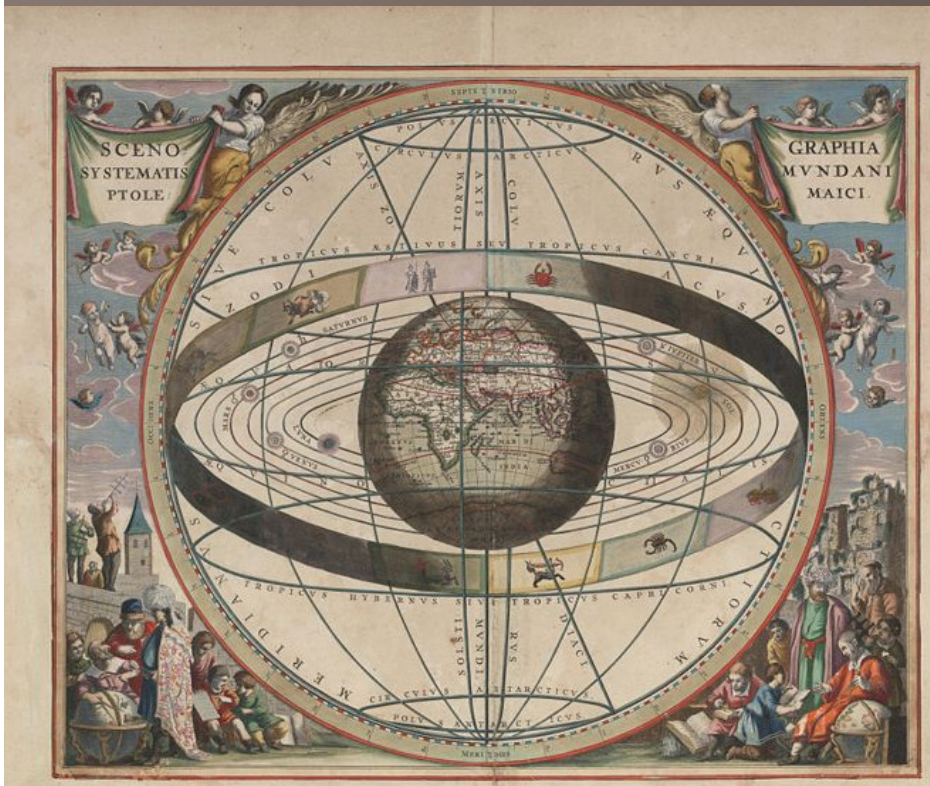
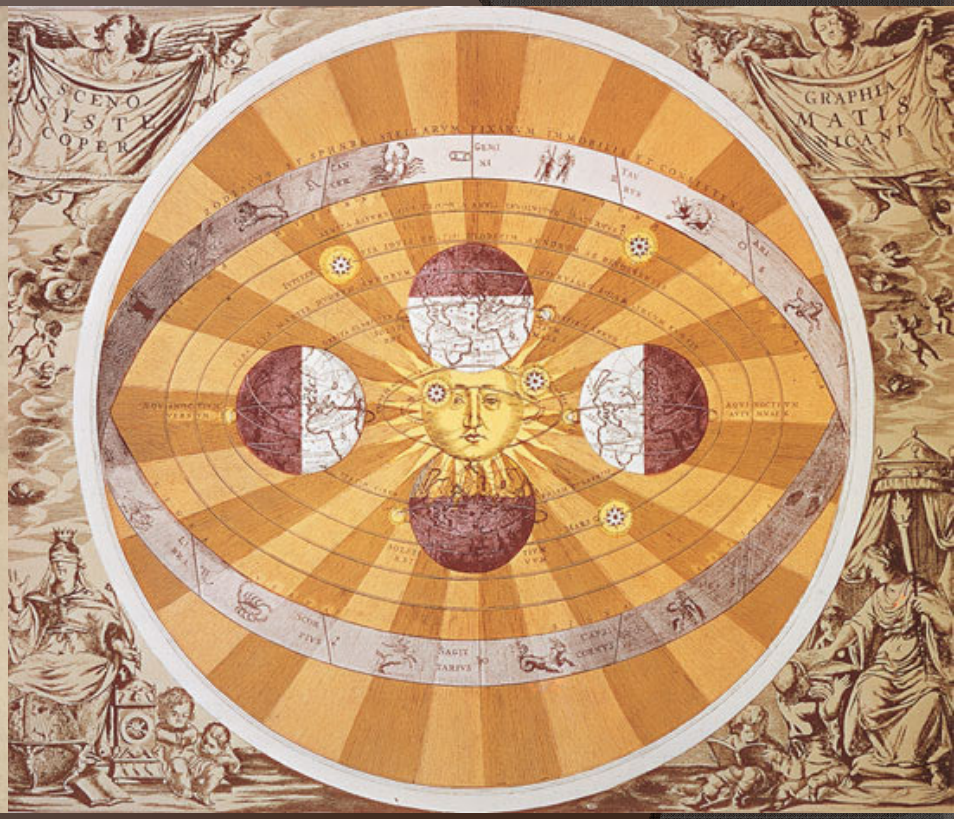
4th International Scientific Meeting

RETHINKING QUALITY CONTROL IN THE TRACEABILITY ERA

Milano - 30 November 2010





TRACEABILITY IN LABORATORY MEDICINE: COPERNICAN REVOLUTION OR ACTIVITY FOR A RESTRICTED PROFESSIONAL CLUB?

Mauro Panteghini

The issue: an absolute priority for public health

→ Our customers (i.e., doctors and patients) expect laboratory results to be ***accurate and comparable*** and interpreted in a reliable and consistent manner: so we urgently need to make them the same

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Potential impacts of the issue

- CLINICAL
- ECONOMICAL
- ETHICAL

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Standardization: clinical impact

Interchangeability of results over time and space would significantly contribute to improvements in healthcare by allowing results of clinical studies undertaken in different locations or times to be universally applied

Standardize clinical decision limits (i.e., cutpoints for intervention)

Effective application of evidence-based medicine

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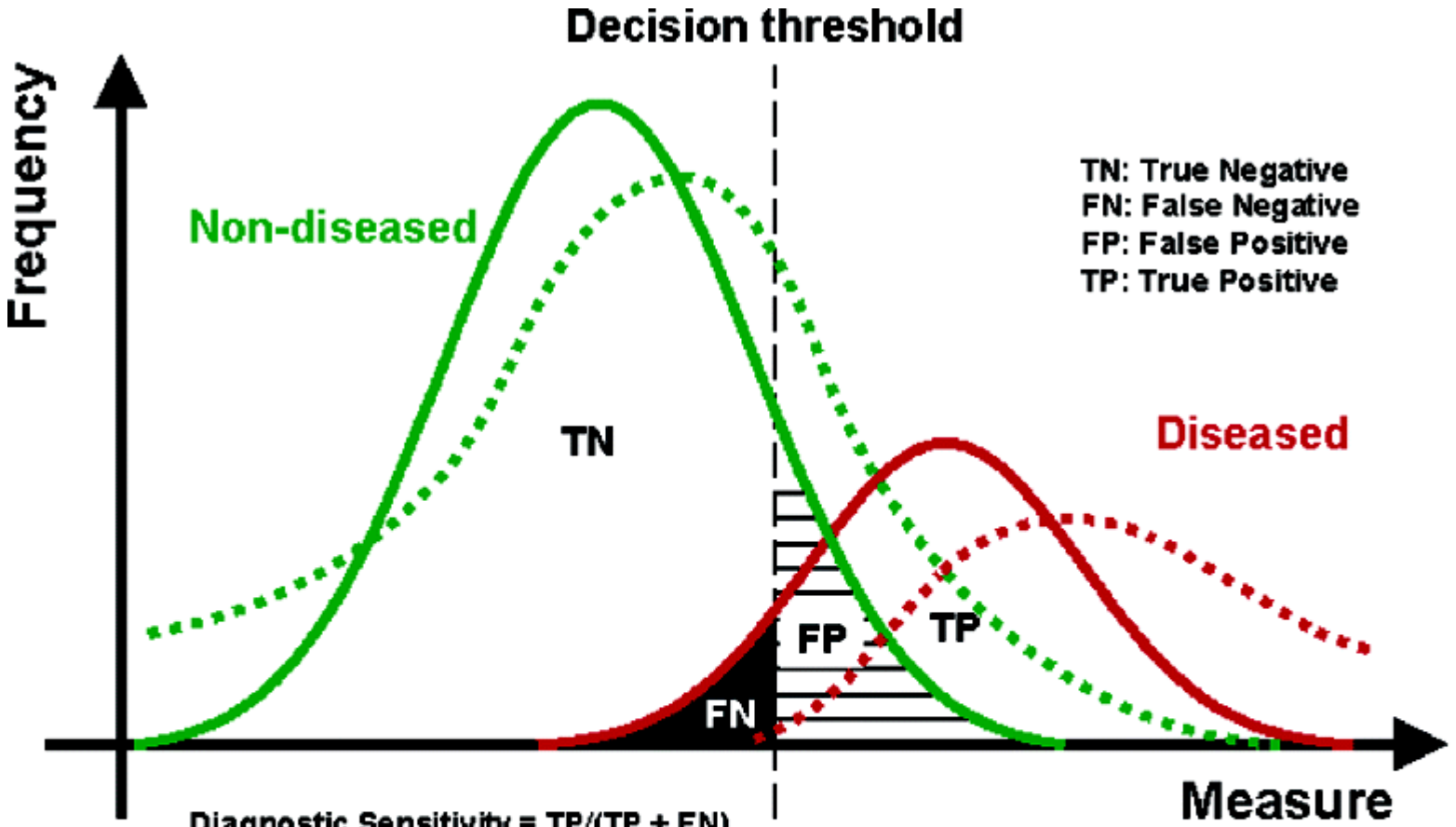

Diagnostic Sensitivity = TP/(TP + FN)
Diagnostic Specificity = TN/(TN + FP)

Positive Predictive Value (PPV) = TP/(TP + FP)
Negative Predictive Value (NPV) = TN/(TN + FN)

Disease frequency ($AUC_{diseased}/AUC_{non\text{-}diseased}$) affects PPV and NPV

Impact of test accuracy (bias shifts and imprecision skews and broadens curves)

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Growth Hormone in clinical guidelines

Port Stevens consensus
(adult GHD, JCE&M 1998)

Most normal subjects respond to insulin-induced hypoglycemia with a peak GH concentration of more than 5 μg/L. Severe GH deficiency is defined by a peak GH response to hypoglycemia of less than 3 μg/L.

Eilat consensus
(childhood GHD, JCE&M 2000)

In a child with clinical criteria for GHD, a peak GH concentration below 10 μg/L has traditionally been used to support the diagnosis.

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NOTA 39 AIFA Ormone della crescita (somatotropina)

ALLEGATO 1

La prescrizione a carico del SSN, su diagnosi e piano terapeutico di centri specializzati, Università, Aziende Ospedaliere, Aziende Sanitarie, IRCCS, individuati dalle Regioni e dalle Province autonome di Trento e Bolzano, è limitata alle seguenti condizioni:

Età evolutiva

II: Parametri di laboratorio:

a) risposta di GH < 10 µg/L a due test farmacologici eseguiti in giorni differenti (la risposta ad un solo test farmacologico >10 µg/L esclude la diagnosi di deficit di GH);

Età adulta

E' indicata la terapia con rGH in soggetti adulti, di età superiore a 25 anni, con livelli di GH allo stimolo con ipoglicemia insulinica <3 µg/L

M. Bidlingmaier, Endocrine Research Laboratories, Ludwig-Maximilians University, Munich, GE:
Conclusions @ Euromedlab Innsbruck 2009

- **GH assays have been inaccurate in the past**
- **GH assays are inaccurate today**
- **"Estimates" of circulating GH concentrations vary by more than 300%**
- **Presence or absence of a disease mainly depends on which assay is (by chance?) chosen by the lab**
- **There was no significant improvement over the last 20 years**
- **It is waste of time to discuss about cut-off levels for clinical guidelines**

