
auspices of  **IFCC**  
International Federation  
of Clinical Chemistry  
and Laboratory Medicine

## 1999 Stockholm Consensus revised in Milan 2014

Although the essence of the hierarchy established in Stockholm was supported, new perspectives have been forwarded prompting **simplification** and **explanatory additions**.

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.

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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

**EFLM**  
EUROPEAN FEDERATION  
OF CLINICAL CHEMISTRY  
AND LABORATORY MEDICINE

European Contribution  
Adult Research Centre  
**IRMM**  
Institute for Reference and Research Materials

**CIBME**  
8th

**1<sup>st</sup> EFLM Strategic Conference**  
**Defining analytical performance goals 15 years after the Stockholm Conference**  
8<sup>th</sup> CIBME International Scientific Meeting

**Milan (IT)**  
**24-25 November 2014**

with the support of **IFCC**

**GENERAL INFORMATION**

**REGISTRATION FEE**  
EUR 305.00 (VAT 22% included)

**Who is eligible to register?**  
• Coffee break & lunch buffet as indicated in the programme  
• Certificate of participation

**Cancellations:**  
• registrations cancelled within August 30, 2014 will result in a 20% penalty  
• cancellations between August 30 and September 30, 2014 will be subject to a 50% penalty  
• afterwards, registrations will result in a 100% penalty

To make your registration, please access the following link:  
<http://mg.mcgraw-hill.com/medconferences/eflm2014>

**OFFICIAL LANGUAGE**  
The official language of the conference is English.

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M. Piantoni, Secret.  
e-mail: [info@eflm2014.com](mailto:info@eflm2014.com)

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Located in a strategic privileged position, close to the Porta Garibaldi Railway Station and in the heart of Milan's nightlife (Corso Como and Brera district). Well connected to public transports, the underground Metro (M2 Green line and M5 Blue line) are only few steps from the hotel.  
For more information, please visit:  
<http://www.milelupa.com/eflm2014>

**ACCOMMODATION**  
The following hotels are all located within distance from the congress venue. To book your room please refer to the below indicated hotel reservation system:

- **cityHotel Executive** (conference venue): <http://www.cityhotels.it/eflm2014>
- **cityUNATop Hotel** (200 meters from the congress venue): <http://www.unatop.it/milano>
- **cityHotel AC Milano** (500 meters from the congress venue): <http://www.cityhotels.it/milano>
- **cityHoliday Inn** (750 meters from the congress venue): <http://www.hilton.com/eflm2014>

**EFLM thanks the following companies for the kind and unconditional support**

**Abbott** **BIO-RAD** **Dynex** **Roche** **SIEMENS**

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

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

# Model 1. Based on the effect of analytical performance on clinical outcomes

- *Advantage*: to address the influence of analytical performance on clinical outcomes that are relevant to patients and society.
- *Disadvantage*: it is only useful for examinations where the links between the test, clinical decision-making and clinical outcomes are straightforward and strong.

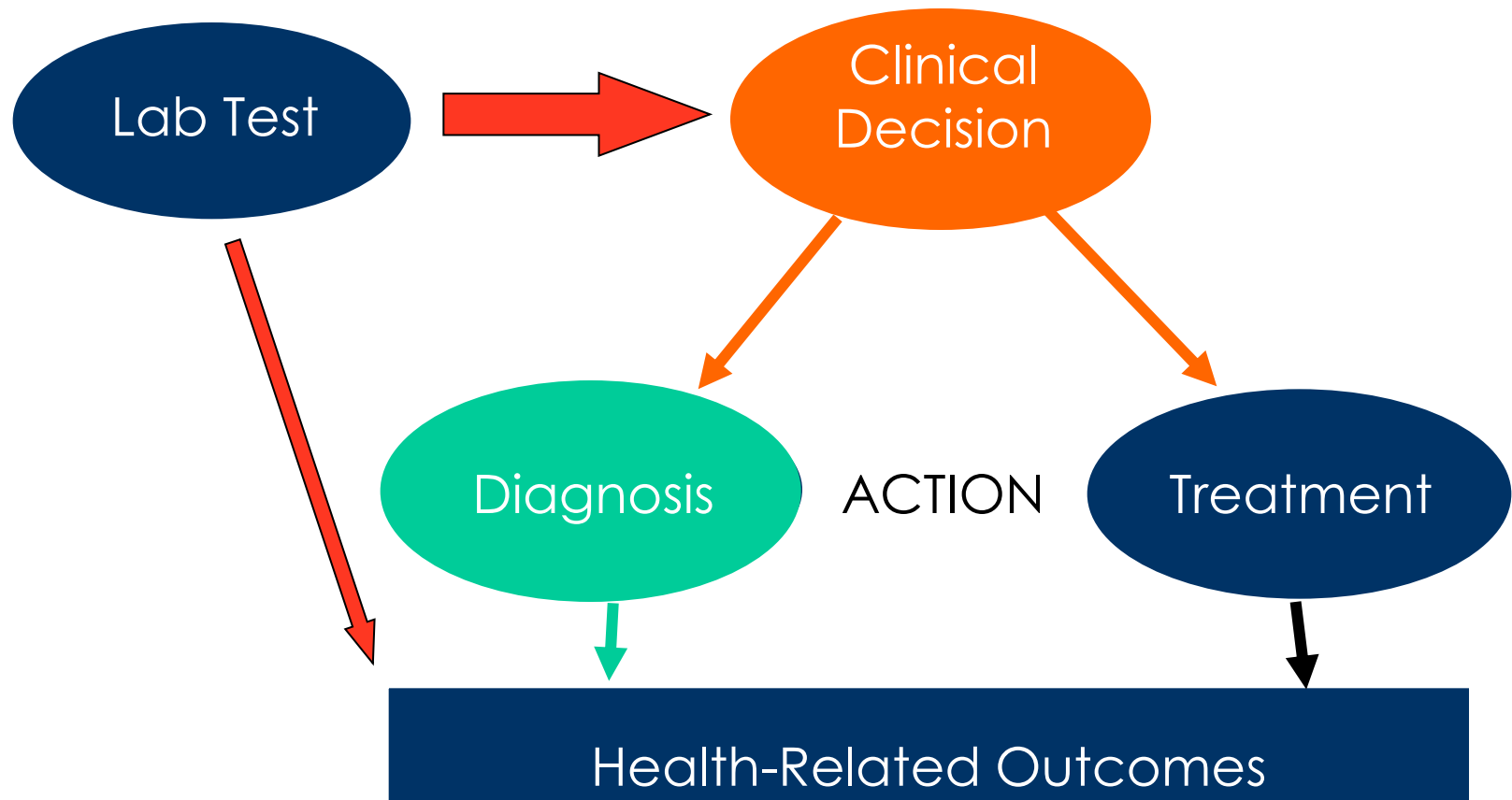
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# Challenge: Connecting Laboratory Testing to Outcomes



