EQALM SYMPOSIUM

BERLIN, JULY 1-2 2009

QUALITY SPECIFICATIONS IN EQA schemes: from theory to practice

Prof. Mario Plebani

University Hospital of Padova, Italy

QUALITY MANAGEMENT IN LABORATORY MEDICINE

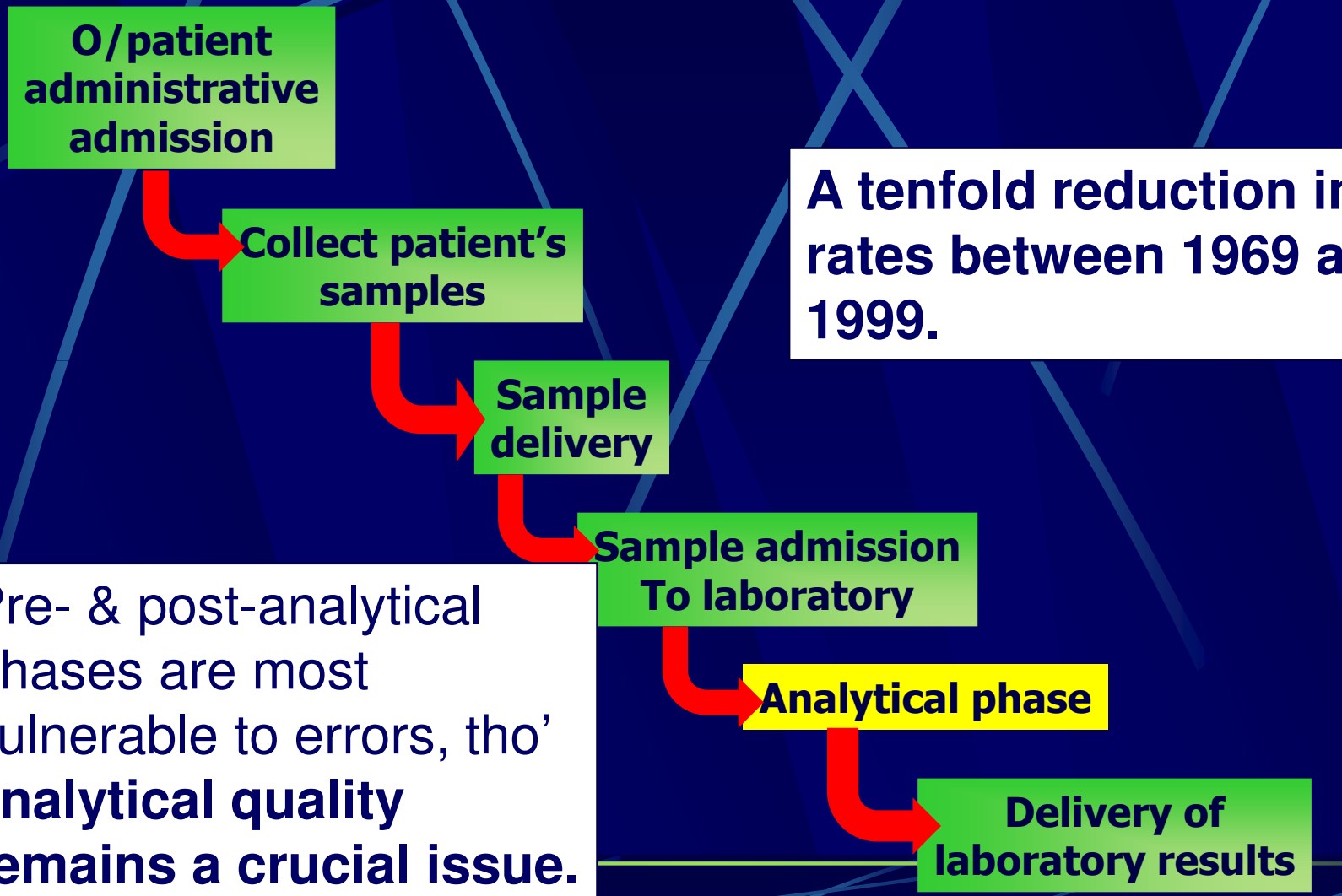
The importance of quality management and error reduction has always been recognized in laboratory medicine, and in many ways, the ***laboratory has been ahead of other health care areas*** in its efforts to improve quality and reduce adverse patient outcomes.

Wagar EA, Yuan S. Clin Lab Med 2007

Has the unacceptable result rate improved over time?

	ppm
Belk and Sunderman (1947)	162,116
McSwiney and Woodrow (1969)	30,000
College of American Pathologists (1996)	12,904
Witte et al. (1997)	447

TTP for o/patients: systemic aspects



A tenfold reduction in error rates between 1969 and 1999.

Pre- & post-analytical phases are most vulnerable to errors, tho' **analytical quality remains a crucial issue.**

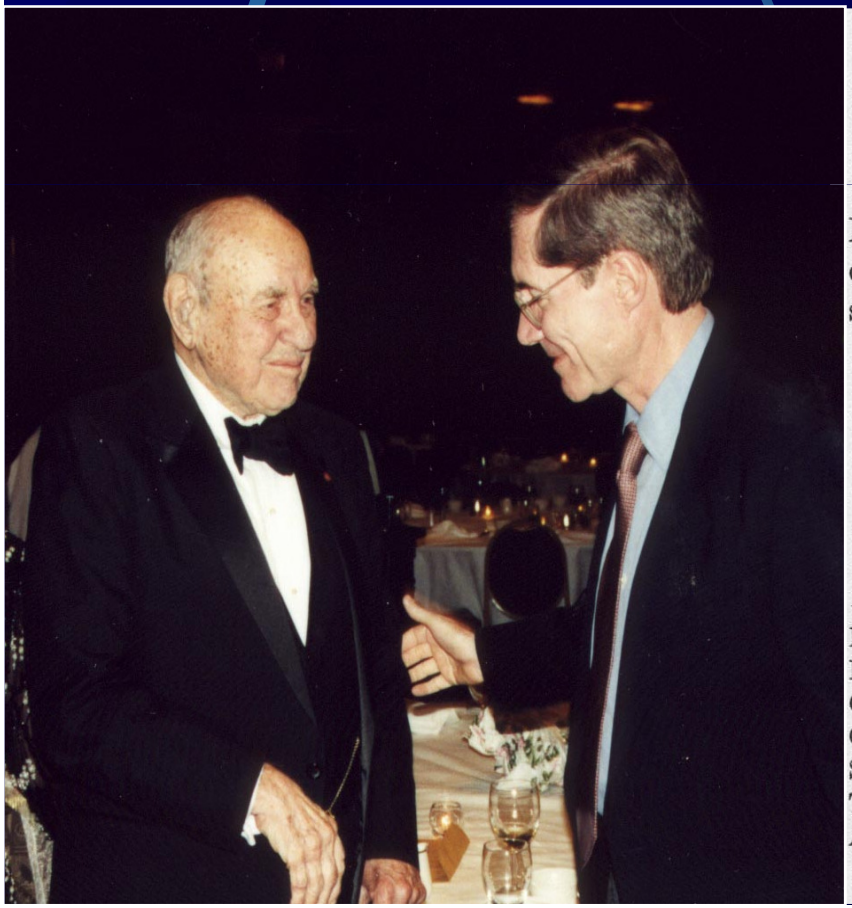
Today

The analytical process and its control are becoming increasingly reliable thanks to improvements made to instruments and methods, the application of internal quality control (IQC) and **external quality assessment (EQA)** procedures.

Sciacovelli L, et al Clin Chim Acta 2004

F. William Sunderman, Sr.

(23 October 1898 – 9 March 2003)



A SURVEY OF THE ACCURACY OF CHEMICAL ANALYSES IN CLINICAL LABORATORIES*

WILLIAM P. BELK, M.D.,† AND F. WILLIAM SUNDERMAN, M.D.†

In 1946 the Committee on Laboratories of the Medical Society of the State of Pennsylvania proposed a survey‡ to check the accuracy of some of the more common chemical measurements made in hospital laboratories throughout the state. It undertook to do this by distributing solutions which had been carefully

TABLE 1

NUMBER OF DETERMINATIONS CLASSED AS SATISFACTORY, UNSATISFACTORY AND GROSS ERROR

September Analyses

SUBSTANCE TESTED	SATISFACTORY LIMITS OF RESULTS PER 100 ML.	NUMBER SATISFACTORY	NUMBER UNSATISFACTORY**	GROSS ERROR**
Hemoglobin	9.8 ± 0.3 gm.	17	34	11
Hemoglobin	15.1 ± 0.5 gm.	21	31	3
Glucose	60 ± 10 mg.	33	19	5
Glucose	375 ± 30 mg.	27	24	4
Sodium chloride	456 ± 50 mg.	30	14	2
Total protein	6.6 ± 0.4 gm.	18	29	7
Albumin	4.6 ± 0.3 gm.	9	35	7

October Analyses

Link between EQAS and IQC

EQAS performance can be improved by using current instrumentation according to manufactures' recommendations.

In one study of causes of unsatisfactory performance in EQAS, more than 50% of the laboratories used an "allowable error" for routine QC of analytical systems that exceeded the manufacturers' recommended threshold error limit for stable instrument performance.

Jenny RW, Jackson-Tarentino KY. Clin Chem 2000;46(1):89-99.

External Quality Assessment Today

Medical laboratories have a long tradition of EQA procedures but, continuous progress made in laboratory medicine, imposes a constant ***development and change in the design and management of effective EQA*** schemes.