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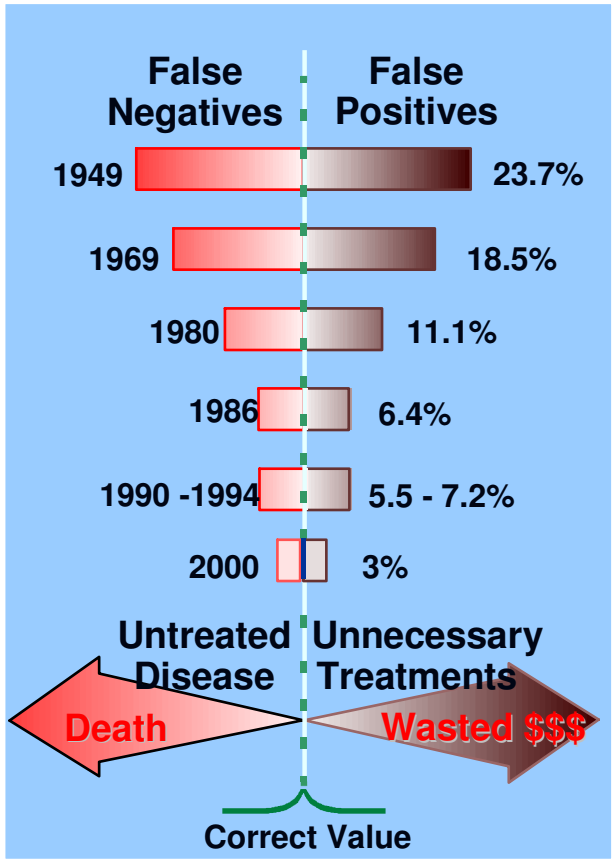
Standardization: economic impact



Improvement in accuracy of cholesterol measurements since 1968 has been estimated to save $100M/yr in treatment costs

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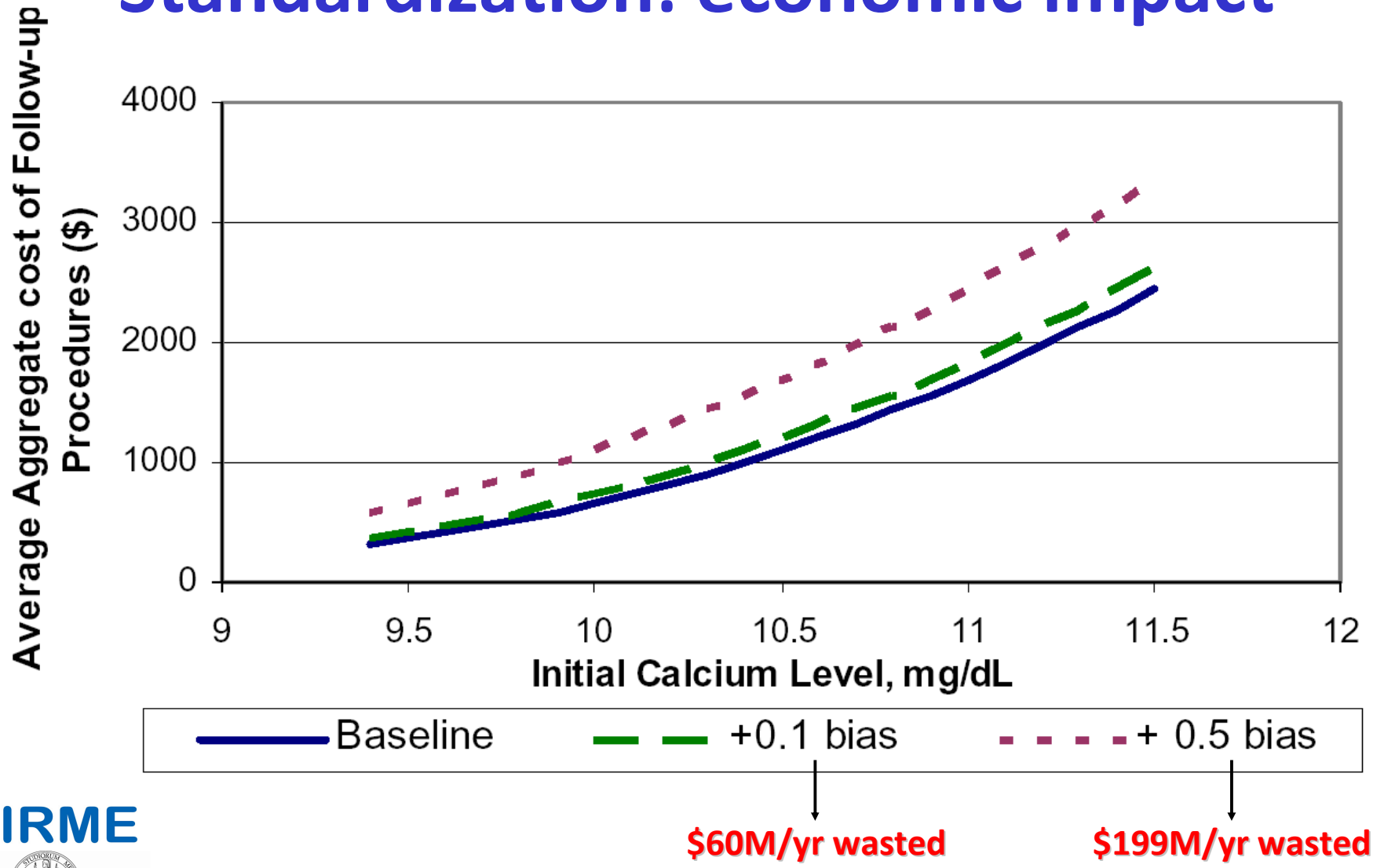
Data from U.S. Government Accounting Office and College of American Pathologists

Standardization: economic impact



Source: NIST Planning Report 04-1, 2004

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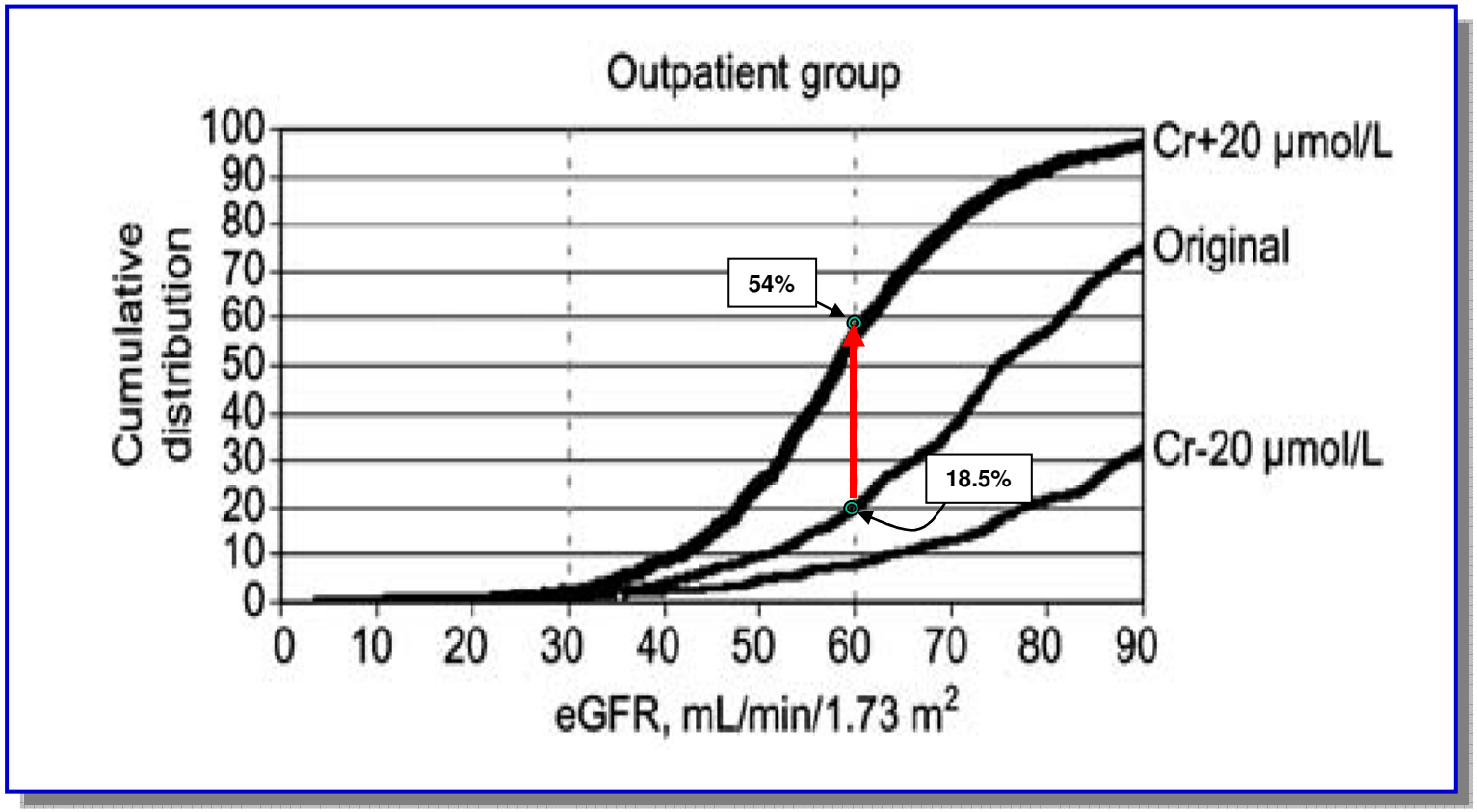
Effect of analytic inaccuracy in creatinine on the distribution of estimated GFR values



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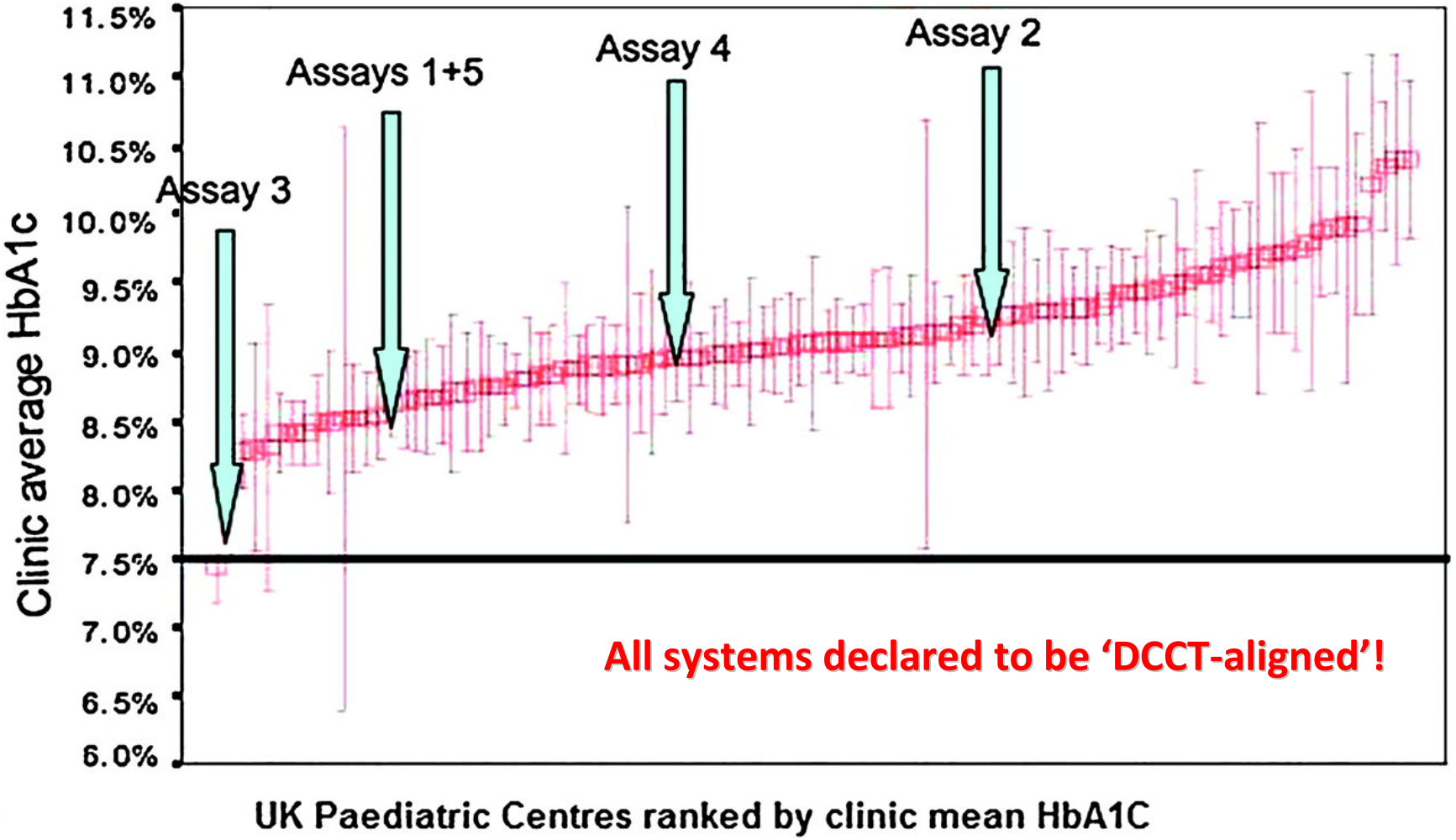
Klee GG et al., Clin Chem Lab Med 2007;45:737

The impact of the different HbA $_{1c}$ assays on position relative to other UK paediatric diabetes centres. The mean HbA$_{1c}$ of patients within a diabetes clinic or GP practice is being utilized by commissioners as a metric by which to assess the quality of diabetes care provided, which are likely to reach the public domain and used to determine remuneration.