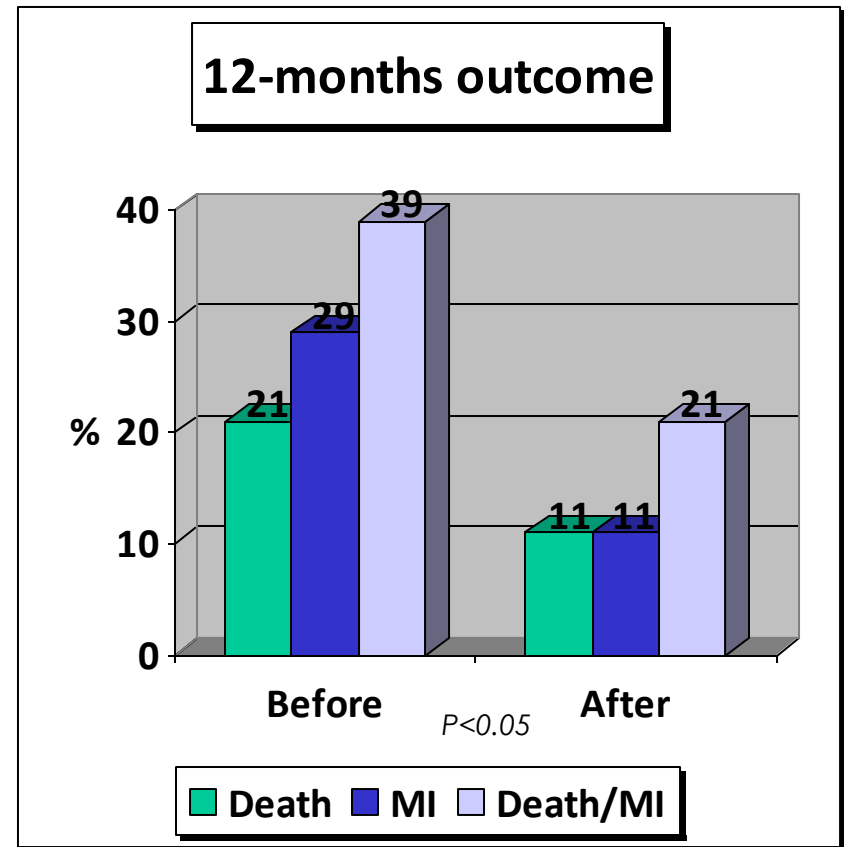
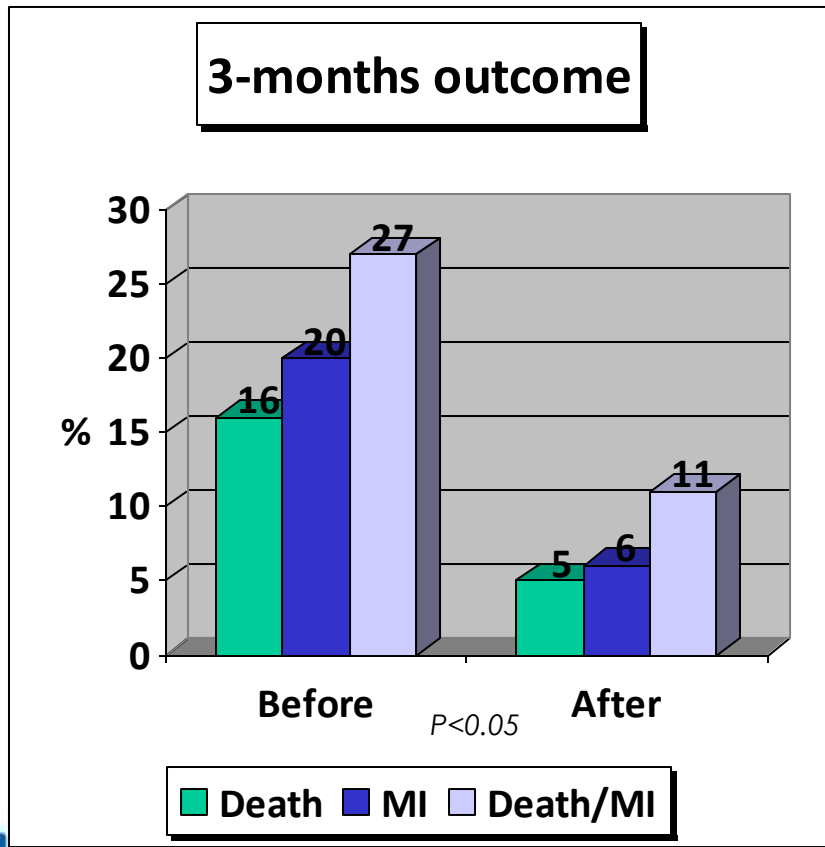
Demonstrating the value of lab tests on health outcomes is reliant on linking the test with processes that directly impact outcomes