Errors in laboratory medicine: the evolving scenario

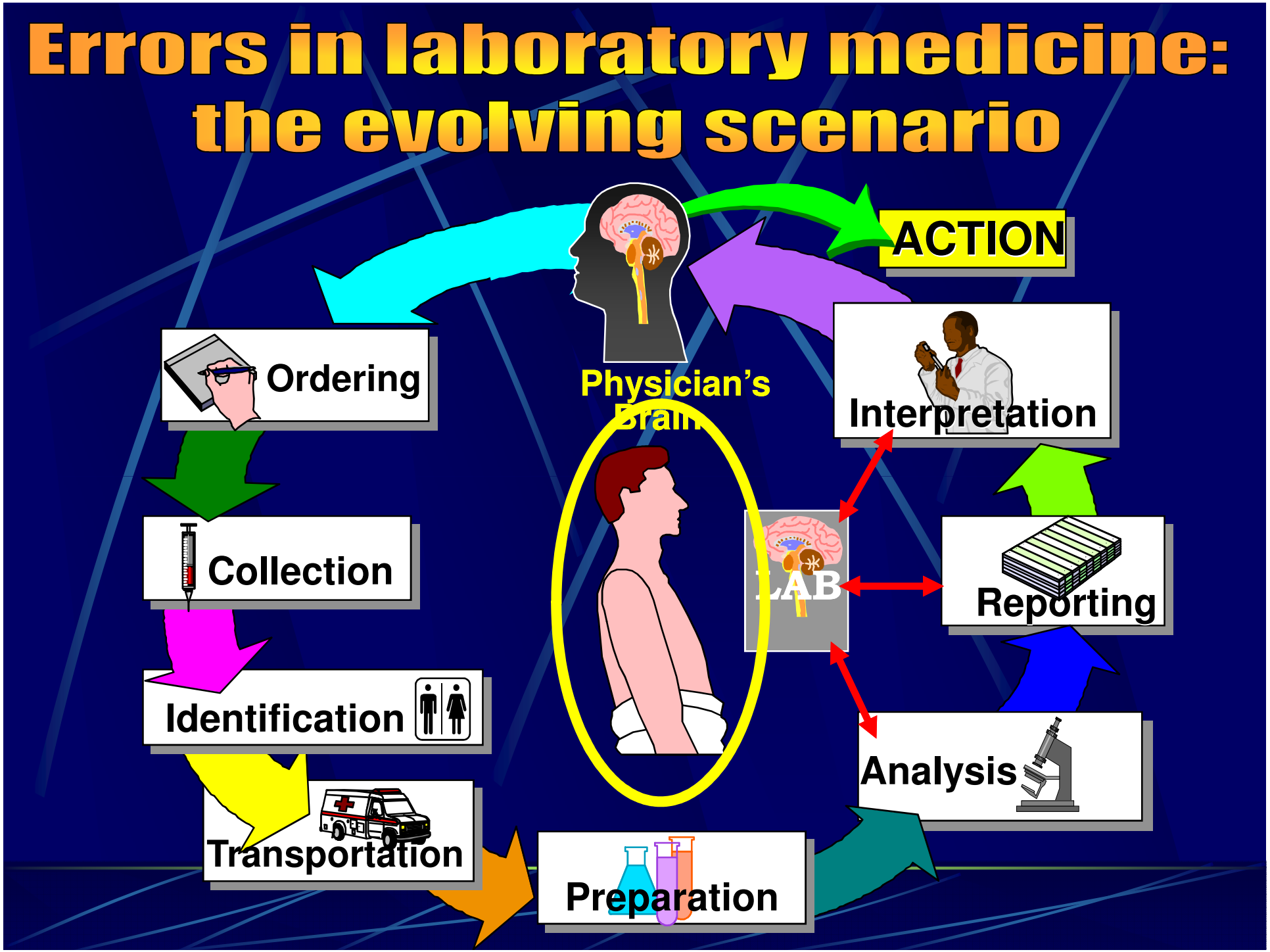
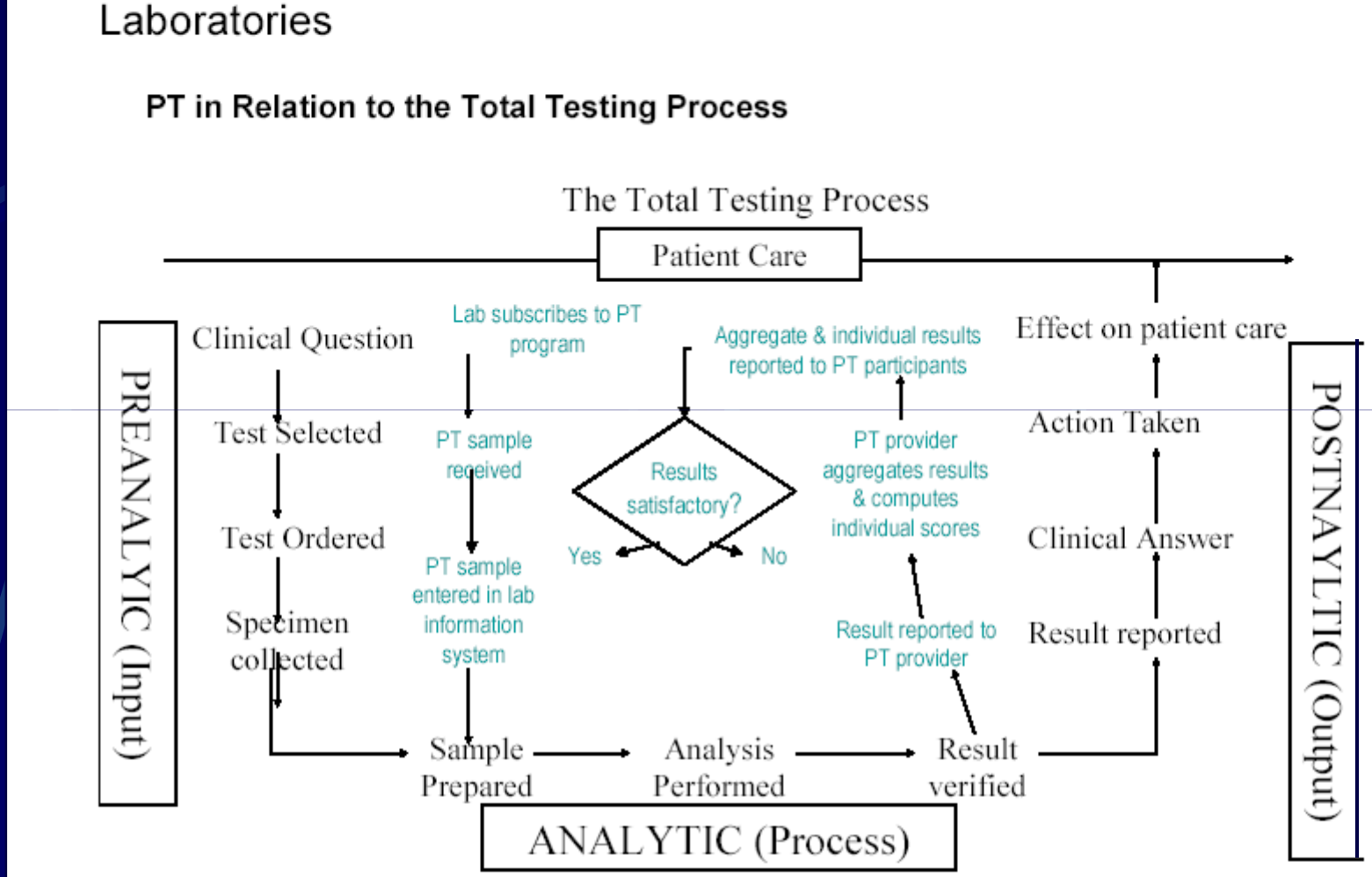


Figure 2-1. Proficiency Testing in the Total Testing Process for Clinical Laboratories



JC Petersen, R. Hill, RS Black, J Winkelman, D. Tholen. Battelle Memorial Institute 2008

Laboratory Performance and EQA results

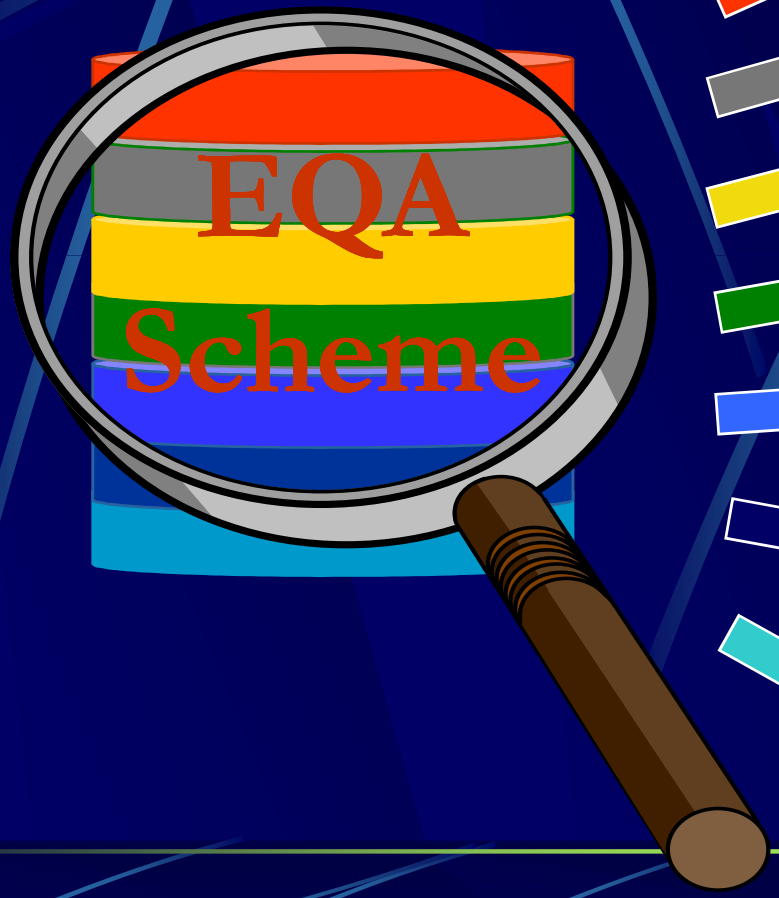
Several studies illustrate that the value of EQA as a part of a proactive, integrated approach to laboratory quality management.

Laboratories can take proactive steps such as:

- narrowing their internal quality control ranges
- increasing the frequency of calibration
- performing instrument function verification
- **examining EQA results closely for trends and bias, even when they are deemed acceptable**

Jenny RW, Jackson-Tarentino KY. Clin Chem 2000;46(1):89-99.
Kroll MH, Styer PE, Vasquez DA. Arch Pathol Lab Med 2004;128(5):544-8.

Reliability?



- Purpose
- Objectives
- Organization
- Control Materials
- Criteria
- Complaints procedure
- Communications procedure

Reliability of EQA Scheme

- Control materials
- Statistical procedure
  - to estimate the assigned value
  - to identify the outlier values
- Limits for evaluation of performances

Laboratory Performance

Requirements

1997 ISO IEC GUIDE 43
Proficiency testing by interlaboratory comparison

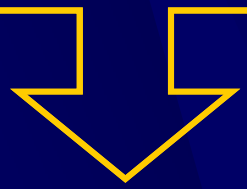
2000 ILAC-G13
Guidelines for the Requirements for the Competence of Providers of Proficency Testing Schemes.

2007 CLINICAL PATHOLOGY ACCREDITATION (UK)
Standards for EQA Schemes in Laboratory Medicine.

2008 ISO/IEC DIS 17043 (draft)
Conformity assessment - General requirements for proficiency testing

Reliability of EQA Scheme

- Control materials
- Statistical procedure
  - to estimate the assigned value
  - to identify the outlier values
- Criteria for performance evaluation



Laboratory Performance

It has been possible to set

Quality Specifications

based on the Hierarchy of Models

to evaluate the laboratory

performance in EQA Schemes

?

Quality Management

From Callum G. Fraser, 2001

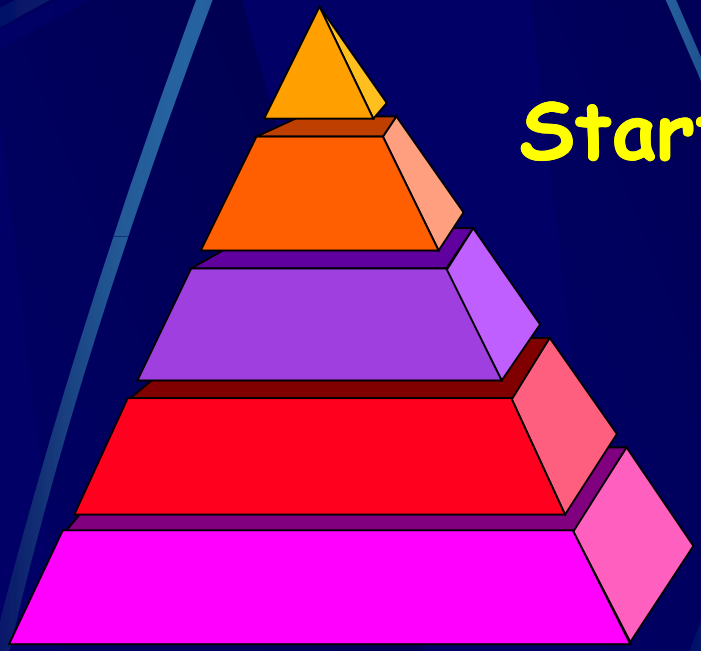
Setting Quality Specifications

- Quality specifications represent the *level of performance required to facilitate results interpretation and utilization, thus contributing to an effective clinical decision-making that, ultimately, may assure appropriate clinical outcomes*.

- There is the need of identifying, applying and monitoring indicators and related quality specifications not only for analytical performances, but also ***for pre- and post-analytic phases.***

M. Plebani, 2006

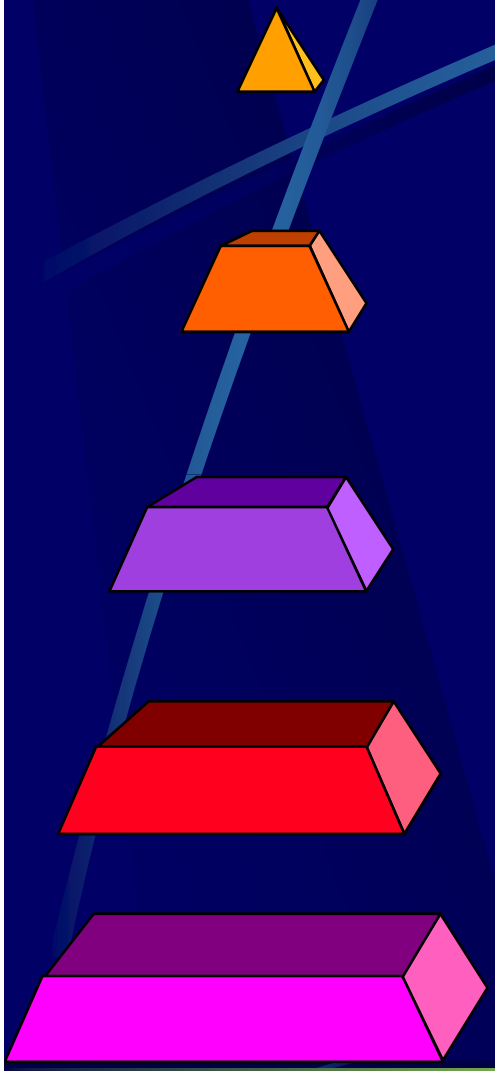
Quality Specifications



Starting point: the consensus on the hierarchy of models for setting quality specifications

Consensus Conference, Stockholm, April 1999
Sponsored by IUPAC, IFCC, WHO

Hierarchy of models



Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings

Evaluation of the effect of analytical performance on clinical decisions in general:
- data based on components of biological variation
- data based on analysis of clinicians' opinions

Published professional recommendations
- from national and international expert bodies
- from expert local groups or individuals

Performance goals set by
- regulatory Bodies
- Organizers of EQA schemes

Goals based on the current state of the art:
- as demonstrated by data from EQA or PT scheme
- as found in current publications on methodology

Performance Goals

Allowable Total Error (ETa)

Clinical	Scientific Recommendations
Biological	Fraser's Formula (biological variability)
State of the Art	Inter-laboratory Variability

Quality specifications and clinical outcome

Quality specifications are strictly related to and derives from clinical needs. The goal is that analytical imprecision and bias influence the clinical outcome to a negligible extent.

ELSEVIER

Clinica Chimica Acta 346 (2004) 87–97

www.elsevier.com/locate/clinchim

Quality specifications in EQA schemes: from theory to practice

Laura Sciacovelli*, Lorena Zardo, Sandra Secchiero, Mario Plebani

Centro di Ricerca Biomedica, Via Ospedale 18, 31033 Castelfranco Veneto (TV), Italy

Received 13 February 2004; accepted 22 February 2004

...from Theory to Practice....