Elder C et al. J Clin Pathol 2010;63:660

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."

Bossuyt X et al., Ann Rheum Dis 2008;67:1061

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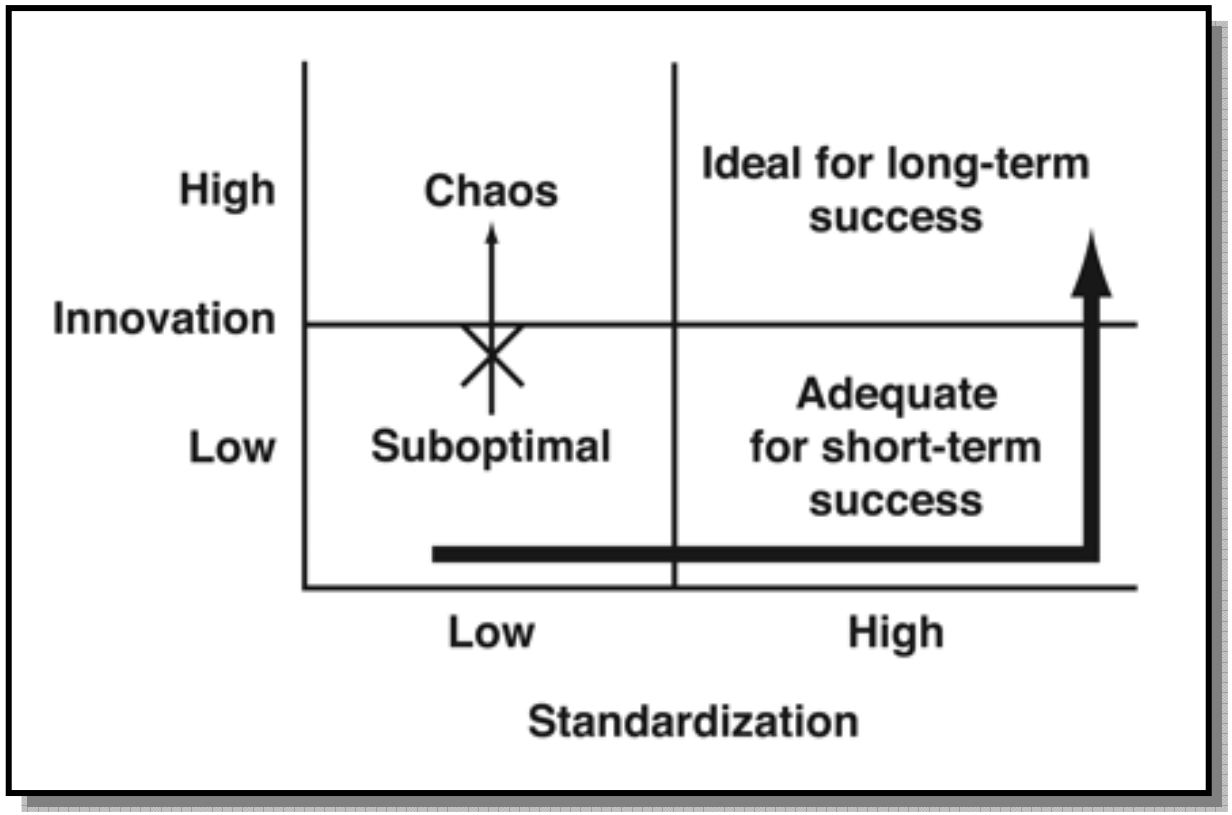
Ethical lag occurs when the speed of technological change (innovation) exceeds that of ethical development (standardization)



Hernandez JS X et al., Am J Clin Pathol 2010;133:8

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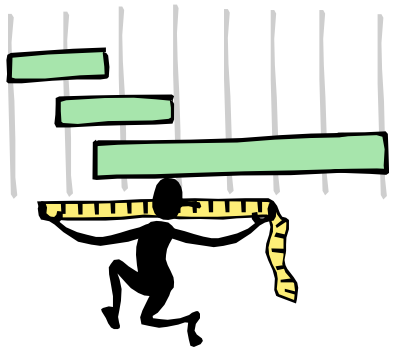

Solution

→ To be accurate and comparable, results must be traceable: only traceability to high-order references can manage the issue and support evidence-based medicine in a global world

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Objective of traceability implementation

To enable the results obtained by the calibrated routine procedure to be expressed in terms of the values obtained at the highest available level of the calibration hierarchy

Advantages:

- **All routine methods will be standardized to the same reference with no additional effort by laboratories**
- **The process can be sustained over time by the IVD manufacturers**

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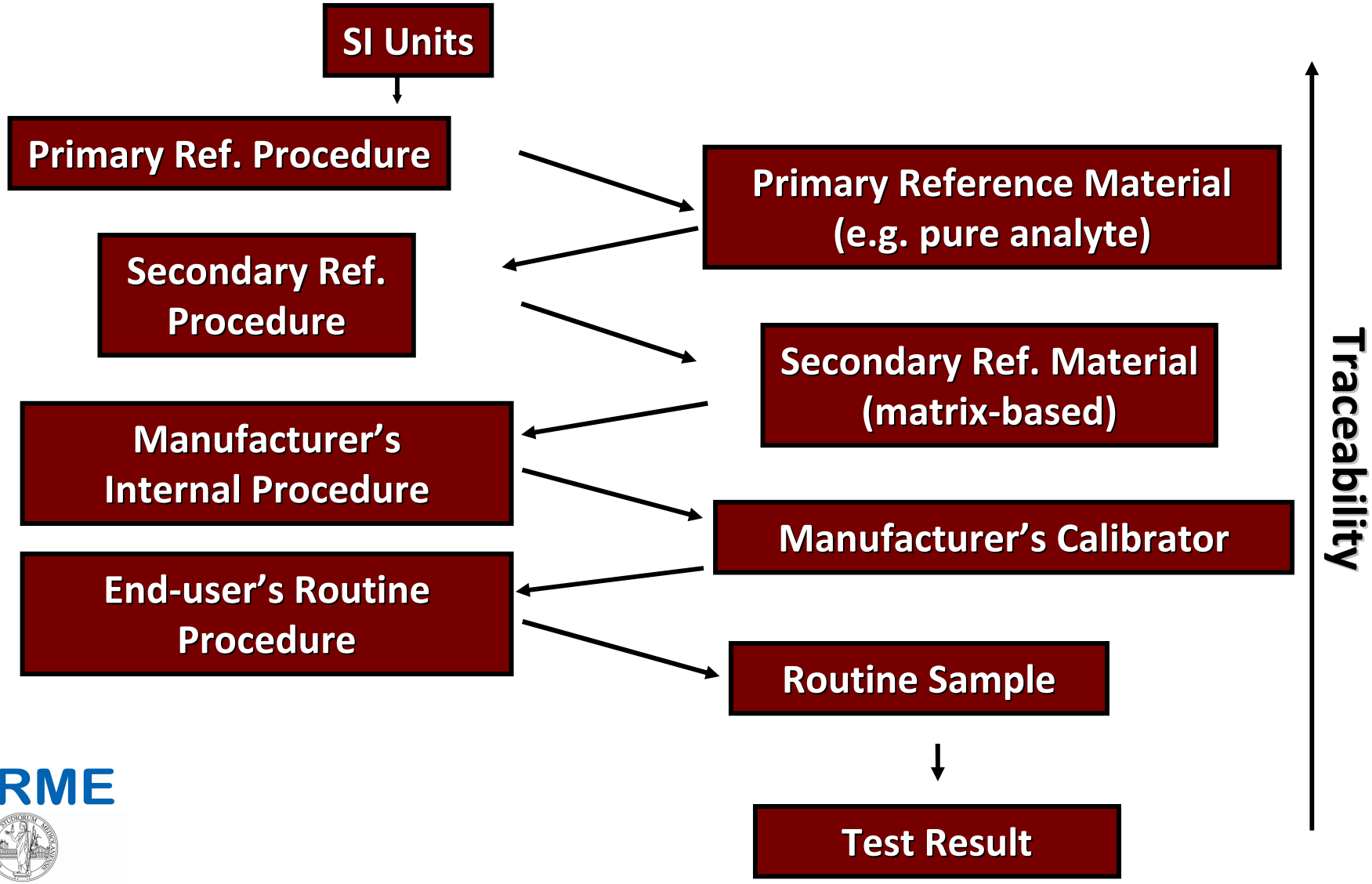
Reference Measurement System



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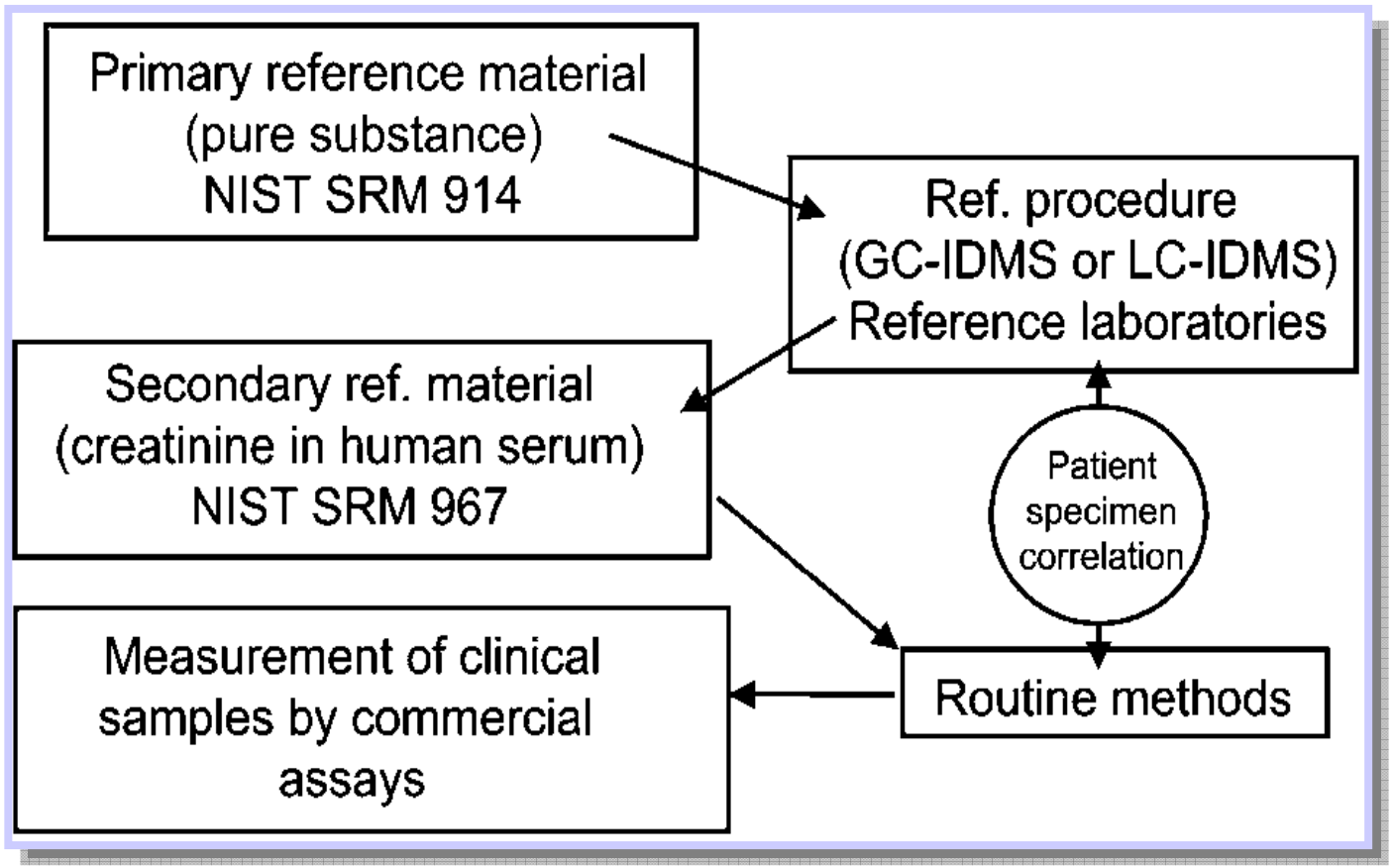
Panteghini M, Clin Biochem 2009;42:236