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# Clinical outcomes of patients with only hs troponin positive before and after the introduction of a sensitive troponin assay



# APS based on clinical needs may be defined in terms of allowable misclassification rates

**Table.** Recommended analytical performance goals for cardiac troponin measurement for definition of the limit of quantitation of assays.

Quality level	Imprecision goal (as CV)			Bias goal <sup>a</sup>
	Outcome-based	Biological variability <sup>a</sup>	Expert opinion	
Minimum	<13% <sup>b</sup>	<7.3%	<20%	±21.6 %
Desirable	<10% <sup>c</sup>	<4.9%	<10%	±14.4 %
Optimum	<6% <sup>d</sup>	<2.4%	—	±7.2 %

<sup>a</sup> Calculated according to Fraser CG, Hytøft Petersen P, Libeer JC, Ricos C. Proposal for setting generally applicable quality goals solely based on biology. Ann Clin Biochem 1997;34:8-12.

<sup>b</sup> Assuming a diagnostic misclassification of 1.8%, <sup>c</sup> 1.0%, and <sup>d</sup> 0.5%.

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

- Intra-individual (within-subject) variation: represents the random fluctuation around an individual's own homeostatic set-point.
- Inter-individual (between-subject) variation: represents differences in homeostatic set-points among different individuals.
- Data on biological variation can be used to derive allowable limits for analytical imprecision and bias.

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

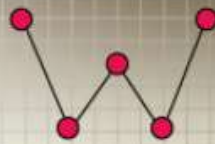
- *Advantage*: it can be applied to most measurands for which a “steady state” biologic model can be established.
- *Disadvantage*: need to carefully assess the relevance of biological variation data.

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## DESIRABLE BIOLOGICAL VARIATION DATABASE SPECIFICATIONS



Updated for 2014! Desirable Specifications for imprecision, inaccuracy, and total allowable error, calculated from data on within-subject and between-subject biologic variation. This database is updated and compiled by Dr. Carmen Ricos and colleagues. We are honored to be able to host this database.

DE GRUYTER

Clin Chem Lab Med 2015; 53(2): 299–305

Carmen Perich, Joana Minchinela, Carmen Ricós\*, Pilar Fernández-Calle, Virtudes Alvarez, María Vicenta Doménech, Margarita Simón, Carmen Biosca, Beatriz Boned, José Vicente García-Lario, Fernando Cava, Pilar Fernández-Fernández and Callum G. Fraser