1. Performance Limits in EQA Schemes

To determine the criteria to be used for the evaluation of laboratory performance in EQA Schemes of the Centre of Biomedical Research, we used the participants' results obtained in previous EQA cycles.

...from Theory to Practice....

2. Performance Limits in EQA Schemes

We calculated the index score that means the "distance" of each result from assigned value (median value calculated on homogenous method-related data after outliers exclusion or value obtained with reference method).

...from Theory to Practice....

3. Performance Limits in EQA Schemes

We calculated the percentage of **Satisfactory Performances** comparing the calculated score with ETa based on

- clinical recommendation: **Clinical goal**
- biological variability: **Biological goal**
- inter-laboratory variability: **State-of-the-art**

Hemoglobin A1c

Integral component of the management of patients with diabetes

- ✓ Measurement of HbA1c is widely used in patients with diabetes as a monitor of long-term glycemic control.
- ✓ Prospective randomizated clinical trials, DCCT and UKPDS, have demonstrated that HbA1c is a measure of the risk for development of diabetes complications

ADA/EASD/IDF WG-HbA1c. Clin Chem 2005;51,4:681-3.

Hemoglobin A1c

- **Intra-laboratory analytical precision target (CV%) = <2%**
  It is achievable and supported by statistical and scientific precision requirements to differentiate recommended targets from upper limit of the reference range, and by previous expert recommendations for biological variation grounds and clinical need.

- **Method bias should be as close zero as possible in all patient samples**

- **Methods chosen with low imprecision and minimal or no interference** (such as carbamylated Hb, uraemic adduct and abnormal non HbAA variants) **should be used**

AACB/ADS/RCPA/ESA/ADEA. Clin Chem Lab Med 2007;45,8:1083-97.

Hemoglobin A1c

- **Clinical goal = 3.3%**

  AACB/ADS/RCPA/ESA/ADEA recommendation (Clin Chem Lab Med 2007;45,8:1083-97)

- **Biological goal = 4.3%**

  Westgard Desirable Specifications for total error, imprecision, and bias from biological Variation. Update 2008. www.westagrd.com

- **State-of-the-art goal = 3.2%**

  Average of inter-laboratory variability obtained in EQA Scheme 2008 of Centre of Biomedical Research

HbA1c

Glycemic control ➡ HbA1C < 7%

referenced to a non diabetic

Reference Range of 4% - 6%

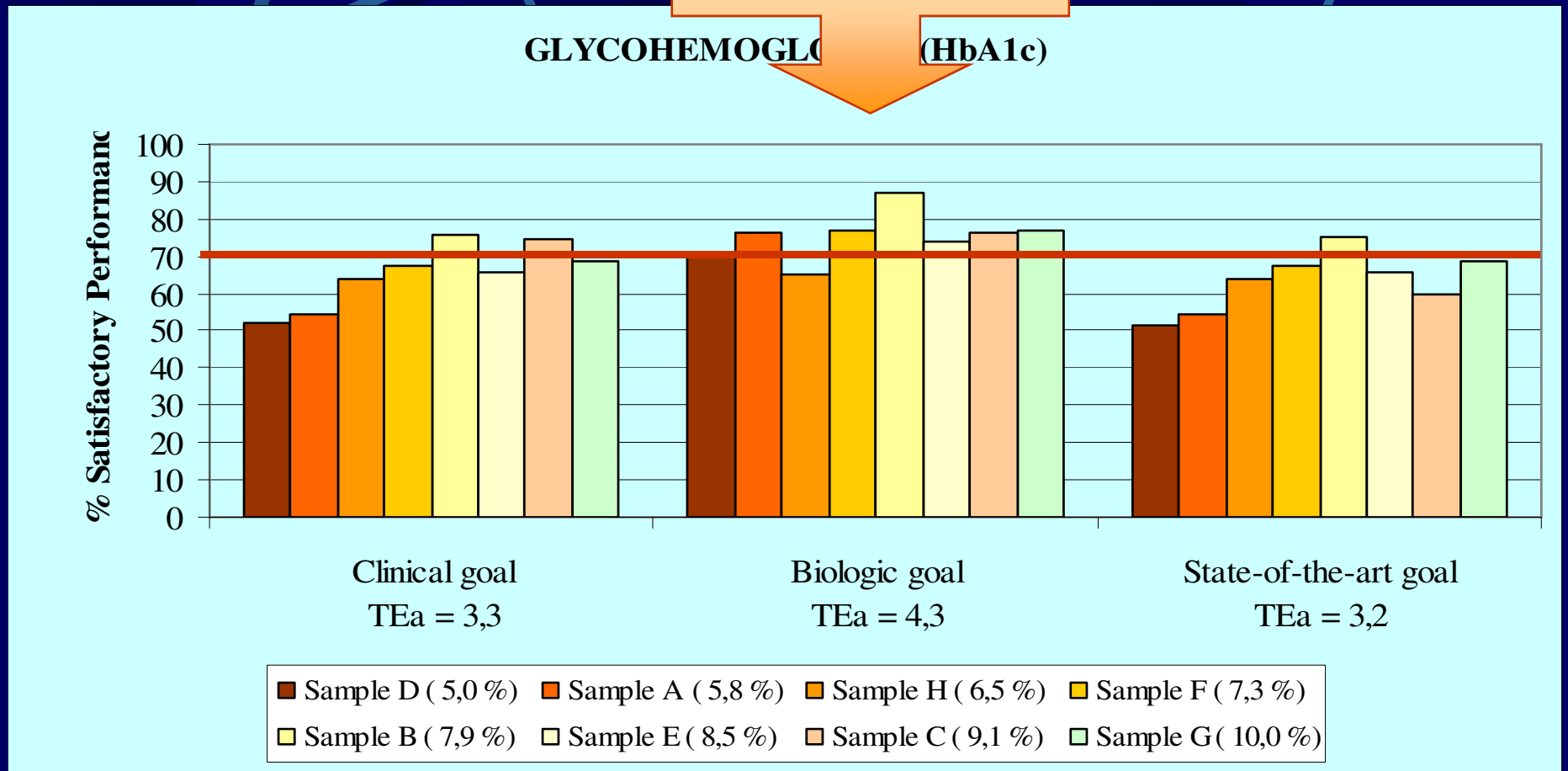
(with a deviation < 0,5%)

using a DCCT based assay

Clinical Practice Recommendation - ADA, 2001

Standard od Medical Care in Diabetes. ADA 2008

EQA goal


GLYCOHEMOGLO (HbA1c)
% Satisfactory Performanc
100
90
80
70
60
50
40
30
20
10
0
Clinical goal
TEa = 3,3
Biologic goal
TEa = 4,3
State-of-the-art goal
TEa = 3,2
Sample D (5,0 %)
Sample A (5,8 %)
Sample H (6,5 %)
Sample F (7,3 %)
Sample B (7,9 %)
Sample E (8,5 %)
Sample C (9,1 %)
Sample G (10,0 %)

HbA1c

Valutazione delle prestazioni analitiche — *Laboratorio :* 01PD01

			Risultato del laboratorio		Valutazione della prestazione			
Costituente	Metodo/Sistema	Camp.	Unità Lab.	Unità Std.	VA	N.	IS	Prest.
Emoglobina glicata	Bio-Rad Variant II dual kit	07-C	9.83 %	9.83 %	10.10	24	-51	Buona
		07-D	8.38 %	8.38 %	8.70	24	-71	Buona

Centro di Ricerca Biomedica — *Emoglobina Glicata 2° esercizio 2007 - 04/06/2007 (Rev. 0) R01/0N*

Unit

DCCT

Score of laboratory result from DCCT value

HbA1c

	DCCT Value = 7.3					DCCT Value = 5.9				
	Campione 07-E					Campione 07-F				
	N.	Mediana	DS	CV%	Bias%	N.	Mediana	DS	CV%	Bias%
Tutti i metodi	209					209				
Bio Kit Quantex su ILAB 600	3					3				
Bio-Rad D10 A1c	18	7,30	0,30	4,06	0,00	14	5,88	0,07	1,26	-0,42
Bio-Rad Diamat						1				
Bio-Rad Variant dual kit	7	7,30	0,52	7,11	0,00	7	5,90	0,15	2,51	0,00
Bio-Rad Variant II dual kit	20	7,35	0,30	4,03	0,68	20	5,90	0,19	3,14	0,00
Bio-Rad Variant II HbA1c program	5	7,10	0,22	3,13	-2,74	5	5,60	0,22	3,97	-5,08
Dade Behring Dimension	5	7,30	0,07	1,02	0,00	5	6,10	0,15	2,43	3,39
Eurogenetics Tosoh A1c 2.2 (G5)	9	7,30	0,44	6,09	0,00	8	5,90	0,19	3,14	0,00
Eurogenetics Tosoh G7	14	7,30	0,15	2,03	0,00	14	5,85	0,22	3,80	-0,85
Menarini HA 8121	9	7,10	0,22	3,13	-2,74	9	5,80	0,37	6,39	-1,69
Menarini HA 8140	21	7,30	0,15	2,03	0,00	23	5,80	0,22	3,83	-1,69
Menarini HA 8160	54	7,10	0,15	2,09	-2,74	53	5,70	0,15	2,60	-3,39
Olympus	4	8,35	0,11	1,38	14,38	4	6,39	0,27	4,18	8,31
Roche su Integra 400/700/800	3					3				
Tina quant su Hitachi	12	7,70	0,33	4,28	5,48	11	6,20	0,22	3,59	5,08
Tina quant su Modular	4	7,61	1,07	14,03	4,25	4	6,40	0,65	10,19	8,47

$$\text{Bias \%} = \frac{\text{Median - DCCT value}}{\text{DCCT value}} \; 100$$

HbA1c standardization

- The new IFCC reference system for HA1c represents the only valid anchor to implement standardization of the measurements
- HA1c results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%) using the IFCC-NGSP master equation
- A HA1c-derived average glucose (ADAG) value calculated from the HA1c result will be also be reported as an interpretation of HA1c results

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Implementation of standardization of HbA_{1c} measurement
Summary of the meeting with manufacturers held in Milan, IT - Dec 12, 2007

HbA1c

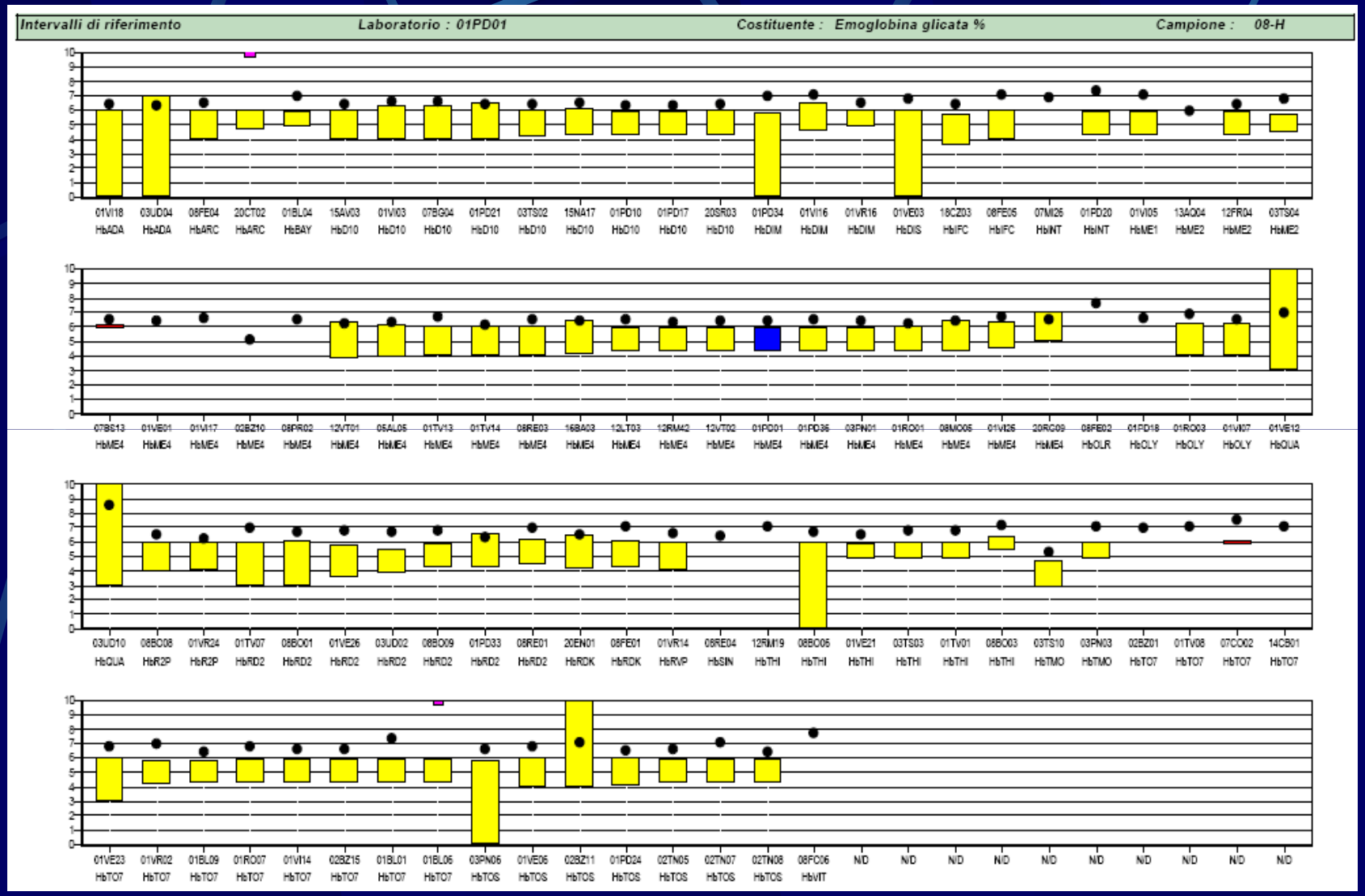
Table 1 Suggested units and target values for HbA1c when measured with methods traceable to the IFCC reference system. A comparison with the current figures is also given.