Reference System for Creatinine



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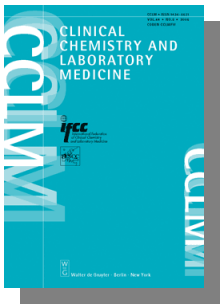
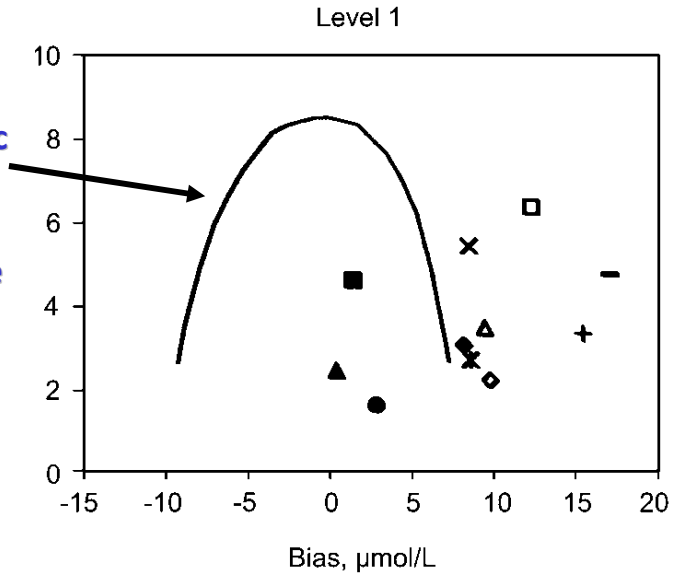
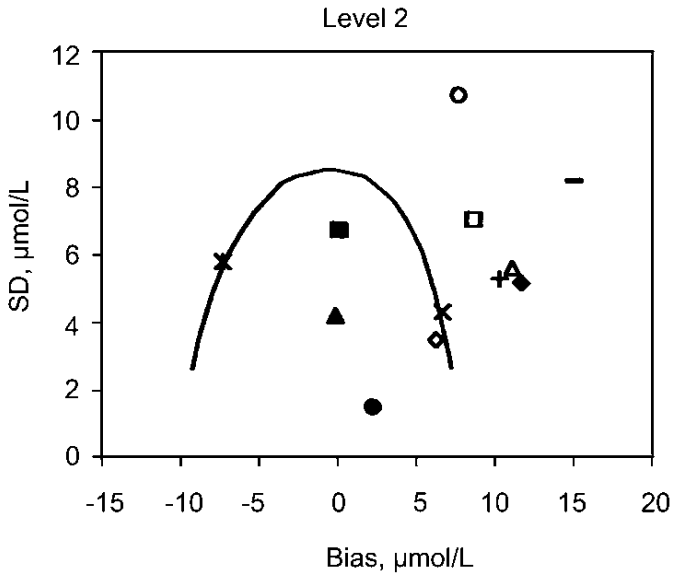
Panteghini M et al., Clin Chem Lab Med 2006;44:1187

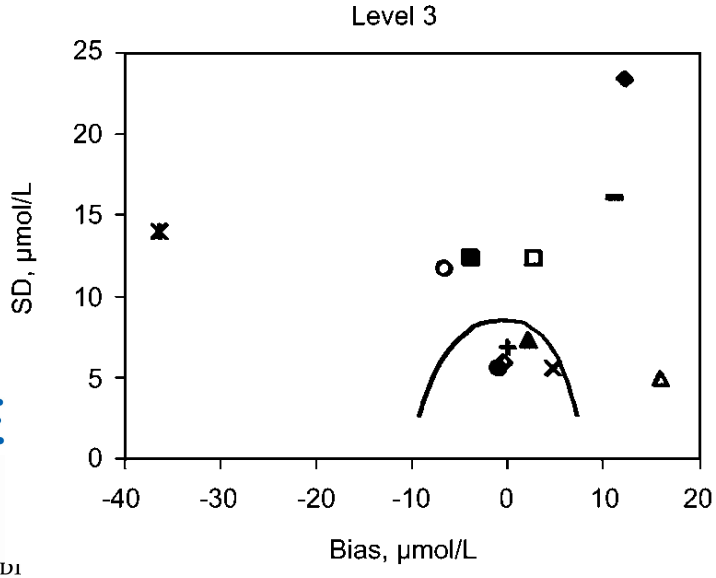


2005 accuracy verification study of creatinine measurements in 189 European labs

The line represents the limit of systematic bias and imprecision that produce a relative increase of <10% in the mean error when estimating GFR using the MDRD Study equation







- Compensated Jaffe (n=29)
- Enzymatic (n=33)
- Enzymatic dry chemistry (n=19)
- Enzymatic UV (n=5)
- Jaffe (all) (n=103)
- Jaffe Abbott (n=20)
- Jaffe Bayer (n=17)
- Jaffe Beckman Coulter (n=16)
- Jaffe Dade Behring (n=16)
- Jaffe Konelab (n=5)
- Jaffe Olympus (n=23)
- Jaffe Roche (n=9)

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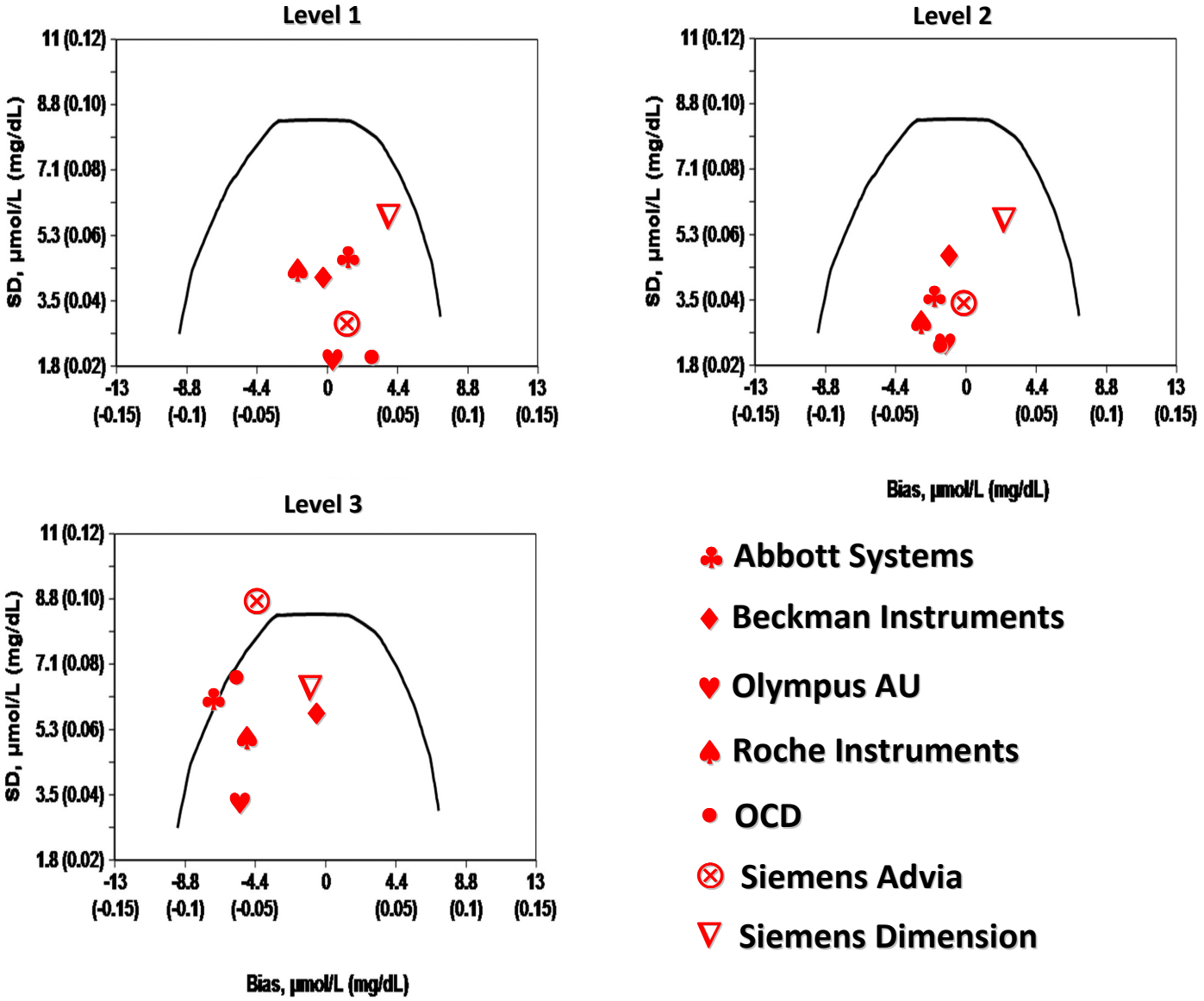
Delanghe JR et al., Clin Chem Lab Med 2008;46:1319

Creatinine Accuracy Calibration Verification/Linearity Survey LN24-B

Results from 2009 mailing



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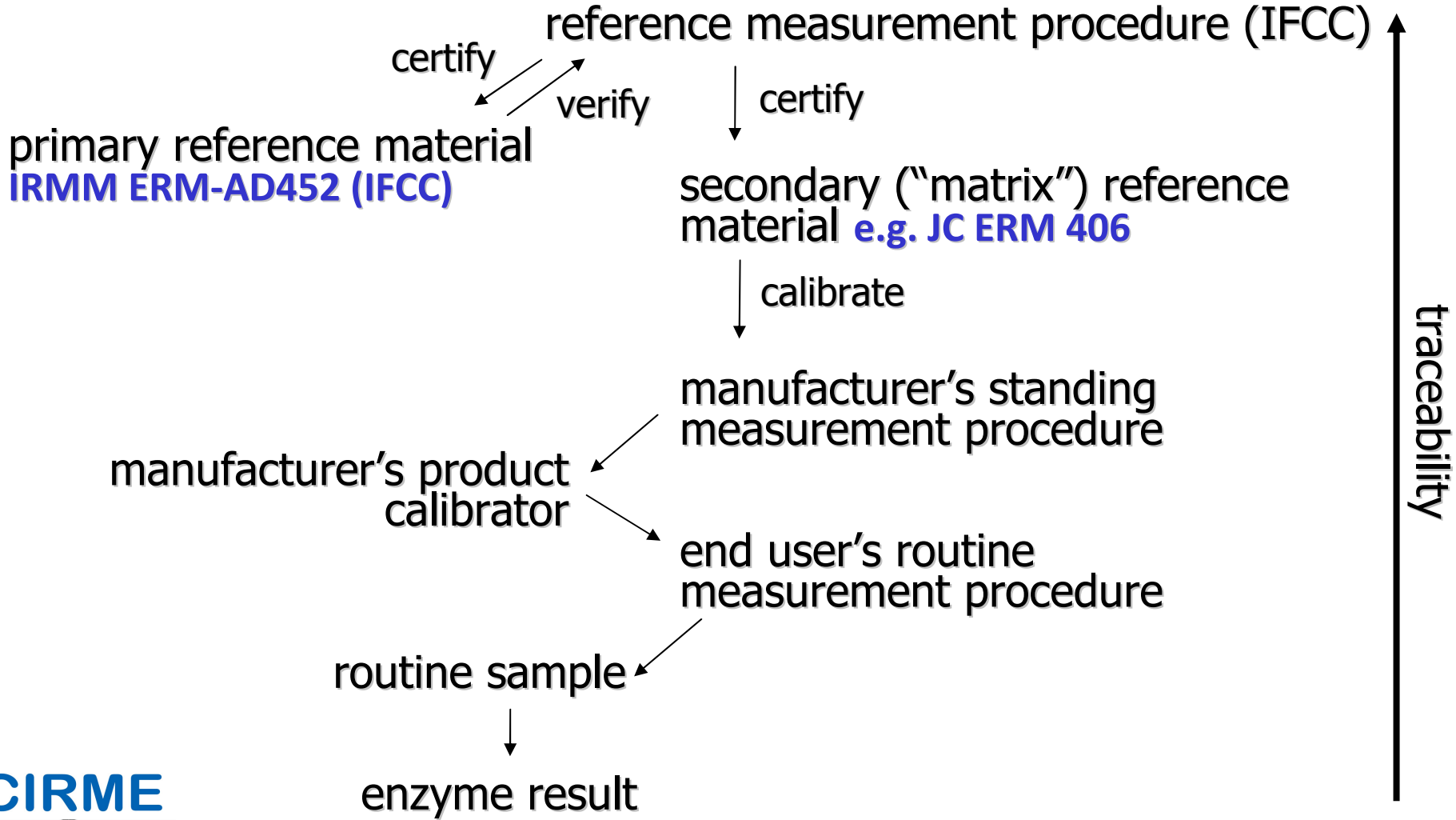
Reference System for γ-Glutamyltransferase