## Biological variation database: structure and criteria used for generation and update

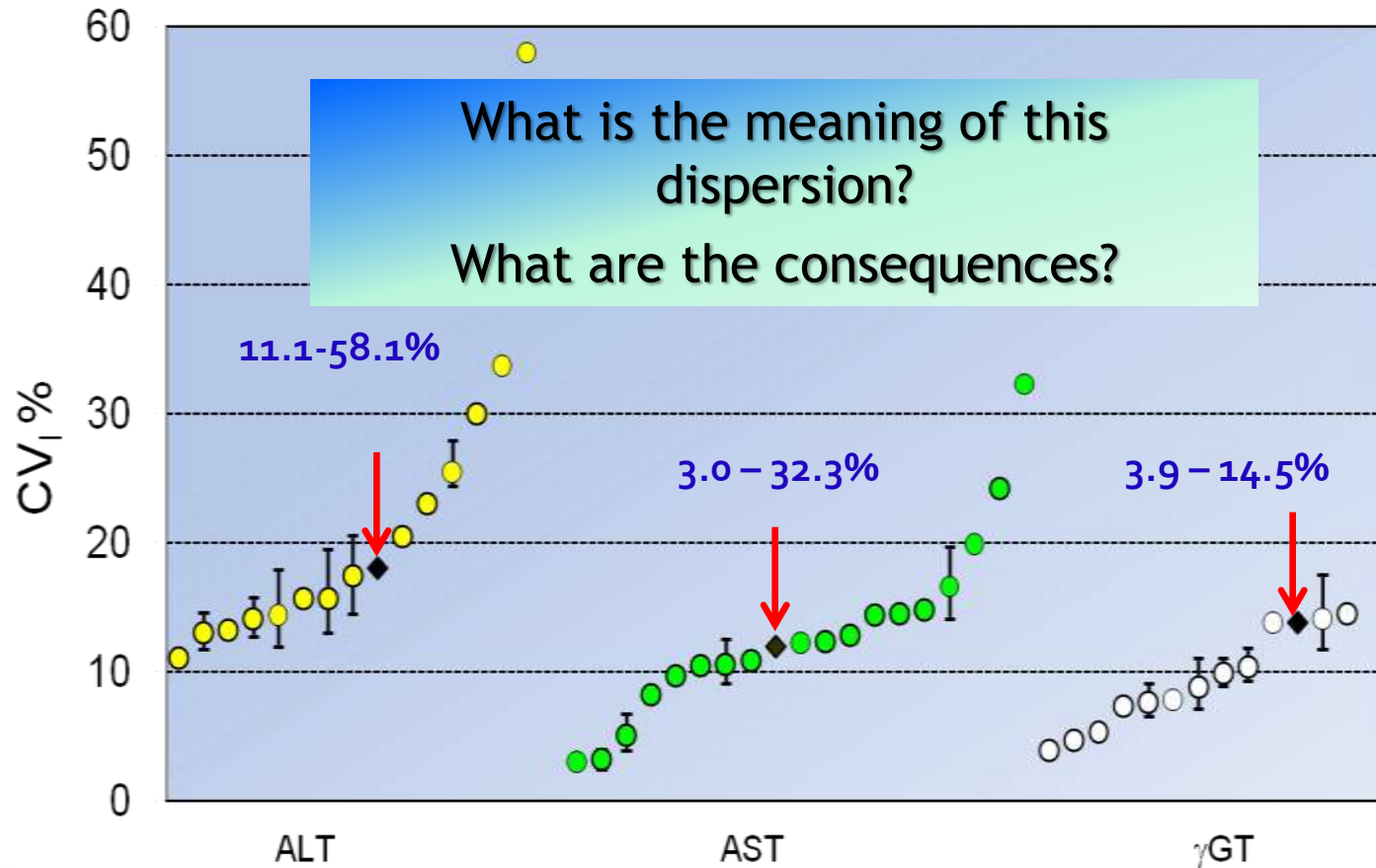


More than 240 articles  
More than 350 measurands

Generation of estimates of  $CV_I$  and  $CV_G$   
using the MEDIAN of all data compiled

## ALT, AST and $\gamma$ GT

Within-subject biological variation (CVI)



*The arrows show the values currently present in the Ricos' database*

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# Quantifying Biological Variation

How do you do the experiment?

- |                     |                                |
|---------------------|--------------------------------|
| ▶ Subjects          | How many?                      |
| ▶ Collect specimens | Number? Frequency?             |
| ▶ Analyse specimens | Minimise analytical variation? |
| ▶ Analyse data      | Outliers? Statistics?          |

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# Experimental Protocol for Biological Variability Estimate

- **Select healthy subjects (n=20)\***  
(subjects must be representative of the population)
- Specimens taken at set time intervals
- Specimens processed & stored frozen @  $-80^{\circ}\text{C}$
- When ALL specimens are available:  
analysis of all samples in a single run in duplicate

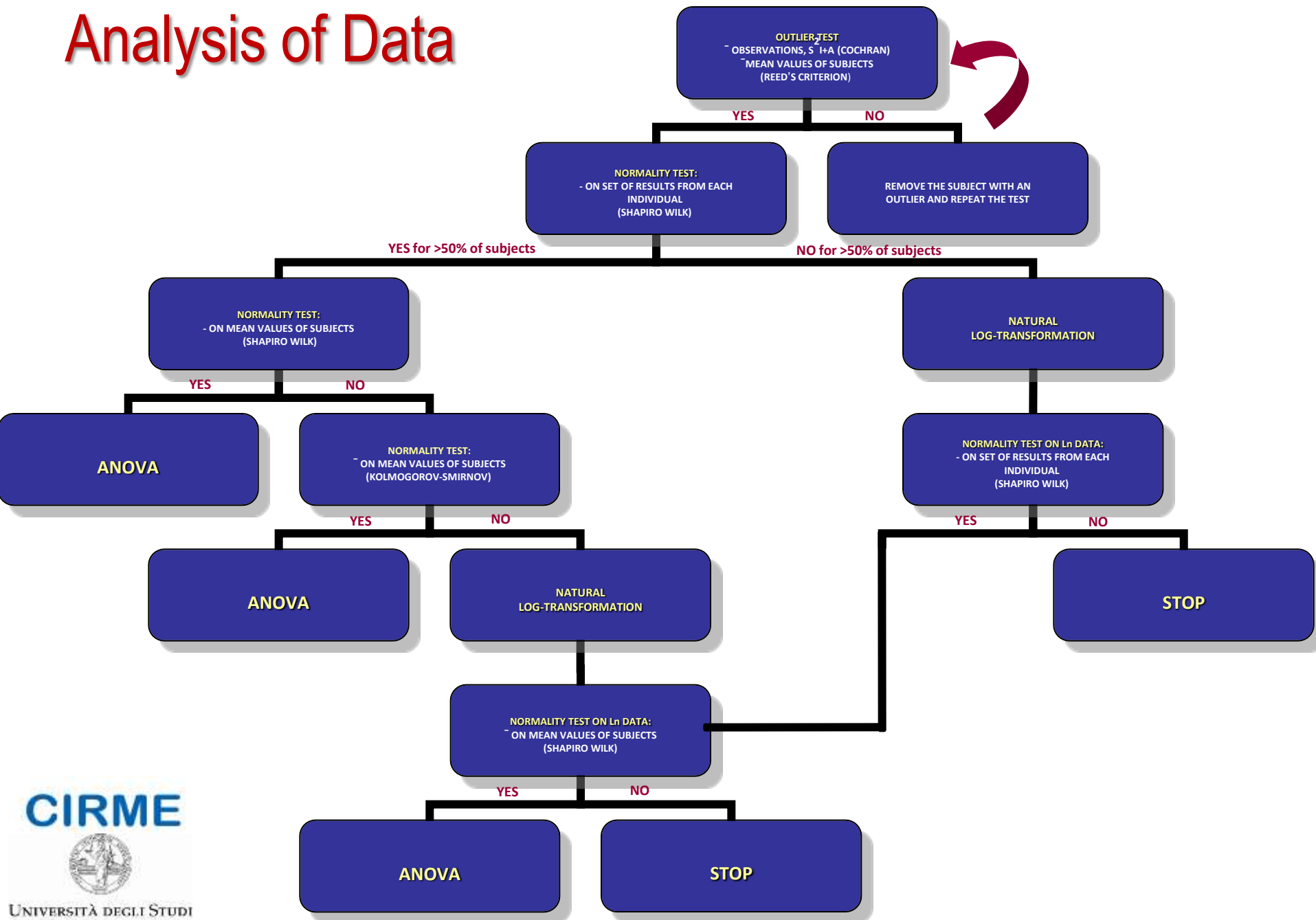
\*Conditions should minimise pre-analytical variables:

- ✓ Usual life style
- ✓ No drugs (alcohol, smoking?)
- ✓ Phlebotomy by same person at the same time of day
- ✓ Optimal protocol for sample transport, processing & storage

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# Analysis of Data



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# Is available information on biological variability reliable?

**Table 4**

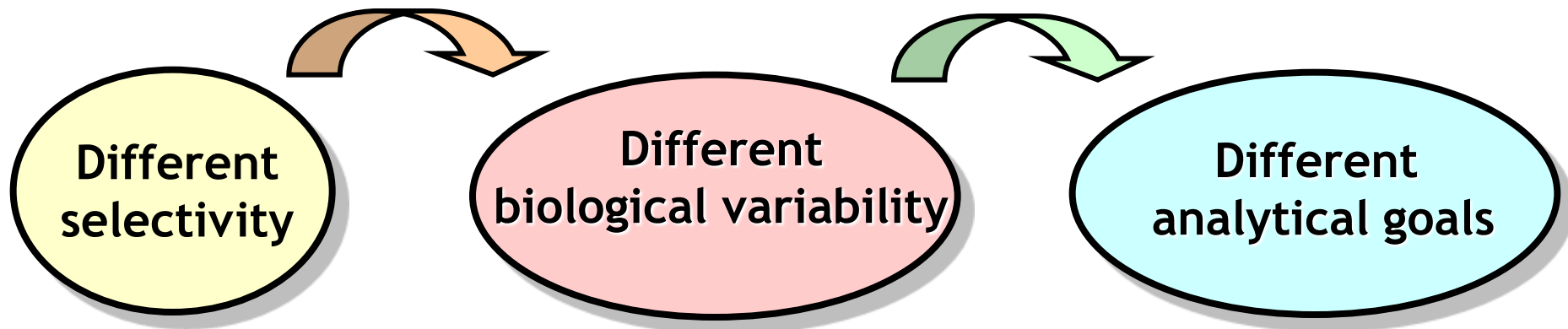
Summary of the characteristics of studies on biological variability of HbA<sub>1c</sub> evaluated in this systematic review.

Study no.	Method specificity as per HbA <sub>1c</sub> measurand definition	Recruitment of healthy subjects	Optimal study duration	Optimal protocol of sample analysis	Statistical analysis described
1	No	Yes	±	No	No
2	No	No	Yes	No	Yes
3	No	No	No	No	No
4	±	No	No	No	No
5	±	No	No	No	No
6	±	No	No	No	No
7	Yes	No	No	No	No
8	No	Yes (M only)	Yes	No	Yes
9	±	No	No	No	Yes

The majority of studies assayed a measurand different from that defined by IFCC, like total glycated hemoglobins, also including hemoglobins glycated on other sites differing from N-terminal valine of the  $\beta$ -chain.

# Assay selectivity is an important biological variation qualifier

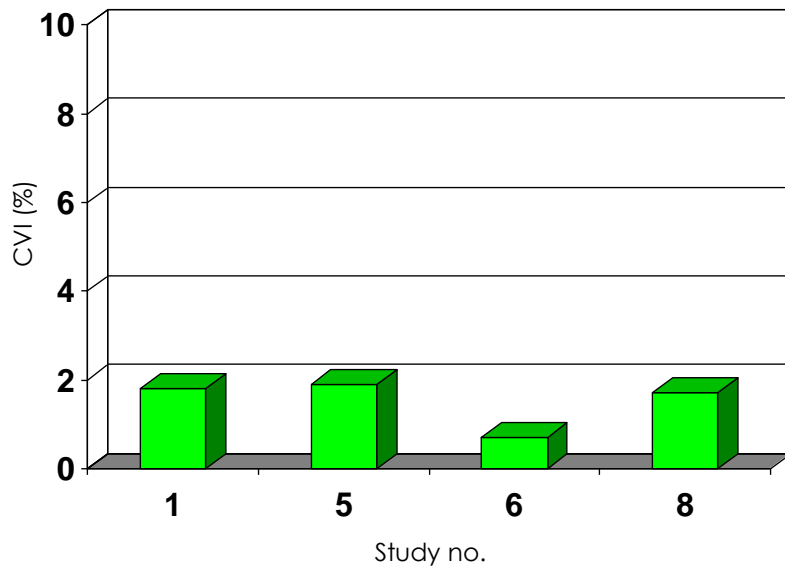
If the used methodology has different specificity for the measured analyte, one can expect that also the biological variability, a property closely associated with the characteristics of the analyte itself, significantly changes. And, if the biological variability changes, the analytical goals derived from it may be different.