	Current[a]	IFCC traceable methods
Reference interval (non-diabetics)	4–6%	20–42 mmol/mol
Target for treatment in diabetics[b]	<7%	<53 mmol/mol
Change of therapy in diabetics[b]	>8%	>64 mmol/mol

[a]Refer to methods aligned to the US National Glycohemoglobin Standardization Program. [b]As recommended by the American Diabetes Association.

HbA1c (NGSP) = 0.915 x HbA1c (IFCC) + 2.15

IFCC-WG on HbA1c Standardization


Intervalli di riferimento
Laboratorio : 01PD01
Costituente : Emoglobina glicata %
Campione : 08-H

HbA1c standardization

- All manufacturers should implement worldwide the traceability to the IFCC reference system for HbA1c.
- The deadline for implementing traceability to the IFCC reference system is December 31st, 2009 for all the instruments in current use.
- All new instruments sold after January 1st, 2011 will report (as a result of an HbA1c test) both SI (mmol/mol – no decimals) and NGSP derived units (percentage – one decimal), in agreement with the Consensus Statement.

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Implementation of standardization of HbA_{1c} measurement
Summary of the meeting with manufacturers held in Milan, IT - Dec 12, 2007

IFCC-WG on HbA1c Standardization

HbA1c standardization

Introduction of External Quality Assessment (EQA) programs that use commutable control materials with **target values assigned using the IFCC reference measurement procedure** together with a clear definition of the **clinically allowable total error of measurements is required.** True value assignment to commutable EQA materials facilitates objective evaluation of the performance of IVD devices, together with an accuracy-based (instead of the inferior consensus-based) grading of the competency of participating laboratories

IFCC-WG on HbA1c Standardization

Glucose

- **Clinical goal = 4.7%**

  PH. Petersen, I. Brandslund, L. Jorgensen, et al. Scan J Clin Lab Invest 2001;61:191-204.

- **Biological goal = 6.9%**

  Westgard Desirable Specifications for total error, imprecision, and bias from biological Variation. Update 2008. www.westagrd.com

- **State-of-the-art goal = 3.8%**

  Average of inter-laboratory variability obtained in EQA Scheme 2008 of Centre of Biomedical Research

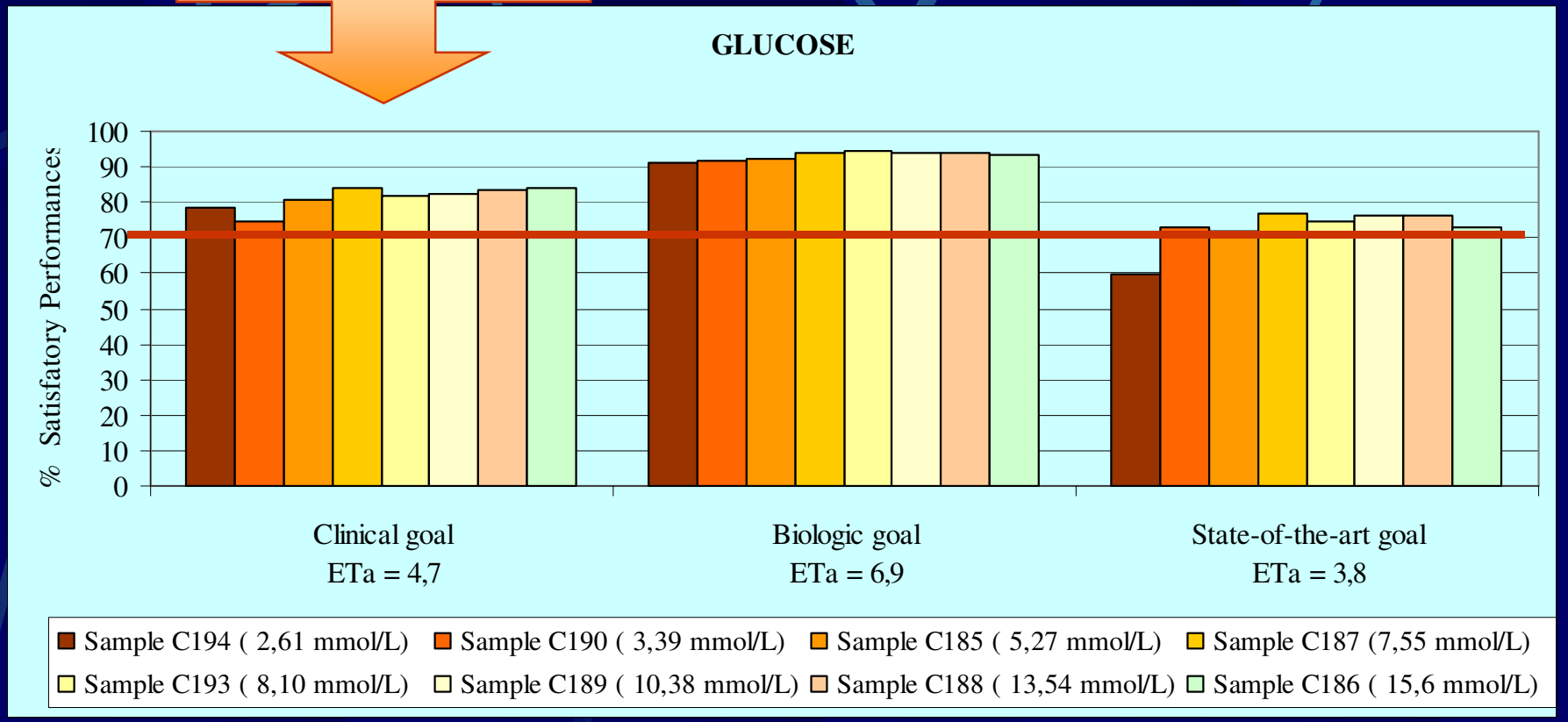
Glucose

Table 2—*Criteria for the diagnosis of diabetes*

1.	FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
	OR
2.	Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
	OR
3.	2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

EQA goal


GLUCOSE
% Satisfatory Performances
100
90
80
70
60
50
40
30
20
10
0
Clinical goal
ETa = 4,7
Biologic goal
ETa = 6,9
State-of-the-art goal
ETa = 3,8
Sample C194 (2,61 mmol/L)
Sample C190 (3,39 mmol/L)
Sample C185 (5,27 mmol/L)
Sample C187 (7,55 mmol/L)
Sample C193 (8,10 mmol/L)
Sample C189 (10,38 mmol/L)
Sample C188 (13,54 mmol/L)
Sample C186 (15,6 mmol/L)

Opinion

Glucose: A Simple Molecule That Is Not Simple to Quantify

Raymond Gambino

Clinical Chemistry 53, No. 12, 2007

"Small increments in blood glucose substantially increase the risk of developing diabetes mellitus, but preanalytical and analytical variables, such as the absence of harmonization for glucose assays, make it difficult to correctly applied these epidemiological insights to individual patients"

	Campione C191			
	N.	Mediana	DS	CV%
Tutti i metodi	477	5,33	0,21	3,86
Chimica secca	28	5,00	0,10	2,06
Ortho Clinical Diagnos.	28	5,00	0,10	2,06
Enzimatico uv (HK)	209	5,33	0,12	2,32
Abbott, Aeroset/Architect	27	5,33	0,12	2,32
Beckman, Syncron CX	3			
Olympus, AU	53	5,33	0,12	2,32
Roche, Cobas 6000	13	5,27	0,08	1,51
Roche, Cobas Integra	30	5,27	0,12	2,34
Roche, Hitachi/Modular	36	5,33	0,12	2,25
Siemens, Advia	15	5,44	0,08	1,51
Siemens, Dimension	28	5,32	0,12	2,32
GOD, POD	196	5,33	0,23	4,25
ABX, Pentra	4	5,47	0,31	5,64
Assel, Liasys	10	5,61	0,41	7,34
BioSystems, Targa	4	5,38	0,12	2,17
Biotecnica, Targa	5	5,61	0,12	2,20
DiaSys	3			
Futura System, Targa	7	5,49	0,38	6,89
Gesan	3			
IL, ILAB	49	5,22	0,21	3,94
Roche, Hitachi/Modular	32	5,33	0,14	2,70
Sclavo	3			
Sclavo, Konelab	14	5,27	0,21	3,90
Sentinel, Hitachi/Modular	6	5,52	0,33	5,96
SGM Italia	4	5,49	0,41	7,49
Spinreact	8	5,30	0,21	3,88
Thermo, Konelab	5	5,44	0,00	0,00
Polarografico	26	5,58	0,12	2,21
Beckman, LX/DxC	18	5,61	0,08	1,47
Beckman, Syncron CX	7	5,55	0,16	2,97

1.47 - 7.49

5.00 - 5.61

	Campione C187			
	N.	Mediana	DS	CV%
Tutti i metodi	458	7,55	0,25	3,27
Chimica secca	26	7,27	0,25	3,40
Ortho Clinical Diagnos.	26	7,27	0,25	3,40
Enzimatico uv (HK)	213	7,55	0,20	2,68
Abbott, Aeroset/Architect	28	7,55	0,22	2,97
Beckman, LX/DxC	3			
Olympus, AU	53	7,55	0,19	2,45
Roche, Cobas 6000	11	7,54	0,08	1,09
Roche, Cobas Integra	33	7,55	0,21	2,73
Roche, Hitachi/Modular	35	7,55	0,12	1,64
Siemens, Advia	14	7,71	0,19	2,40
Siemens, Dimension	28	7,57	0,14	1,90
GOD, POD	175	7,55	0,33	4,36
ABX, Pentra	4	7,58	0,10	1,36
Assel, Liasys	9	7,44	0,41	5,53
BioSystems, Targa	3			
DiaSys	5	7,49	0,33	4,39
Futura System, Targa	7	7,60	0,37	4,87
IL, ILAB	43	7,27	0,21	2,83
Roche, Hitachi/Modular	33	7,52	0,21	2,74
Sclavo, Konelab	11	7,55	0,33	4,36
Sentinel, Hitachi/Modular	6	7,80	0,33	4,22
SGM Italia	4	8,05	0,68	8,44
Spinreact	4	7,46	0,16	2,20
Thermo, Konelab	12	7,80	0,41	5,28
Polarografico	30	7,71	0,25	3,20
Beckman, LX/DxC	21	7,73	0,16	2,13
Beckman, Syncron CX	8	7,44	0,25	3,32

1.36 - 8.44

7.27 - 8.05

Opinion

Glucose: A Simple Molecule That Is Not Simple to Quantify

Raymond Gambino — *Clinical Chemistry* 53, No. 12, 2007

Unfortunately, until glucose measurements are harmonized these epidemiologically correct cut points cannot be applied with confidence to individual patients.

Diagnosis of diabetes

- Casual plasma glucose 11.1 mmol/L (200 mg/dL)
- Fasting Plasma Glucose 7.0 mmol/L (126 mg/dL)
- 2-h Plasma Gluocose ≥ 11.1 mmol/L during an oral glucose tolerance test

Reference range

- children: 3.3 - 5.6 mmol/L
- adults: 4.1 - 5.9 mmol/L

Clinical Practice Recommendation - ADA, 2001

Opinion

Glucose: A Simple Molecule That Is Not Simple to Quantify

Raymond Gambino — *Clinical Chemistry* 53, No. 12, 2007

Three major variables must be addressed to achieve harmonization:

- **Proficiency test programs should be accuracy based rather than consensus based**
- Glycolysis in the specimen must be effectively limited
- The time of day blood is collected must be taken into account

Troponin I or T

- The preferred biomarker for myocardial necrosis is cardiac Troponin (I or T)
- It is pivotal that these clinically biomarkers are measured with highly reliable and standardized methods to achive comparable results

Troponin I

- **Clinical goals = 10%**

  NACB/IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines; Analytical Issue for Biochemical Markers of Acute Coronary Syndromes. Clin Clem 2007;53:547-51.