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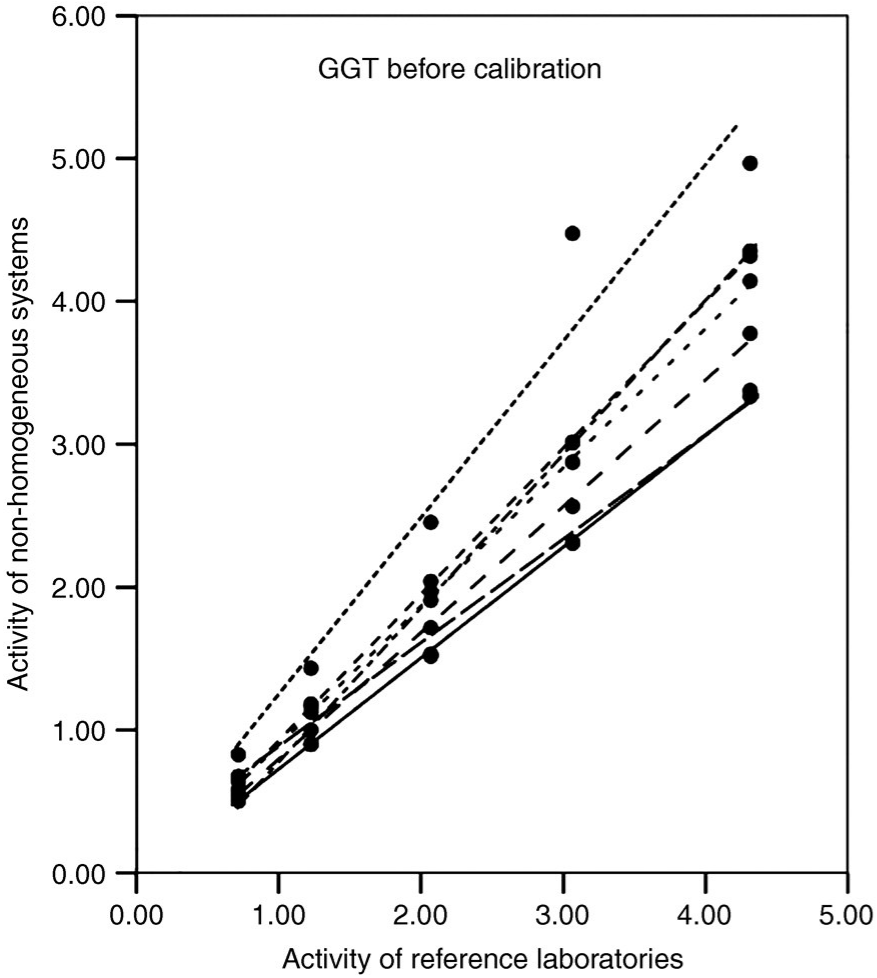
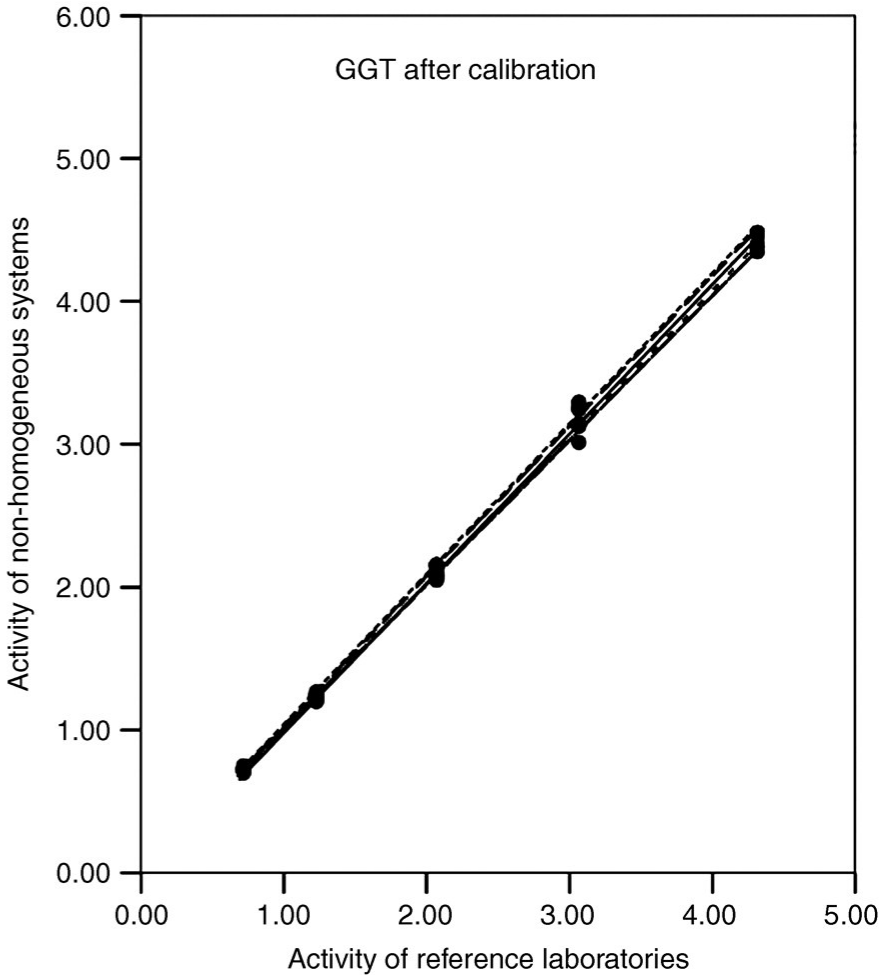
Adapted from Infusino I et al., Clin Chem Lab Med 2010;48:301

Traceability investigation of γ-glutamyltransferase measurements in China





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Xia C et al., Ann Clin Biochem 2010;47:189

Common reference intervals as fourth pillar of the reference measurement system

Until today

Method-dependent results

↓

Method-dependent reference intervals

From today

Standardized methods that provide traceable results

↓

Common reference intervals (at least within homogeneous ethnic groups)

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Infusino I et al., Clin Chem Lab Med 2010;48:301

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.

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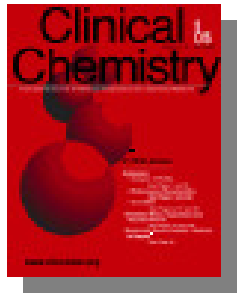
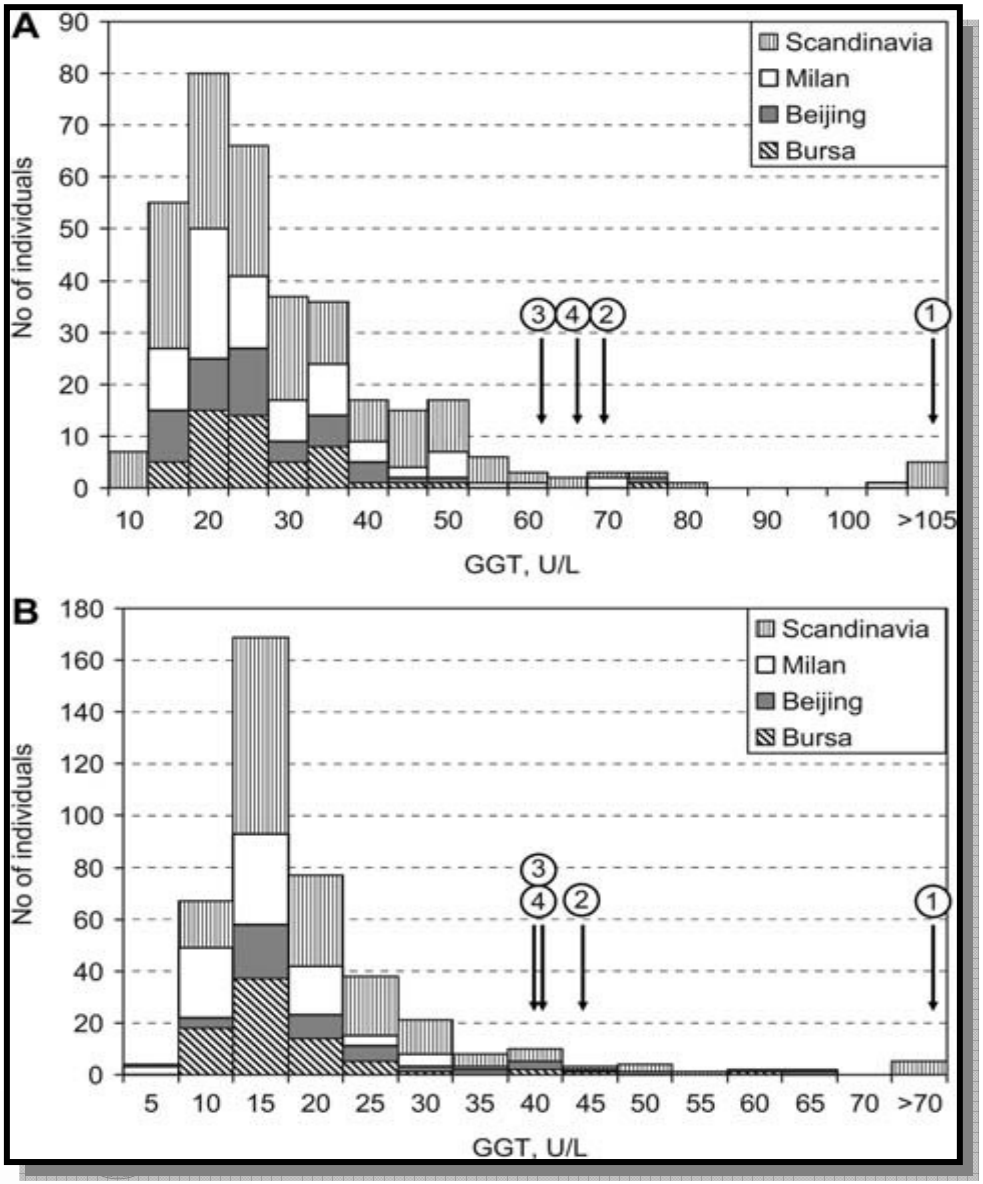
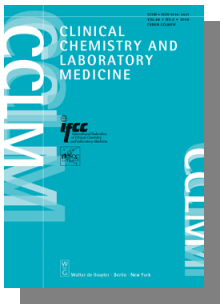
Clin Chem 2008;54:559-66



Common reference intervals for γ-GT in adults



γGT	12-68 U/L for males 6-40 U/L for females



Ceriotti F et al., Clin Chem Lab Med 2010;48:1593

Profession (e.g., IFCC, JCTLM): 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: testing system controls to confirm and verify manufacturer's declared performance (CE marked – virtually unbiased)
- EQA (true value in commutable materials): defining uncertainty of laboratory measurements

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

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Need to define the clinically acceptable limits for validation of metrologically traceable calibration

The absence of clearly defined tolerable deviations derived from clinical needs "might results in a large grey zone with respect to the extent of traceability expected from IVD manufacturers, partially or totally invalidating its theoretical advantages, i.e. the concept of common decision-making criteria."

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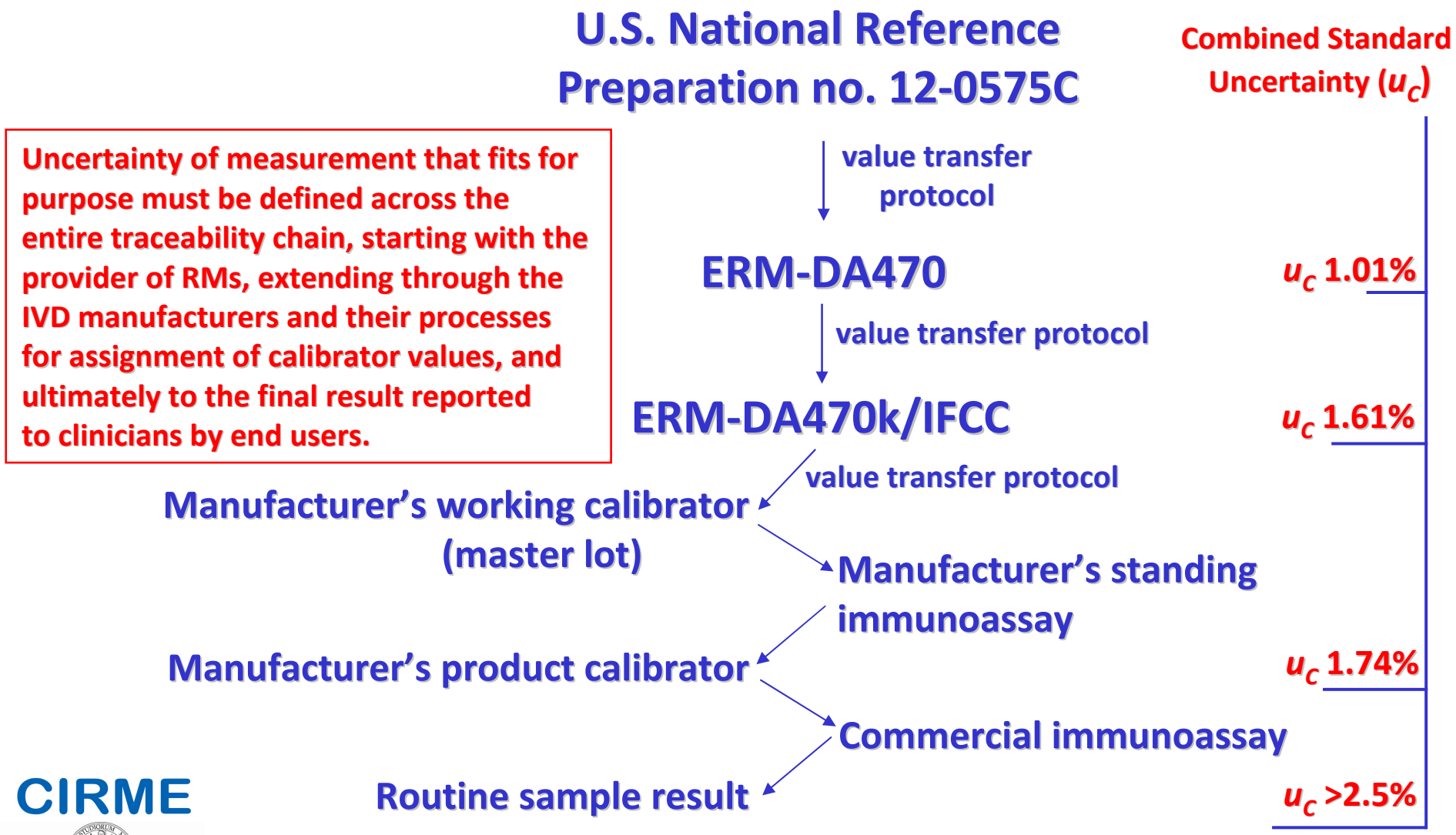
L Thienpont et al., Clin Chem Lab Med 2004;42:842