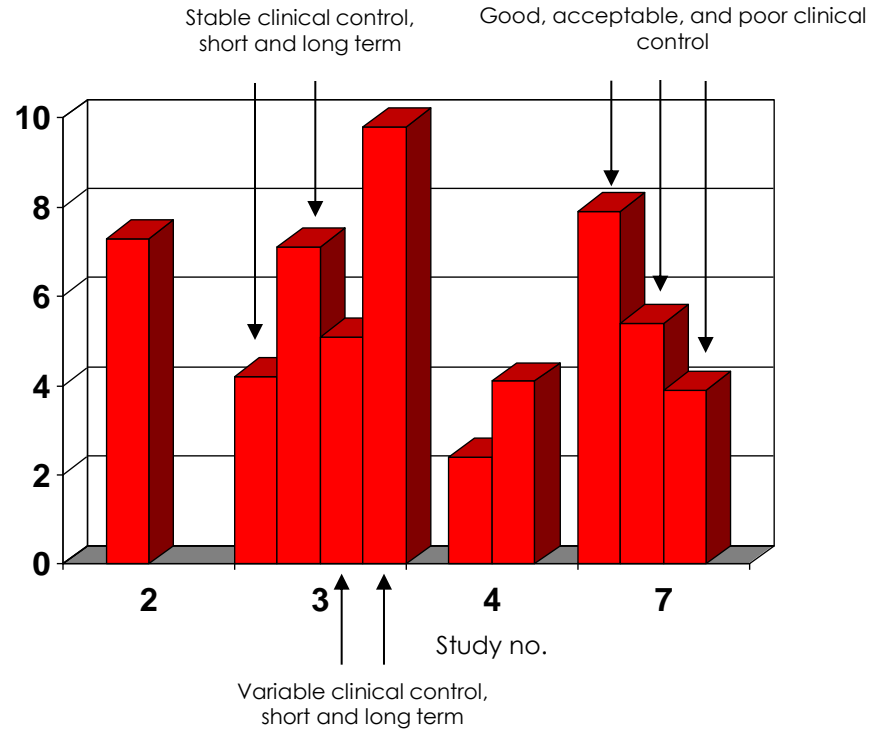
# Biological variation from patients

## Should they be used?

Healthy subjects



Diabetics



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Intra-individual variation in pathology >>  $CV_i$  of healthy individuals



Invited critical review

## Biologic variability of C-reactive protein: Is the available information reliable?

Federica Braga\*, Mauro Panteghini

**Table 2**

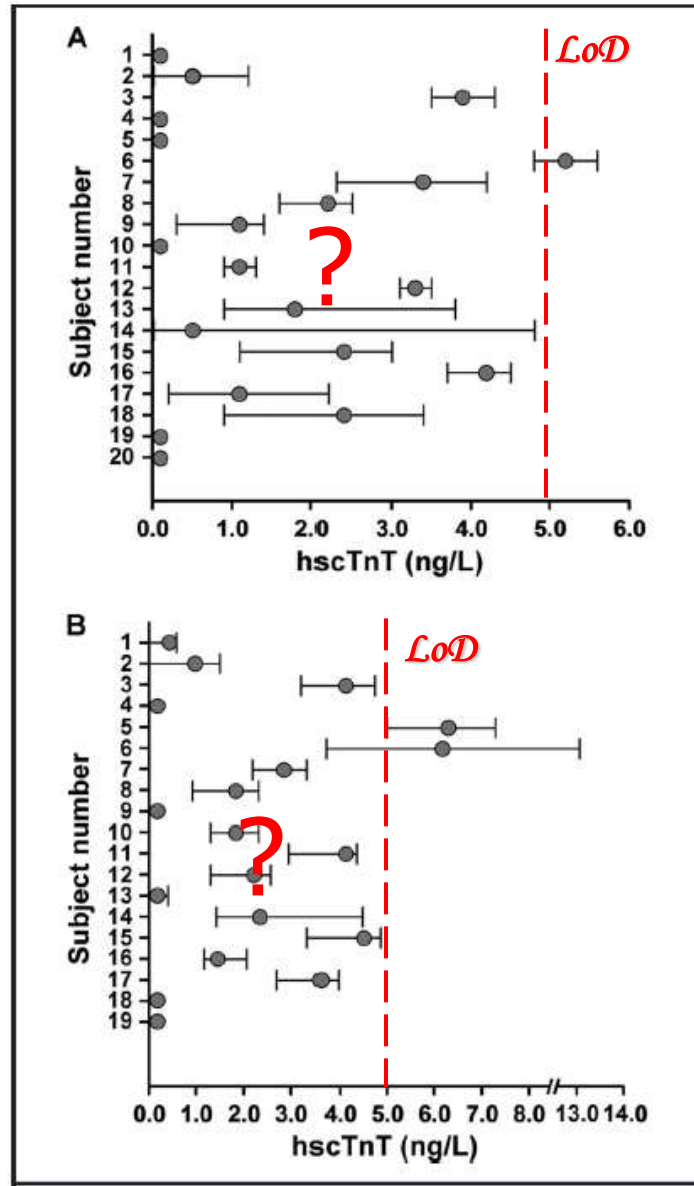
Summary of the characteristics of studies on biologic variability of C-reactive protein (CRP) evaluated in this systematic review.