- **Biological goals = 24.46 (short term)**
  27.68 (long term)

  A. Wu. Clin Chem 2009;55,1:52-8

- **State-of-the-art goals =<15%**

  Average of inter-laboratory variability obtained in EQA Scheme 2008 of Centre of Biomedical Research

European Heart Journal (2007) 28, 2525–2538
doi:10.1093/eurheartj/ehm355

Expert consensus document

Universal definition of myocardial infarction

Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction

Biomarker evaluation

Myocardial cell death can be recognized by the appearance in the blood of different proteins released into the circulation from the damaged myocytes: myoglobin, cardiac troponin T and I, CK, LDH, as well as many others.[3] Myocardial infarction is diagnosed when blood levels of sensitive and specific biomarkers such as cardiac troponin or CKMB are increased in the clinical setting of acute myocardial ischaemia.[1] Although elevations in these biomarkers reflect myocardial necrosis, they do not indicate its mechanism.[3,4] Thus, an elevated value of cardiac troponin in the absence of clinical evidence of ischaemia should prompt a search for other aetiologies of myocardial necrosis, such as myocarditis, aortic dissection, pulmonary embolism, congestive heart failure, renal failure, and other examples indicated in Table 2.

The preferred biomarker for myocardial necrosis is cardiac troponin (I or T), which has nearly absolute myocardial tissue specificity as well as high clinical sensitivity, thereby reflecting even microscopic zones of myocardial necrosis.[3] An increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population (URL = upper reference limit). Detection of a rise and/or fall of the measurements is essential to the diagnosis of acute myocardial infarction.[6] The above-mentioned discriminatory percentile is designated as the decision level for the diagnosis of myocardial infarction, and must be determined for each specific assay with appropriate quality control.[7–9] Optimal precision [coefficient of variation (CV)] at the 99th percentile URL for each assay should be defined as $\leq$10%. Better precision (CV $\leq$10%) allows for more sensitive assays.[10,11] The use of assays that do not have independent validation of optimal precision (CV$\leq$10%) is not recommended. The values for the 99th percentile can be found on the International Federation for Clinical Chemistry website http://www.ifcc.org/index.php?option=com_remository&Itemid=120&func=fileinfo&id=7.

NACB/IFCC 2007 Guidelines

Risk stratification

Class I

A cardiac troponin is the preferred marker for risk stratification and, if available, should be measured in all patients with suspected ACS *(Level of Evidence C)*

…. a maximal peak concentration exceeding the 99° percentile of values for a reference control group should be considered indicative of increased risk of death and recurrent ischemic events *(Level of Evidence A)*

Class II

A multimarker strategy that includes measurement of 2 or more pathobiologically diverse biomarkers in addition to a cardiac troponin may aid in enhancing risk stratification …… Natriuretic peptides, hs-CRP are the biomarkers best studied using this approach *(Level of Evidence C)*

Clinical Chemistry 55:1
52–58 (2009)

Short- and Long-Term Biological Variation in Cardiac Troponin I Measured with a High-Sensitivity Assay: Implications for Clinical Practice

Alan H.B. Wu,[1*] Quynh Anh Lu,[2] John Todd,[2] Joachim Moecks,[3] and Frank Wians[4]

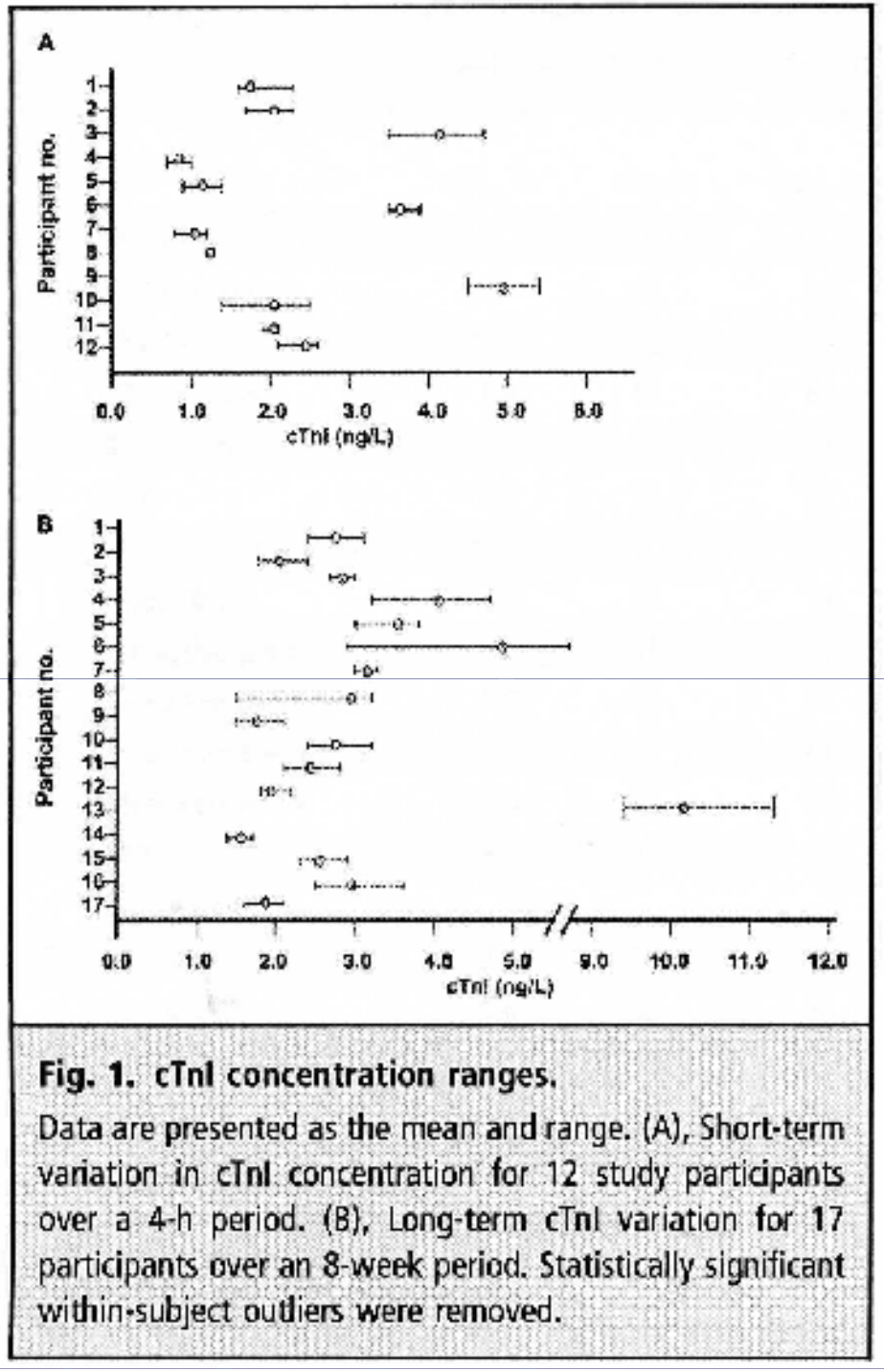


Fig. 1. cTnI concentration ranges.

Data are presented as the mean and range. (A), Short-term variation in cTnI concentration for 12 study participants over a 4-h period. (B), Long-term cTnI variation for 17 participants over an 8-week period. Statistically significant within-subject outliers were removed.

Clinical Chemistry 55:1
52–58 (2009)

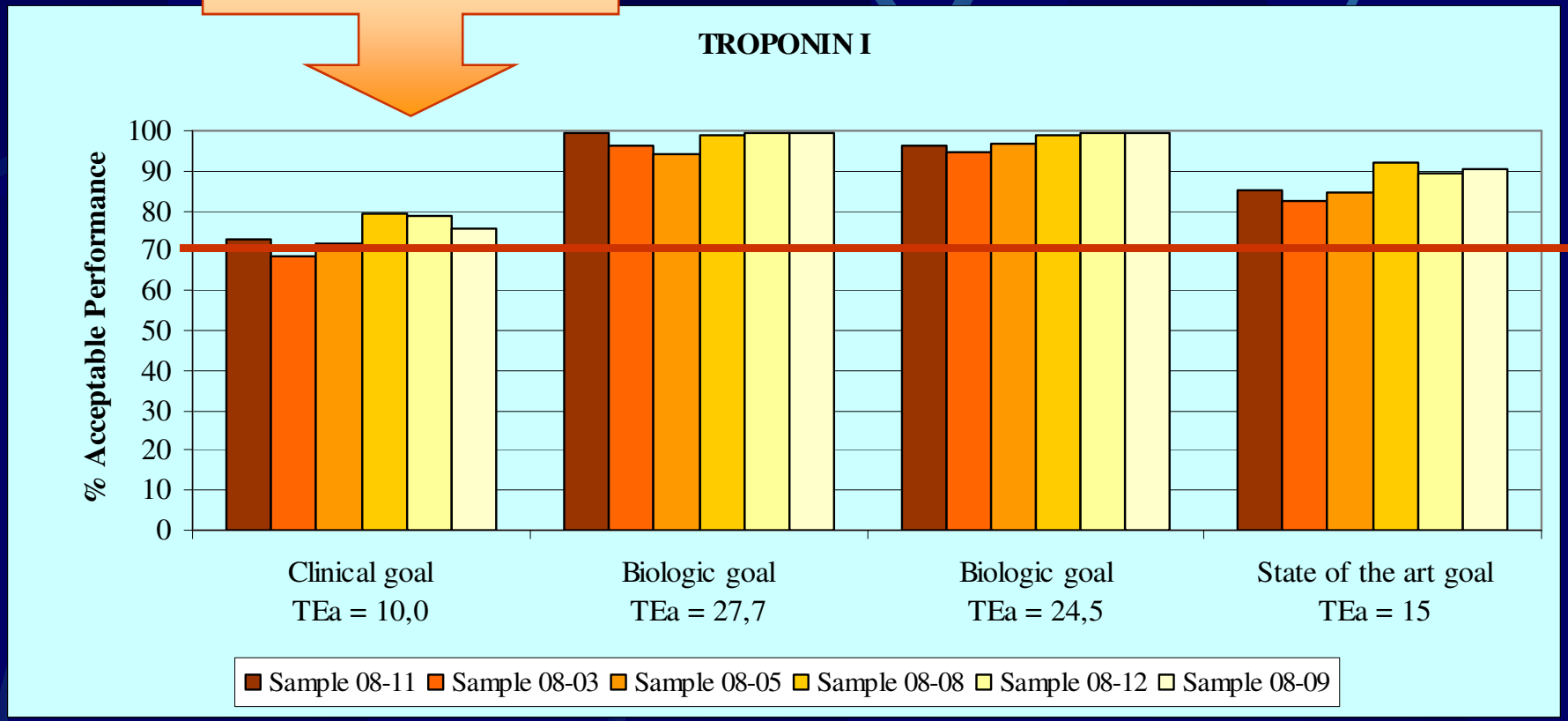
Short- and Long-Term Biological Variation in Cardiac Troponin I Measured with a High-Sensitivity Assay: Implications for Clinical Practice

Alan H.B. Wu,[1*] Quynh Anh Lu,[2] John Todd,[2] Joachim Moecks,[3] and Frank Wians[4]

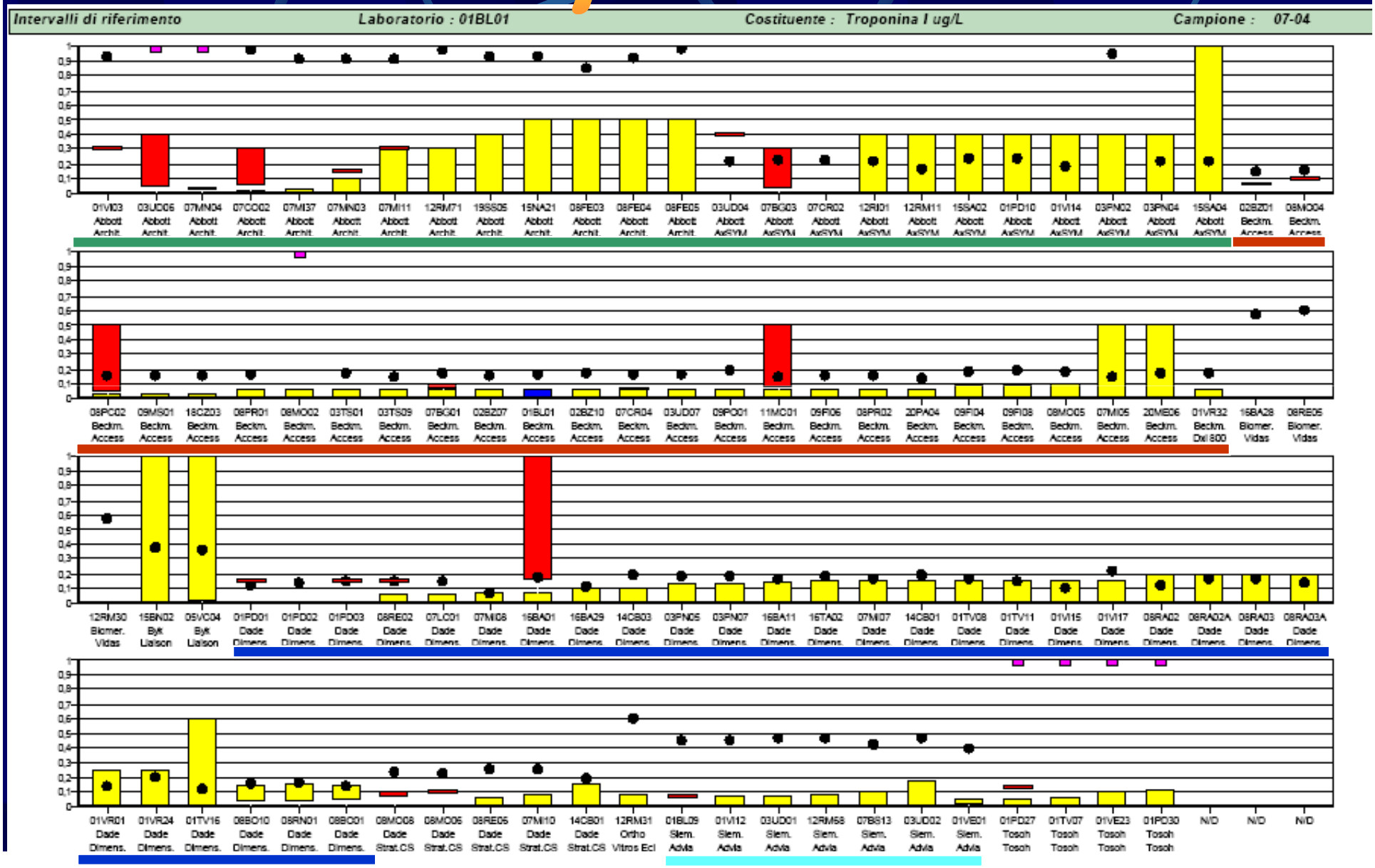
Table 1. Short- and long-term biological variation in cTnI.