Serum albumin: Metrological traceability chain



Note: Minimum imprecision goal ≤2.33%

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

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

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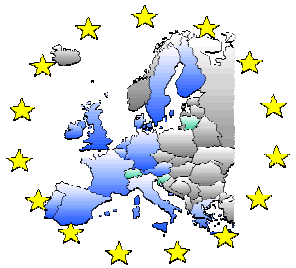
Fulfillment of the Requirements of the EU IVD Directive by Manufacturers



- Preparation of the necessary technical documentation
- All data that characterize the product
- Testing protocols
- Labels and instruction for use
- Assigned values and metrological traceability
  - Traceability chain and calibration hierarchy
  - Transfer protocols
  - Commutability testing
  - Determination of uncertainty (fitness for purpose)
- Stability testing

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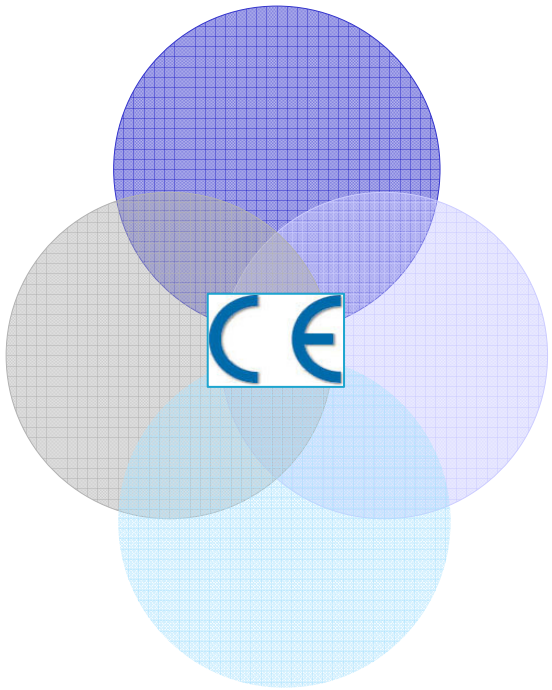
Thus, the laboratory needs to rely on the manufacturers who must ensure traceability of their analytical system to the highest available level

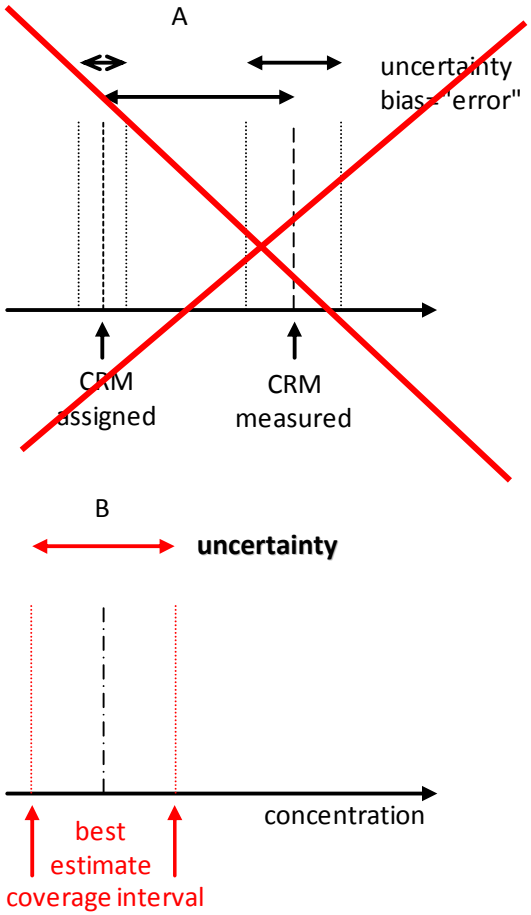
Platform



Reagents

Calibrators

Control material(s)



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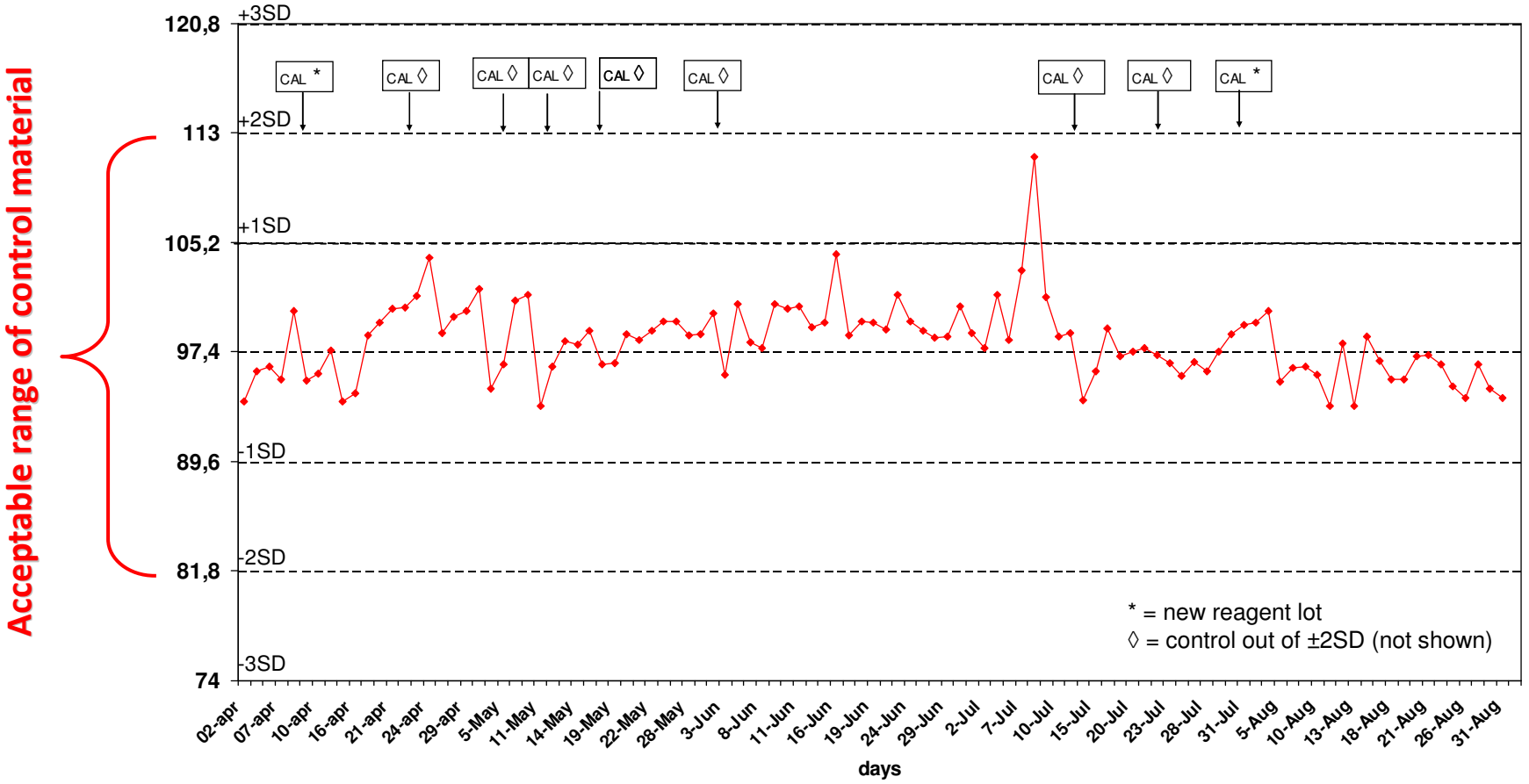
IQC Material Roche Precipath PUC-lot 15352600 for Trueness Verification
Roche Cobas c501 platform



In turn, clinical laboratories must verify the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions, by analyzing the system control materials and confirming that current measurements are in control, with no clinically significant changes in the assumed unbiased results.

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

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- EQA (true value in commutable materials): defining uncertainty of laboratory measurements

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

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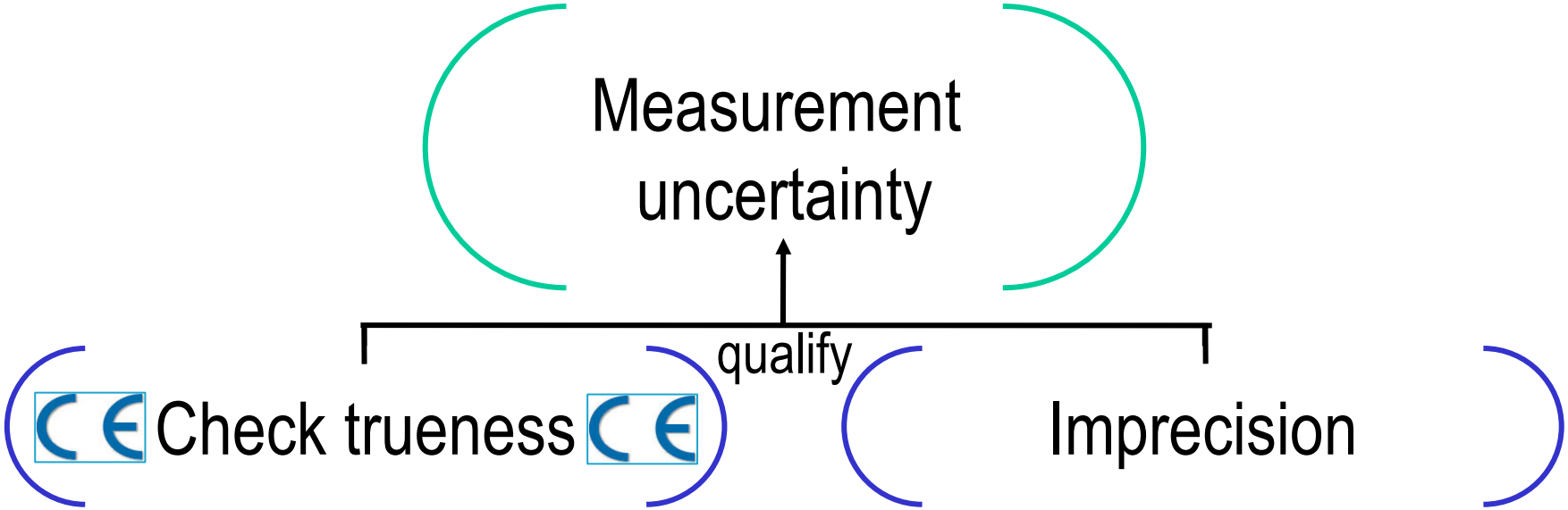
Analytical Quality Control in the Traceability Era

External Quality Assessment

[Analytical quality of measurement]



Internal Quality Control

[Reliability of the analytical system]

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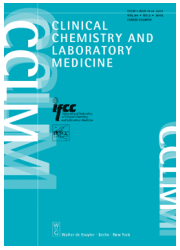
Panteghini M, Clin Chem Lab Med 2010;48:7



Imprecision of tumour biomarker measurements on Roche Modular E170 platform fulfills desirable goals derived from biological variation

Alberto Dolci[1], Luisa Scapellato[1], Roberta Mozzi[1] and Mauro Panteghini[1,2]

[1]Clinical Biochemistry Laboratory, 'Luigi Sacco' University Hospital; [2]Department of Clinical Sciences, University of Milan Medical School, Milan 20157, Italy

Corresponding author: Alberto Dolci, Clinical Biochemistry Laboratory, 'Luigi Sacco' University Hospital, Viale GB Grassi, 74, Milan 20157, Italy. Email: dolci.alberto@hsacco.it

This work was presented in part at the 18th IFCC-EFCC European Congress of Clinical Chemistry and Laboratory Medicine held in Innsbruck, Austria, 7–11 June 2009 as poster. The abstract has been published in Clin Chem Lab Med 2009;47:S157.