Study no.	Assay sensitivity	Recruitment of healthy subjects	Optimal study duration and sampling frequency	Appropriate sample type	Optimal protocol of sample analysis	Statistical test for outliers	Testing normal distribution of data
1	No	Yes	No	Yes	No	Yes	No
2	No	Yes	No	Yes	No	Yes	No
3a	No	Yes	No	No	NA	No	No
3b	No	No	No	No	NA	No	No
4	Yes	Yes	No	No	NA	Yes	No
5	Yes	± <sup>a</sup>	No	No	NA	No	No
6	Yes	Yes	Yes	Yes	Yes	Yes	No
7	Yes	No	Yes	Yes	Yes	No	Yes
8	Yes	Yes	No	Yes	No	No	No
9	Yes	± <sup>b</sup>	No	No	No	Yes	No
10	Yes	No	No	No	NA	No	No
11	NA	No	No	Yes	No	Yes	No

NA, information not available.

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# Is available information on biological variability of troponin T reliable?



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Invited critical review

## Biologic variability of C-reactive protein: Is the available information reliable?

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Summary of the characteristics of studies on biologic variability of C-reactive protein (CRP) evaluated in this systematic review.

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1	No	Yes	No	Yes	No	Yes	No
2	No	Yes	No	Yes	No	Yes	No
3a	No	Yes	No	No	NA	No	No
3b	No	No	No	No	NA	No	No
4	Yes	Yes	No	No	NA	Yes	No
5	Yes	± <sup>a</sup>	No	No	NA	No	No
6	Yes	Yes	Yes	Yes	Yes	Yes	No
7	Yes	No	Yes	Yes	Yes	No	Yes
8	Yes	Yes	No	Yes	No	No	No
9	Yes	± <sup>b</sup>	No	No	No	Yes	No
10	Yes	No	No	No	NA	No	No
11	NA	No	No	Yes	No	Yes	No

NA, information not available.

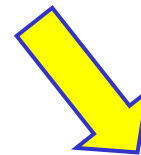
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## Have data not normally distributed been appropriately transformed?



1) This is a critical aspect! Studies using statistical parametric approach on data not normally distributed **should be excluded from database!** Otherwise we will continue to have  $CV > 33\%$ !!



2) When a not normal data distribution is present, a log-transformation of data is recommended, but **this approach does not always solve the distribution problems: Check normality after log-transformation!!**

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	Analyte	Number of papers	Biological Variation		Desirable specification		
			CVw	CVg	I(%)	B(%)	TE(%)
S-	C reactive protein	3	42.2	76.3	21.1	21.8	56.6

24. Clark GH, Fraser CG. Biological variation of acute phase proteins. Ann Clin Biochem 1993; 30: 373-376

serum samples

CVw = 63%;

CVg 76.3%

100. Macy EM, Hayes TE, Tracy RP. Variability in the measurements of C- reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem 1997; 43: 52-58

plasma samples

CVw = 42.2%;

CVg 92.5%

197. Cho Li Wei, Jayagopal V, Kilpatrick ES, Atkin SL. The biological variation of C-reactive protein in polycystic ovarian syndrome. Clin Chem 2005;51:1905-1907

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serum samples

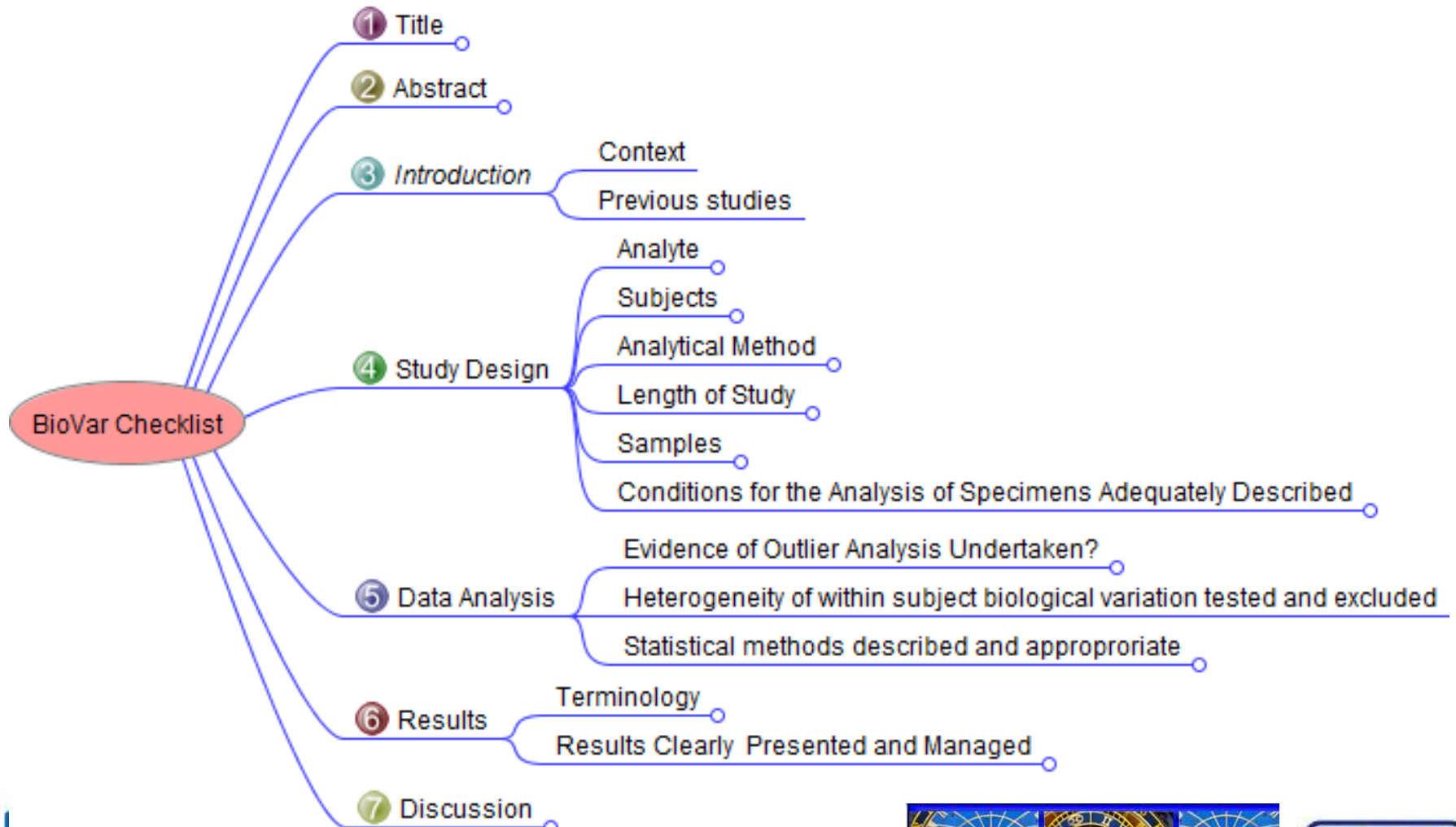
CVw = 36,8%;