Variable	Short term (0–4 h)	Long term (0–8 weeks)
Analytical variation		
CV_A, %[a]	8.3	15
Biological variation		
CV_I, %	9.7	14
CV_G, %	57	63
Index of individuality	0.21	0.39
RCV: log-normal increase, %	+46	+81
RCV: log-normal decrease, %	−32	−45

EQA goal


TROPONIN I
% Acceptable Performance
100
90
80
70
60
50
40
30
20
10
0
Clinical goal
TEa = 10,0
Biologic goal
TEa = 27,7
Biologic goal
TEa = 24,5
State of the art goal
TEa = 15
Sample 08-11
Sample 08-03
Sample 08-05
Sample 08-08
Sample 08-12
Sample 08-09

Troponin I


Intervalli di riferimento
Laboratorio : 01BL01
Costituente : Troponina I ug/L
Campione : 07-04

Troponin I

- Different manufacturers
- Diagnostic systems use different calibration materials
- Variable antibody immunoreactivity to different forms

- Differences between cTnI results

~~One Decisional Limit~~

TROPONIN I

	Campione 09-02			
	N.	Mediana	DS	CV%
Tutti i metodi	64			
Abbott Architect	10	0,410	0,013	3,25
Abbott AxSYM (Advanced 2J44-20)	6	0,060	0,011	18,53
Beckman Access AccuTnI	10	0,035	0,007	21,18
Biomerieux Vidas	6	0,300	0,007	2,47
Mitsubishi Pathfast	1			
Siemens/Bayer, Advia Centaur	11	0,040	0,004	9,27
Siemens/Dade Behring Dimension - 2°	5	0,040	0,007	18,53
Siemens/Dade Behring Stratus CS	2			
Siemens/DPC Immulite	1			
Tosoh Aia-Pack	5	0,740	0,037	5,01
Triage	2			

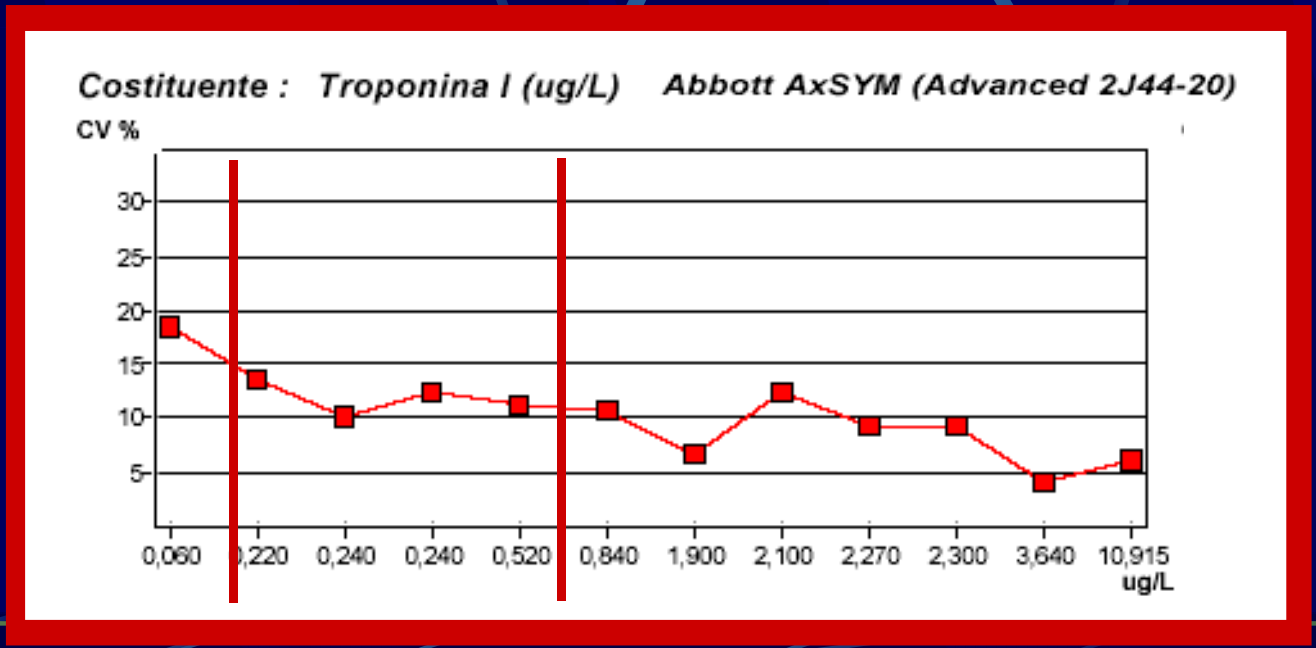
TROPONIN I

	Campione 08-07				Campione 08-05			
	N.	Mediana	DS	CV%	N.	Mediana	DS	CV%
Tutti i metodi	190				273			
Abbott Architech	24	0,982	0,077	7,89	30	3,309	0,189	5,71
Abbott AxSYM (Advanced 2J44-20)	16	0,240	0,024	10,04	25	0,840	0,089	10,59
Beckman Access AccuTnI	52	0,190	0,015	7,80	59	0,640	0,074	11,58
Biomerieux Vidas	12	0,645	0,030	4,60	18	1,685	0,156	9,24
Byk Liaison	5	0,210	0,013	6,35	3			
Dade/Behring Dimension - 2° gen	24	0,130	0,030	22,81	65	0,450	0,059	13,18
Dade/Behring Stratus CS	11	0,210	0,030	14,12	12	0,650	0,074	11,40
DPC Immulite	6	0,510	0,178	34,88	7	1,770	0,170	9,63
Ortho Vitros Eci	8	0,900	0,053	5,85	9	3,560	0,089	2,50
Siemens Advia Centaur	18	0,485	0,053	10,85	26	1,734	0,163	9,41
Tosoh Aia-Pack	7	1,590	0,126	7,93	11	5,680	0,697	12,27
Triage	2				2			

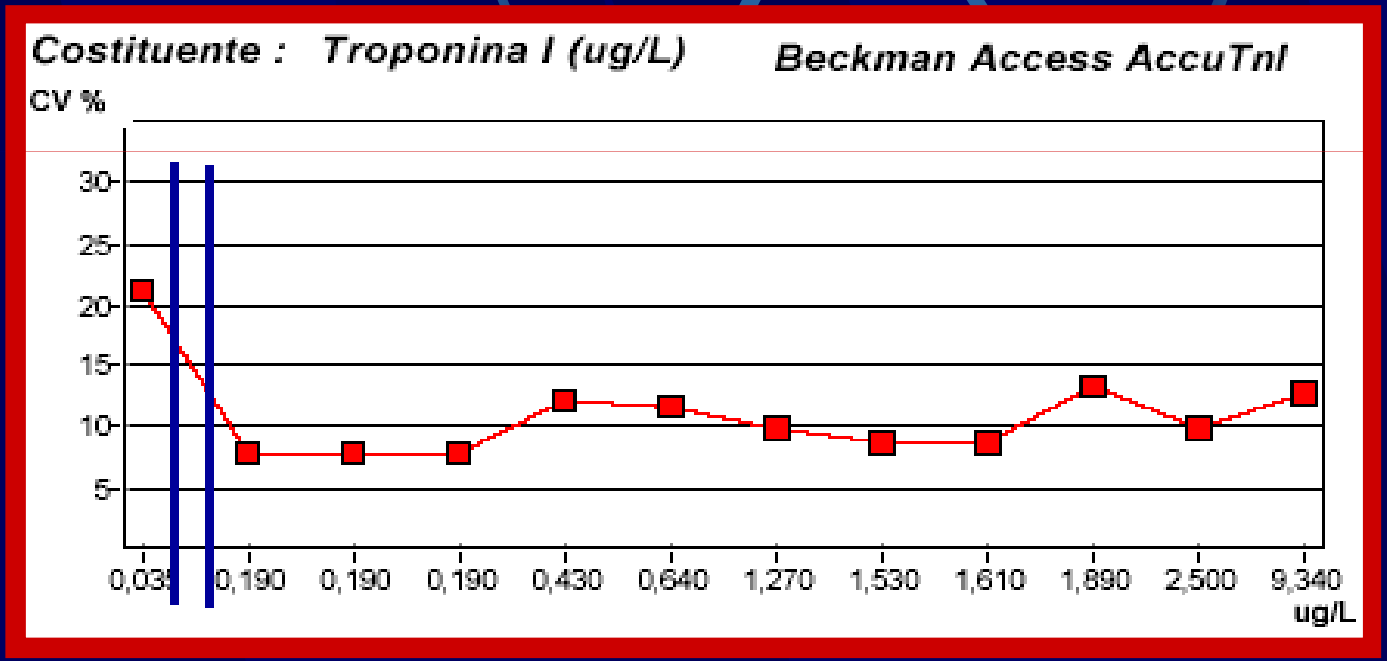
	Campione 08-06				Campione 08-02			
	N.	Mediana	DS	CV%	N.	Mediana	DS	CV%
Tutti i metodi	264				264			
Abbott Architech	27	7,550	0,658	8,71	29	14,263	0,752	5,28
Abbott AxSYM (Advanced 2J44-20)	22	2,100	0,259	12,35	24	3,680	0,289	7,87
Beckman Access AccuTnI	53	1,610	0,141	8,75	55	3,230	0,393	12,16
Biomerieux Vidas	21	3,470	0,215	6,20	13	6,270	0,156	2,48
Byk Liaison	8	1,785	0,252	14,12	9	8,470	0,445	5,25
Dade/Behring Dimension - 2° gen	63	1,000	0,119	11,86	65	1,910	0,185	9,70
Dade/Behring Stratus CS	11	1,480	0,119	8,01	11	2,820	0,141	4,99
DPC Immulite	6	3,960	0,467	11,79	6	7,385	0,430	5,82
Ortho Vitros Eci	11	8,470	0,756	8,93	10	18,050	1,112	6,16
Siemens Advia Centaur	24	4,305	0,436	10,12	22	9,166	0,867	9,46
Tosoh Aia-Pack	7	14,630	0,423	2,89	10	30,300	1,245	4,11
Triage	2				2			

	TROPONIN I (ug/L)		
	LoD	**Dynamic reportable range**	**Imprecision (10% CV)**
Abbott Axsym ADV cTnI (2nd gener.)	<0.01	0.02 – 22.8	0.16 – 0.56