Abstract

Background: Monitoring of test imprecision is one of the most important quality indicators in clinical laboratories. Imprecision goals should be derived from biological variation. The aim of this study was to evaluate the imprecision of eight tumour biomarker assays routinely measured on the Modular E170 system.

Methods: Method coefficient of variations (CVs) were obtained by an appropriate Internal Quality Control programme based on the measurement every working day of a fresh–frozen human serum pool with biomarkers concentrations around the clinical cut-offs. We evaluated data collected along the whole year 2008 (*n* range: 21–461); monthly CVs and their cumulative means were calculated and compared with corresponding goals.

Results: Biomarkers concentration means and average yearly CVs (desirable goals in parentheses) were as follows: α-fetoprotein, 9.6 μg/L, 3.9% (6.0%); CA125, 41.2 U/L, 2.8% (12.4%); CA15.3, 32.7 U/L, 3.1% (3.1%); CA19.9, 35.1 U/L, 2.8% (8.0%); CEA, 7.7 μg/L, 4.3% (6.4%); prostate-specific antigen (PSA), 4.1 μg/L, 4.3% (9.1%); CYFRA 21.1, 2.4 μg/L, 5.7% (11.3%); and ferritin, 64.5 μg/L, 4.0% (7.1%).

Conclusions: Our study shows that in routine laboratory practice and over a clinically and analytically relevant time-span, the imprecision of the tumour biomarker measurements on the Roche Modular E170 fulfills desirable goals. For four assays (CA125, CA19.9, PSA and CYFRA 21.1) the optimum CV can even be achieved.

Ann Clin Biochem 2010; **47**: 171–173. DOI: 10.1258/acb.2009.009228

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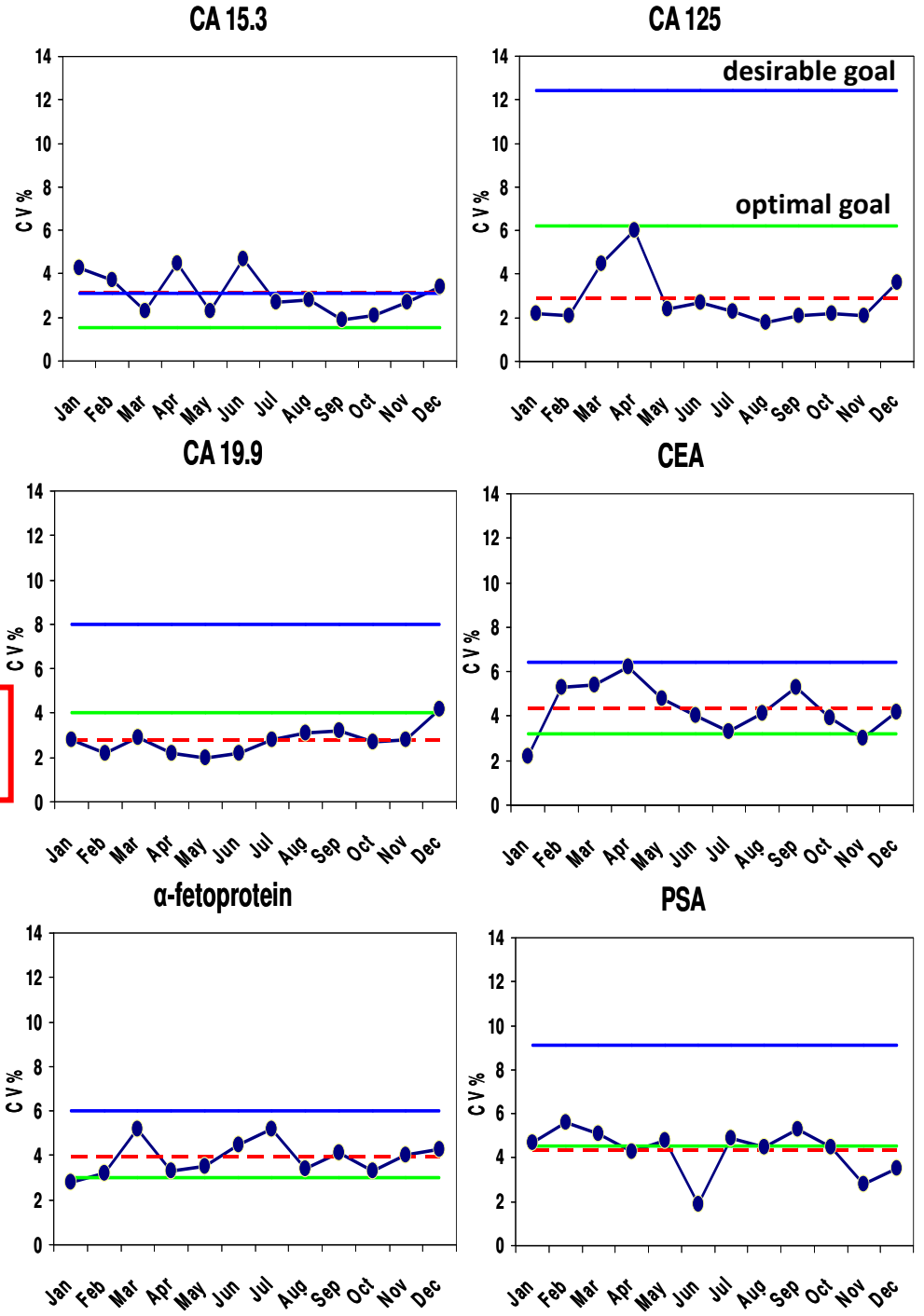

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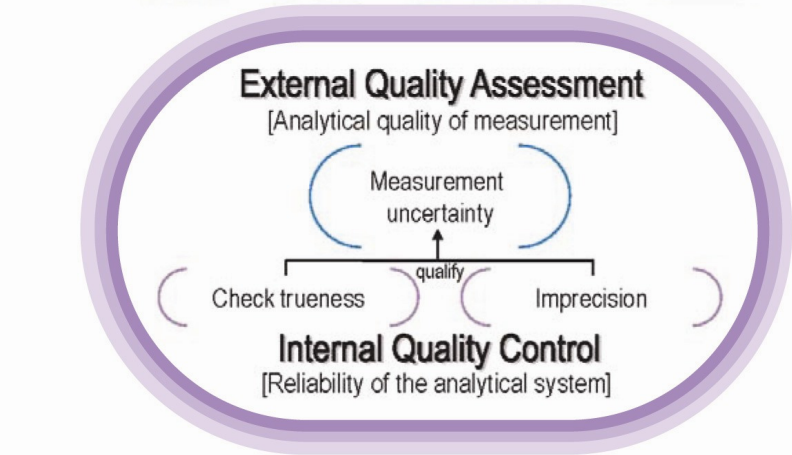
Diagnostic manufacturers: Implement suitable analytical systems (platform, reagents, calibrators, controls) fulfilling the above established goals

End users (clinical laboratories): Survey assay and laboratory performance through

- IQC: testing system controls to confirm and verify manufacturer's declared performance (CE marked – virtually unbiased)
- EQA (true value in commutable materials): defining uncertainty of laboratory measurements



Requirements for the applicability of EQA results to evaluation of the performance of individual laboratories

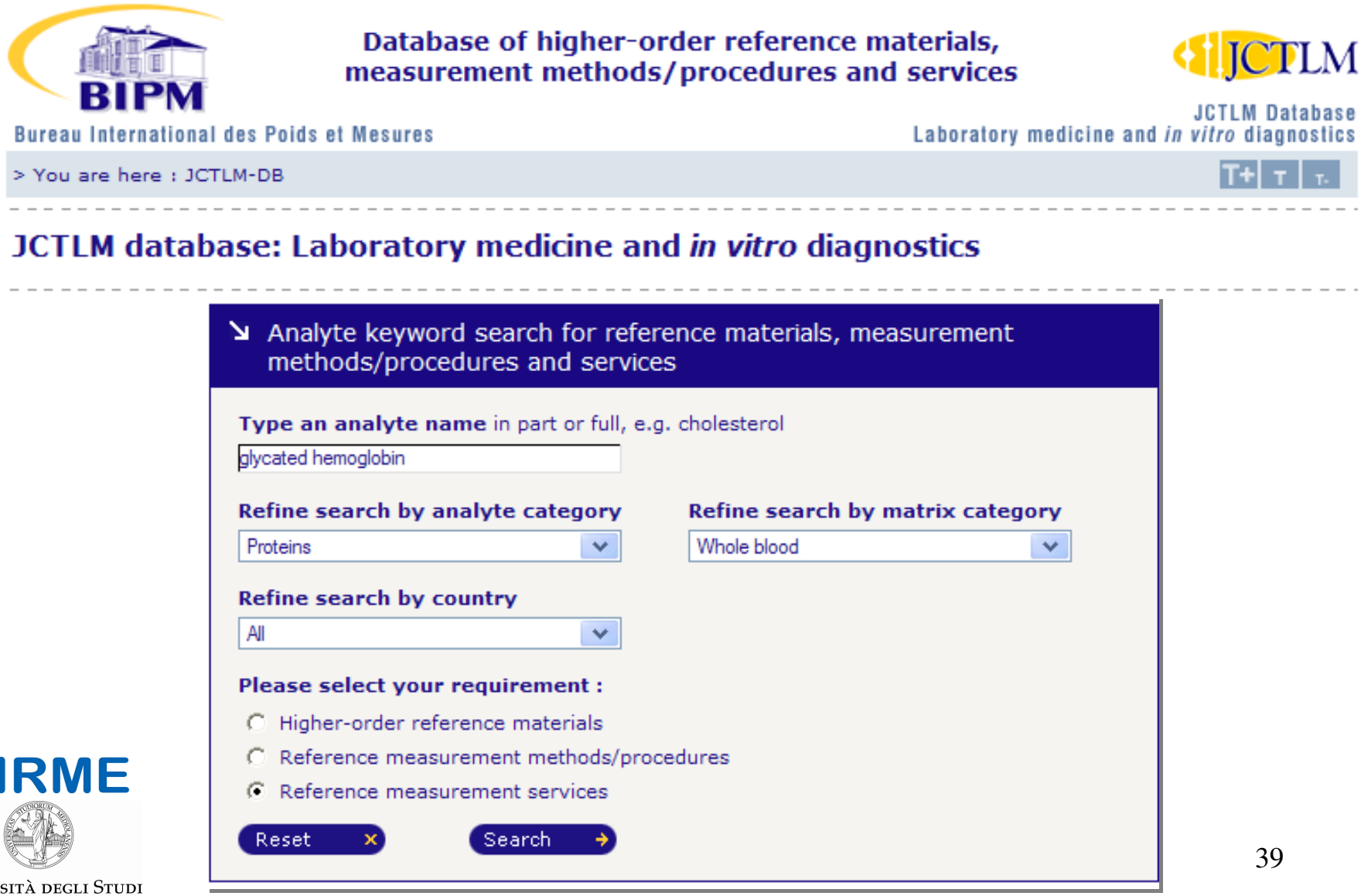
Feature	Aim
EQA material values assigned with reference procedures by an accredited reference laboratory	To check the measurement uncertainty of participating laboratories against the reference systems
Proved commutability of EQA material(s)	To allow transferability of participating laboratory performance to patient samples
Definition of the clinically allowable uncertainty of measurements	To verify the suitability of laboratory measurements in clinical setting

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

Important issue to be considered

- To ensure reliability in the estimate of end user uncertainty alone, the uncertainty of the values assigned by the reference laboratory to EQAS materials should be maintained at a minimum.
- To achieve this, Stöckl and Reinauer [Scan J Clin Lab Invest 1993;53(suppl 212):16] have proposed that the uncertainty of the target should be <0.2 times the EQAS maximal tolerated limit, i.e. the clinically allowable uncertainty of measurements.

http://www.bipm.org/en/committees/jc/jctlm/



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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

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SIT

Servizio di Taratura in Italia
Banca Dati a cura della Segreteria SIT

Centro_217

Laboratorio permanente

TABELLA DI ACCREDITAMENTO SIT

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 %	

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

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Risultati utilizzati per il calcolo dell'incertezza estesa secondo GUM nella misurazione dell'attività catalitica dell'alanina amminotrasferasi (ALT) con procedura di riferimento

Componente	Incertezza massima accettabile	Scarto tipo	Coefficiente di sensibilità	Incertezza standard relativa	Varianza
Lunghezza d'onda	0,1 nm	0,06 nm	0,39	0,02%	0,001%
Assorbanza	0,3%	0,17%	1	0,17%	0,030%
pH	0,05 U	0,03 U	0,34	0,20%	0,039%
Temperatura	0,1 °C	0,06 °C	3,59	0,21%	0,043%
Concentrazione reagenti	1,5%	0,87%	0,56	0,48%	0,235%
Lotto reagenti	1,5%	0,87%	1	0,87%	0,760%
Frazione di volume del campione	0,4%	0,23%	1	0,23%	0,053%
Durata della misura	0,03%	0,02%	1	0,02%	0,000%
Evaporazione	0,1%	0,06%	1	0,06%	0,004%
Invecchiamento del campione	0,5%	0,29%	1	0,29%	0,084%
Ripetibilità	0,65 U/L	0,38 U/L	1	0,38%	0,144%
				Totale	1,393%

EQAS for quantities where no high-order reference is available

System-dependent target values should be used to evaluate the performance (uncertainty) of participating laboratories

HOWEVER

in this case the values assigned to the EQAS materials should be determined by reference institutions (possibly including the manufacturer releasing that specific analytical system), working under strictly controlled conditions in order to maintain measurement uncertainty as low as possible, and not as group mean.