CVg 62.2%

# Summary

- BV data are complex reference data
- Published data are of varying quality
- Safe application requires prior critical appraisal
- Need for standards (i.e. a minimum set of attributes to enable the data to be effectively transmitted and applied)

# A checklist for critical appraisal of studies of biological variation



# Model 3. Based on state-of-the-art

This relates to the highest level of analytical performance technically achievable.  
[Alternatively, it could be defined as the analytical performance achieved by a certain percentage of laboratories]

➤ Advantage: numbers are readily available.

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# Problems with the state-of-the-art concept

- No scientific reasoning
- Often based on „old“ data which may be outdated
- Lack of transparency
- Lack of neutrality (dependency on industry)
- No relationship between what is achievable and on what is needed clinically

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# Possible criteria for allocation of laboratory tests to different models for performance specifications

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

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8th

**1<sup>st</sup> EFLM Strategic Conference**  
**Defining analytical  
performance goals  
15 years after the  
Stockholm Conference**  
8<sup>th</sup> CIRME International Scientific Meeting

Milan (IT)  
24-25 November 2014

with the  
support of  
**IFCC**  
International Federation of Clinical Chemistry

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- Coffee break & lunch buffet as indicated in the programme
- Certificate of participation

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- cancellations between August 30 and September 30, 2014 will be subject to a 50% penalty
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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

### 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. 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.

# Performance criteria

	Analytical Phase	Pre/Post-Analytical Phase
Models for performance specifications	<i>Defined</i>	<i>Not defined</i> Possibly based on the <u>State-of-the-Art</u> and on <u>Outcome measures</u>
Metrics	<i>Well defined</i>	<i>Proposed</i> <ul style="list-style-type: none"><li>- Percentage</li><li>- Parts per million (ppm)</li><li>- Six sigma</li></ul>
Tools of measures	<i>Well defined</i> Internal Quality Control (IQC) External Quality Assessment (EQA)	<i>Recently defined</i> Quality Indicators (QI)

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**Table 1**

Summary of features and requirements for achieving harmonization in laboratory testing.

Phase	Requirements	Vested stakeholders
Pre-pre-analytical	1. Use of evidence-based guidelines for appropriate test selection. 2. Plan for implementation and educational phases.	1. Clinicians; <u>the laboratory community</u> ; guideline organizations. 2. Professional societies; <u>the laboratory community</u> .
Pre-analytical	1. Standardize pre-laboratory/external pre-analytical processes. 2. Implement SOPs to reduce error and ensure patient safety.	1. Healthcare practitioners e.g. phlebotomist; <u>laboratory personnel</u> . 2. WHO World Alliance for Patient Safety; CLSI; IFCC WG-LEPS.
Analytical	1. Harmonize patient results through a standardization and/or harmonization process. 2. Harmonize laboratory test names and units. 3. Standardize test requesting and reporting for the EHR. 4. Harmonize report formats where there are patient safety issues. 5. Monitor reliability of analytical systems and analytical quality of measurements.	1. JCTLM; national metrology institutes; reference material providers; IFCC; IVD manufacturers; EQAS organizers; <u>clinical laboratories</u> . 2–4. Clinical terminology and information systems providers; IUPAC; IFCC C-NPU; Governments; patient safety groups. 5. IVD manufacturers; EQAS organizers; <u>clinical laboratories</u> .
Post-analytical	1. Harmonize reference intervals and clinical decision limits. 2. Plan for implementation and educational phases.	1–2. Professional societies; IFCC C-RIDL; <u>the laboratory community</u> ; clinicians.
Post-post-analytical	3. Report critical patient values according to an agreed critical test list. 1. Educate users about the meaning of laboratory tests. 2. Develop an on-going laboratory-clinical systems provider working relationship for long-term sustainability of pathology harmonization.	3. <u>Laboratory personnel</u> ; clinicians; GPs. 1. Clinicians; GPs; consumer advocate groups; patients. 2. <u>The laboratory community</u> ; clinicians; systems providers.



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## Harmonization of laboratory testing – Current achievements and future strategies

Jillian R Tate<sup>a,\*</sup>, Roger Johnson<sup>b</sup>, Julian Barth<sup>c</sup>, Mauro Panteghini<sup>d</sup>