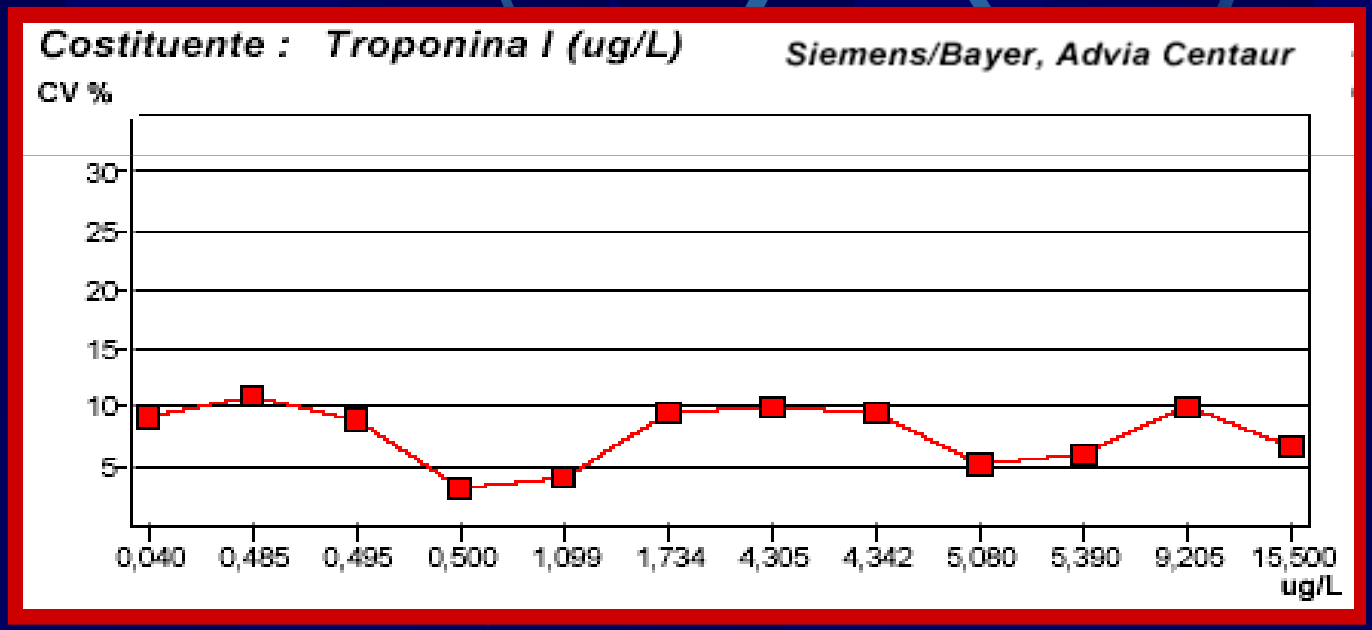
Tate JR, Panteghini M. Bioch Clin 2008



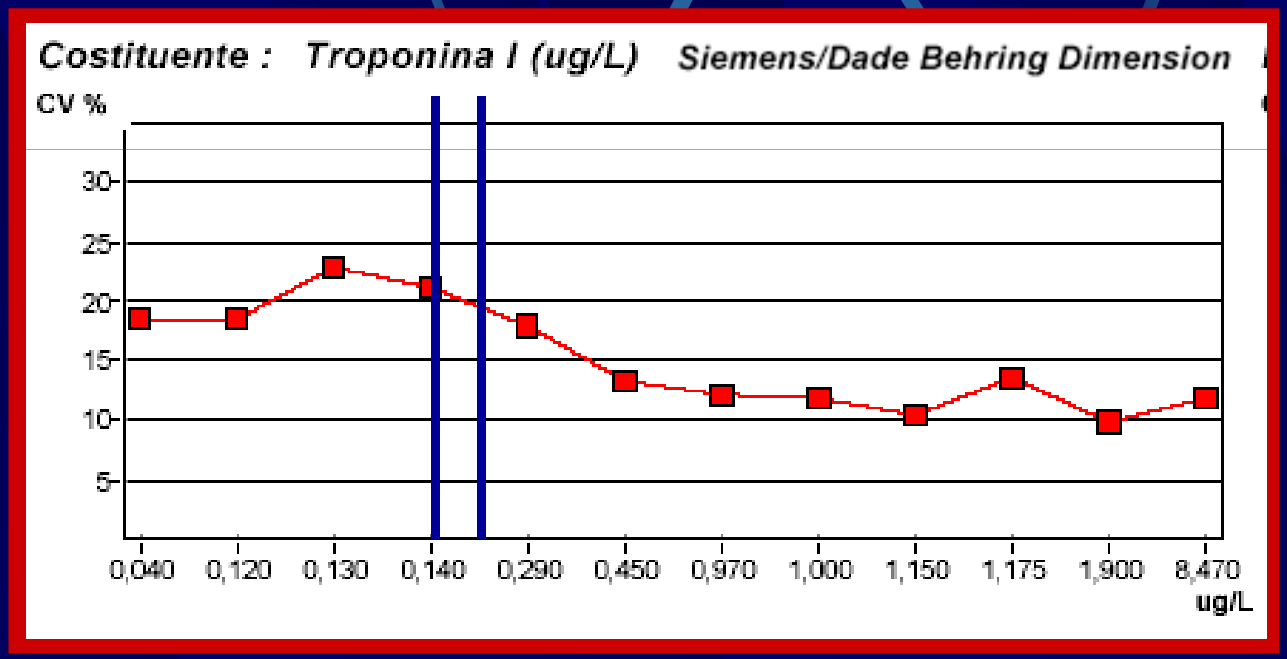
	TROPONIN I (ug/L)		
	LoD	**Dynamic reportable range**	**Imprecision (10% CV)**
Beckman Coulter Access cTnI (2nd gener.)	<0.01	0.01 – 100	0.06 – 0.10



	TROPONIN I (ug/L)		
	LoD	**Dynamic reportable range**	**Imprecision (10% CV)**
Siemens/Bayer ADVIA Centaur cTnI Ultra (2nd gener.)	<0.006	0.01 – 50	0.03 – 0.07



	TROPONIN I (ug/L)		
	LoD	**Dynamic reportable range**	**Imprecision (10% CV)**
Siemens/Dade Behring Dimension cTnI (2nd gener.)	<0.02	0.04 – 40	0.14 – 0.26

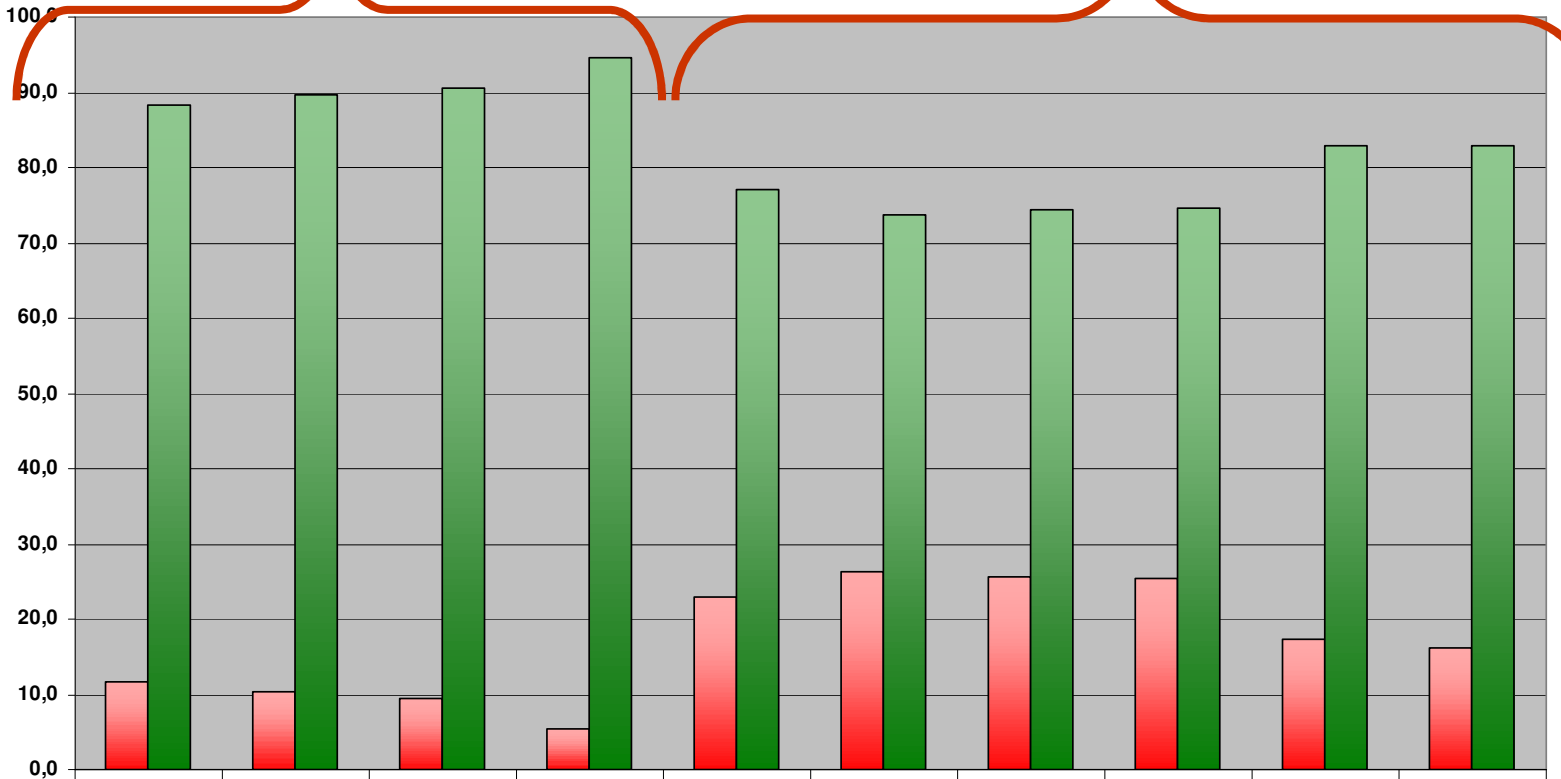


Years 1999 - 2008

Optimum	Desirable	Accept.	Unaccept.
≤ 10	10-20	20-30	>30

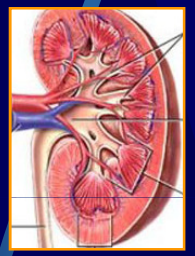
Optimum	Desirable	Accept.	Unaccept.
≤ 5	5-10	10-15	>15

Troponin I



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Unacceptable	11,6	10,3	9,5	5,3	22,8	26,2	25,6	25,4	17,4	16,2
Satisfactory	88,4	89,7	90,5	94,7	77,2	73,8	74,4	74,5	82,9	83,0

Creatinine



Central role in the assessment of renal function and the use of creatinine values for estimation of glomerular rate (eGFR)

Creatinine

- **Clinical goals = <10% in the relative error of eGFR**

  Recommendations for Improving Serum Creatinine Measurement: A Report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem 2008;52:5-18*

- **Biological goals = 8.16%**

  Westgard Desirable Specifications for total error, imprecision, and bias from biological Variation. Update 2008. www.westagrd.com

- **State-of-the-art goals = 7.8%**

  Average of inter-laboratory variability obtained in EQA Scheme 2008 of Centre of Biomedical Research

Clinical Chemistry 52:1
5–18 (2006)

Special Report

Recommendations for Improving Serum Creatinine Measurement: A Report from the Laboratory Working Group of the National Kidney Disease Education Program

Gary L. Myers,[1*] W. Greg Miller,[2] Josef Coresh,[3] James Fleming,[4] Neil Greenberg,[5] Tom Greene,[6] Thomas Hostetter,[7] Andrew S. Levey,[8] Mauro Panteghini,[9] Michael Welch,[10] and John H. Eckfeldt[11] for the National Kidney Disease Education Program Laboratory Working Group

- After recalibration to IDMS, a realistic total error goal for creatinine measurement is a maximum 10% increase in the relative error of the estimated GFR. Routine methods could achieve this total error goal if analytical imprecision (including between-laboratory calibration variability) is <8% and analytical bias (compared with an IDMS reference measurement procedure) is <5% at all serum creatinine concentrations ≥88.4 μmol/L (1.00 mg/dL).

Published ahead of print on November 14, 2007
J Am Soc Nephrol 19: 164-169, 2008

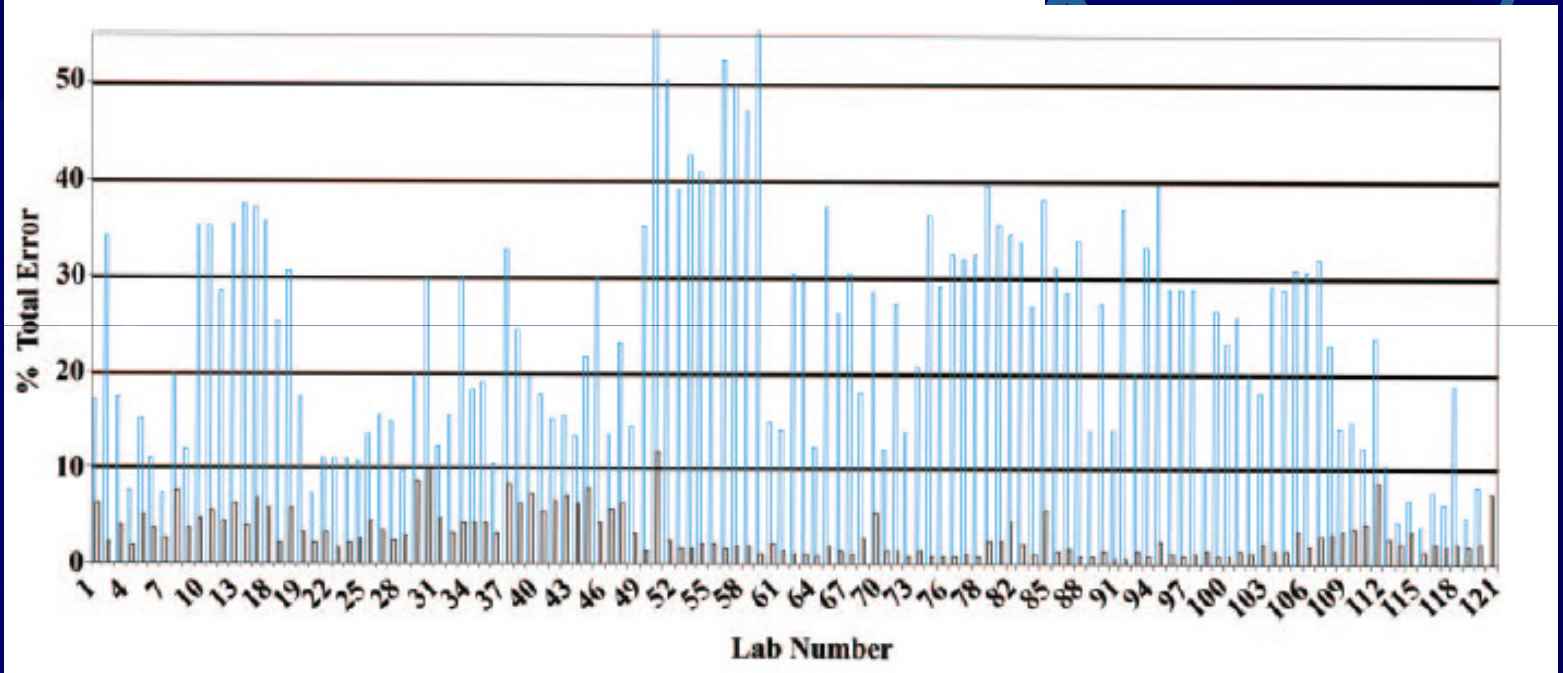
doi: 10.1681/ASN.2007020156

Clinical Epidemiology

Regional Implementation of Creatinine Measurement Standardization

Paul Komenda[*,†], Monica Beaulieu[*,†], David Seccombe[‡,§] and Adeera Levin[*,†]