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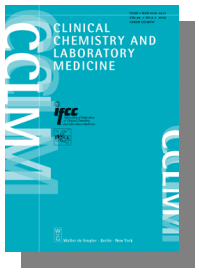
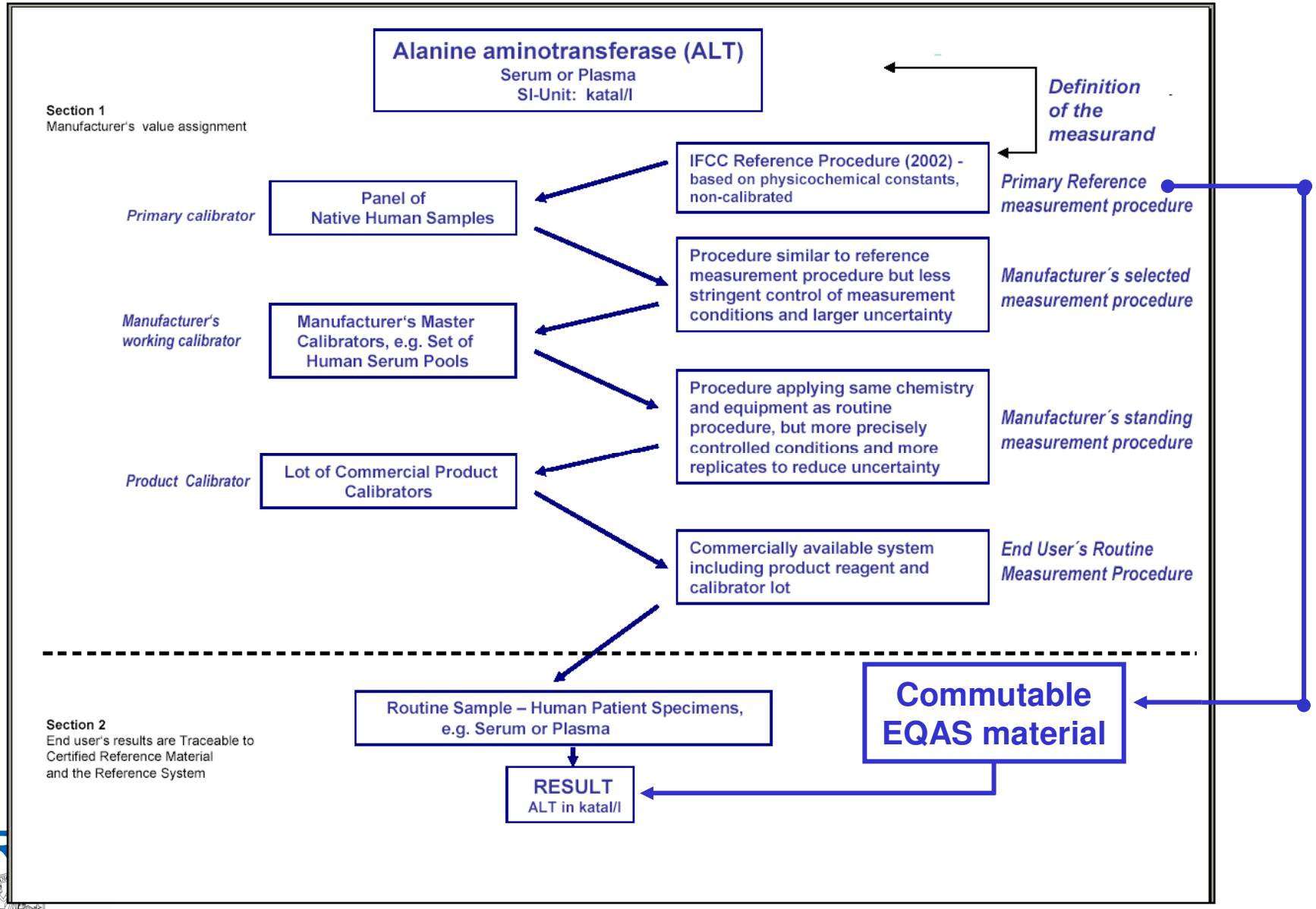
Panteghini M, Clin Chem Lab Med 2010;48:7





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Accuracy verification in EQAS:

time to care about the quality of the samples!

LM Thienpont et al, Scand J Clin Lab Invest 2003;63:195

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Allowable Limits

IFCC-IUPAC Stockholm Conference 1999

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings (e.g. misclassification in diagnosis)
2. Evaluation of the effect of analytical performance on clinical decisions in general
    a. Data based on components of biological variation
    b. Data based on analysis of clinicians opinions
3. Published professional recommendations from national and international expert bodies
4. Performance goals set by
    a. Regulatory bodies
    b. EQAS organizers
5. Goals based on the current state of the art (e.g. as demonstrated by data from EQAS)

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Scan J Clin Lab Invest 1999;49:475-585

Is available information on biological variability reliable?

Table 4
Summary of the characteristics of studies on biological variability of HbA_{1c} evaluated in this systematic review.

Study no.	Method specificity as per HbA_{1c} 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	Yes
4	±	No	No	No	No
5	±	Yes	Yes	No	Yes
6	±	Yes (F only)	Yes	±	Yes
7	Yes	No	No	No	No
8	No	Yes (M only)	Yes	No	Yes
9	±	No	No	No	Yes

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Braga F et al, Chim Clin Acta 2010;411:1606

Traceability as Copernican Revolution in Laboratory Medicine (and in Analytical Quality Control)

Nothing changes as a result of this revolution, and yet everything changes.

In the Quality Control setting, the objective laboratory world producing experimental data does not change, but our 'a priori' concept of it is turned inside out.

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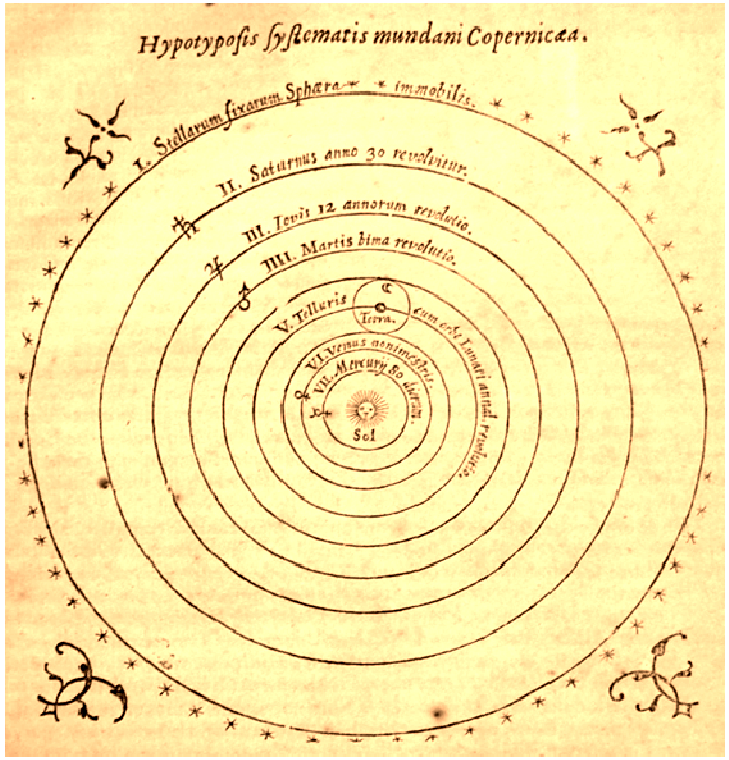
What COPERNICUS did was take the existing ‘a priori’ concept of the world and pose an alternative ‘a priori’ concept

The earth is flat and fixed in space

Equivalency-based grading

The earth is spherical and moves around the sun



Accuracy-based grading

CI **What TRACEABILITY does is take the existing ‘a priori’ concept of the QC and pose an alternative ‘a priori’ concept**

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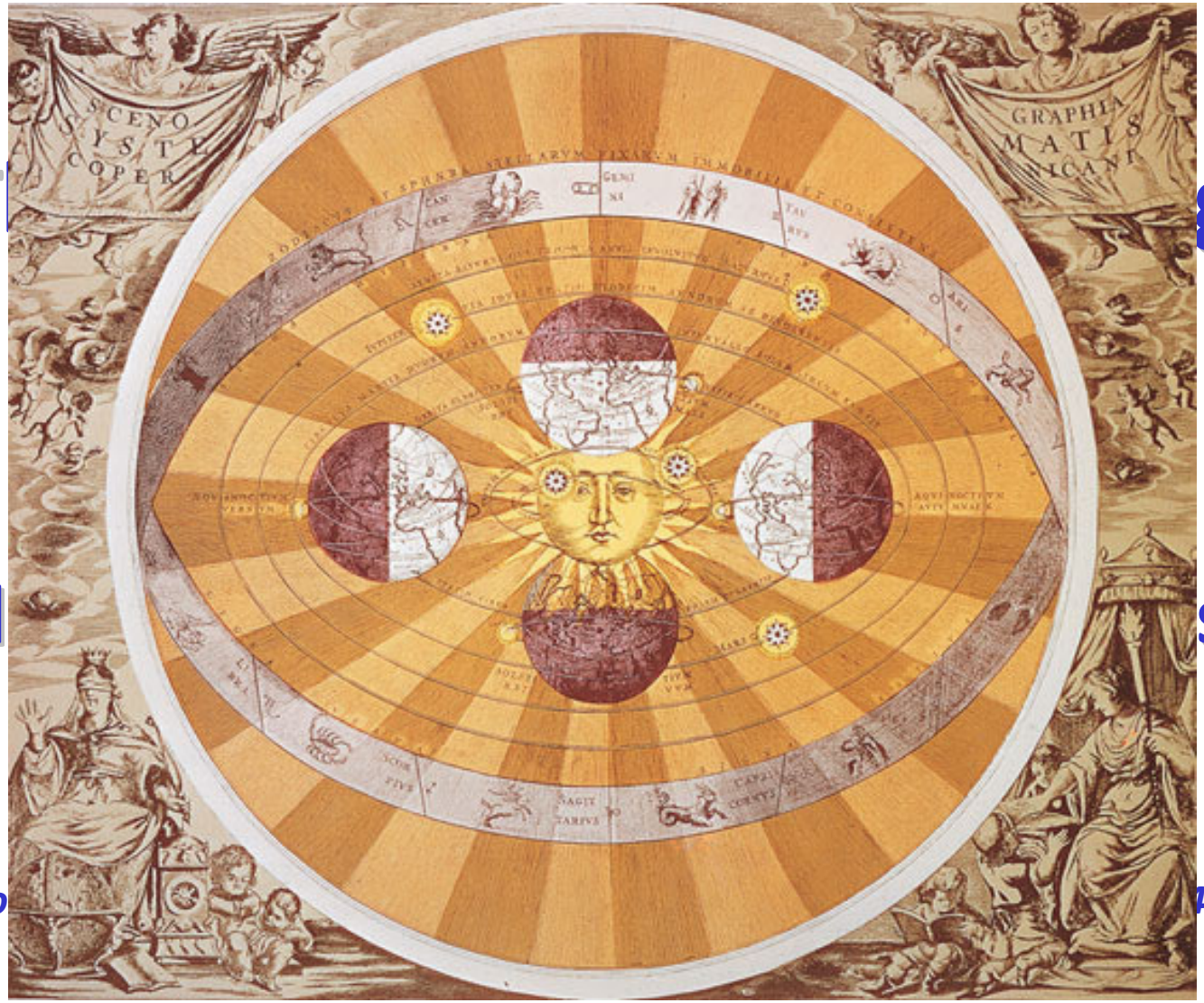

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