Average calibration bias = 16,5%

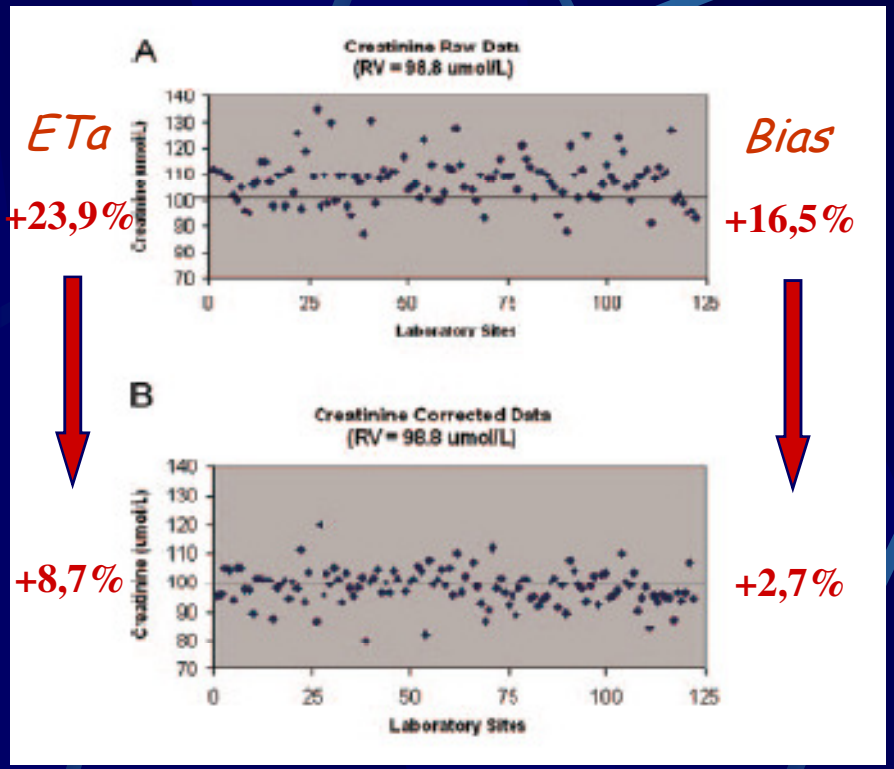


%TE = from 4% to 54% (mean= 23,9%)

96 to 104 umol/L

45 to 154 umol/L

% laboratories which comply the (±10% RV)



Analyte[a]	Pass (%)
Creatinine (uncorrected)	50.4
Creatinine (corrected)	90.3
eGFR (uncorrected creatinine)	58.7
eGFR (corrected creatinine)	86.6

[a]Reference value (RV) = 98.8 μ mol/L.

Monitoring cycle

Sample	A	B	C
Cr (μ mol/L; RV)	117.6	91.1	68.1
eGFR (ml/min per 1.73 m^2; RV)	41	56	99
% of laboratories meeting a performance limit of RV ±10%			
Cr (uncorrected)	50	38	26
Cr (corrected)	94	86	78
eGFR (Cr corrected)	90	80	74

[a]Cr, creatinine.

Komenda P et al, J Am Soc Nephrol, 2008

Published ahead of print on November 14, 2007
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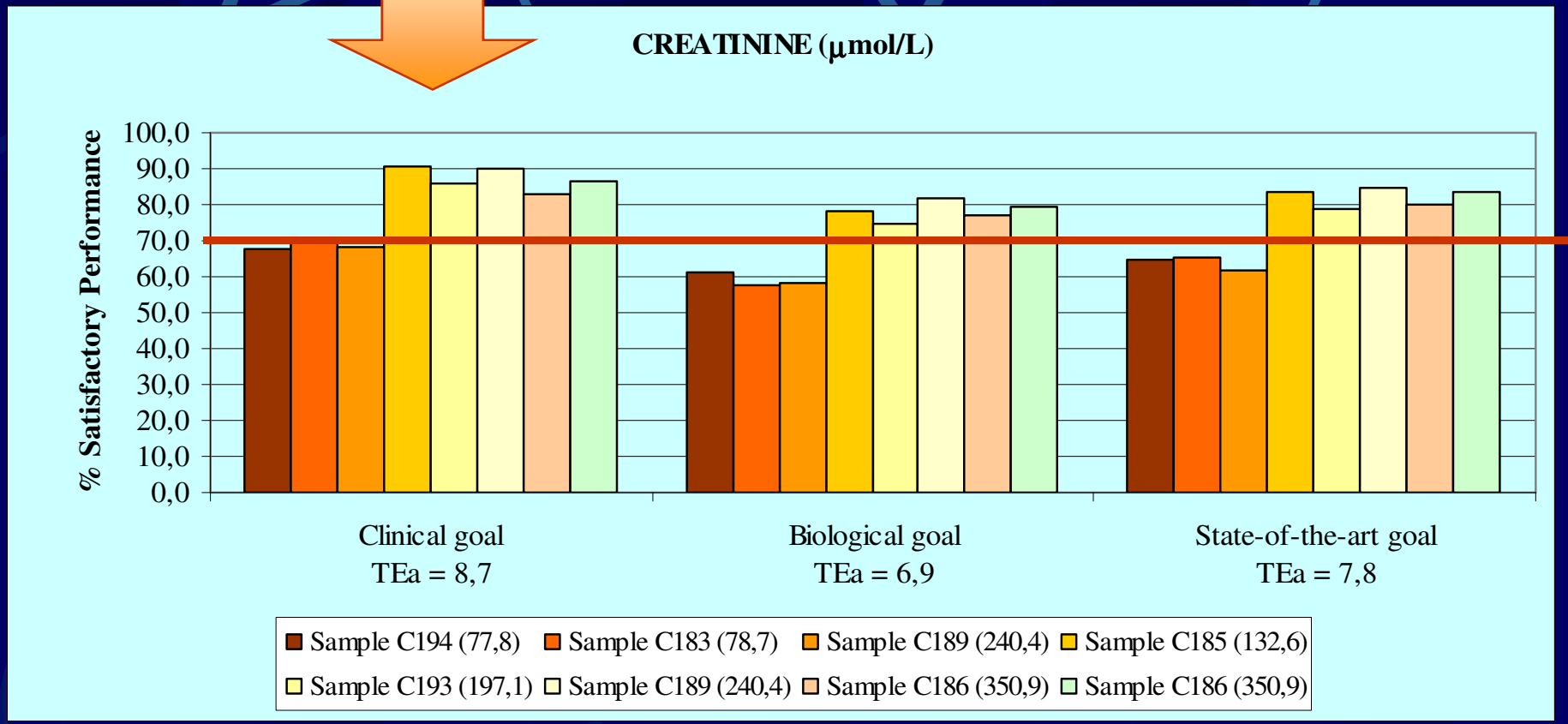
[*] Department of Medicine, Division of Nephrology and [‡] Department of Pathology and Laboratory Medicine, University of British Columbia, [†] British Columbia Renal Agency, and [§] Canadian External Quality Assessment Laboratory, Vancouver, British Columbia, Canada

The 90% of the participating laboratories were able to achieve a 10% TEa performance goal after correction of their calibration bias.

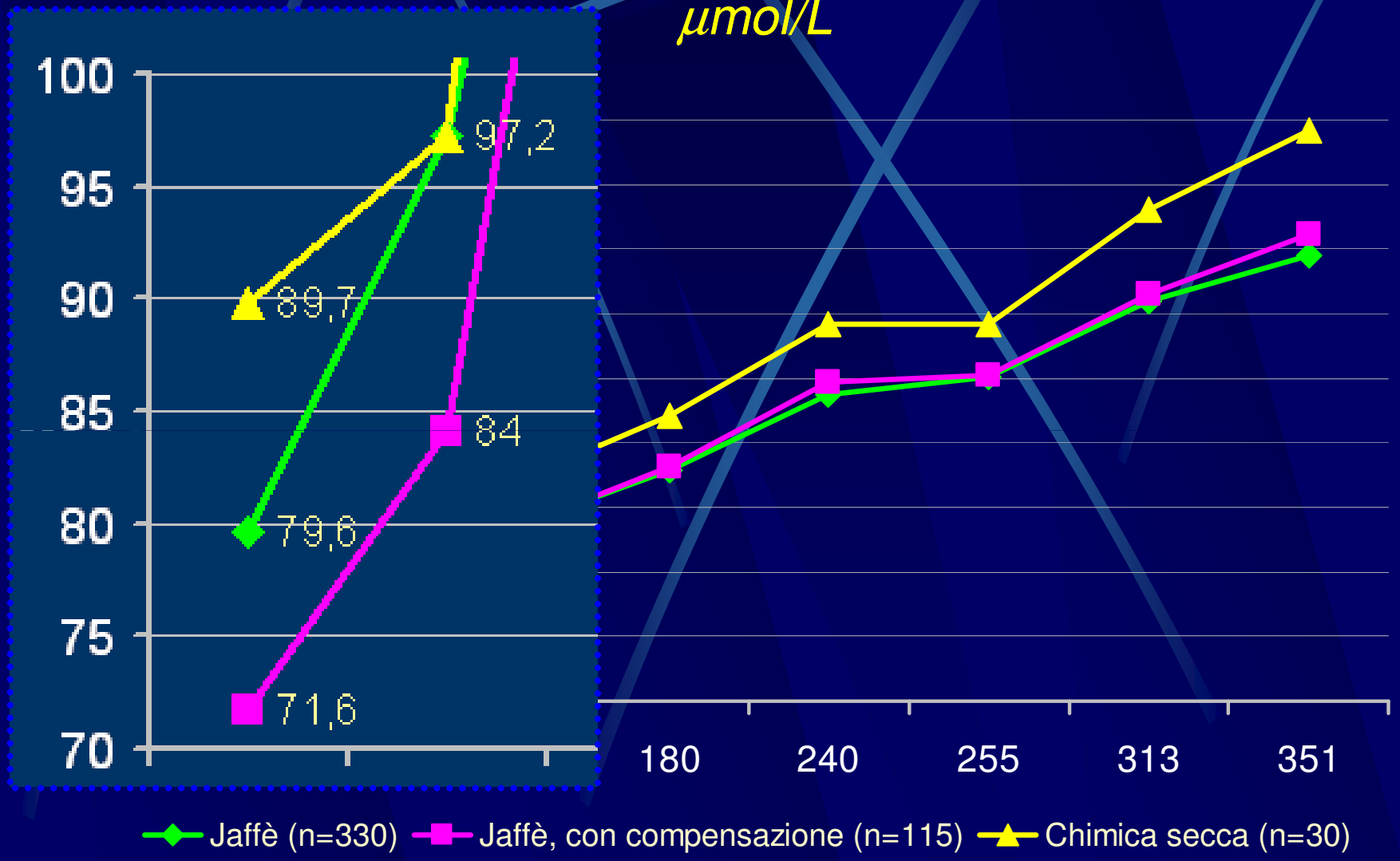
This indicates that, in real terms, this performance goal certainly achievable once the manufacturers have revised their calibration processes to be traceable to the IDMS reference method

EQA goal


CREATININE (µmol/L)
% Satisfactory Performance
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
Clinical goal
TEa = 8,7
Biological goal
TEa = 6,9
State-of-the-art goal
TEa = 7,8
Sample C194 (77,8)
Sample C183 (78,7)
Sample C189 (240,4)
Sample C185 (132,6)
Sample C193 (197,1)
Sample C189 (240,4)
Sample C186 (350,9)
Sample C186 (350,9)

Creatinine

µmol/L



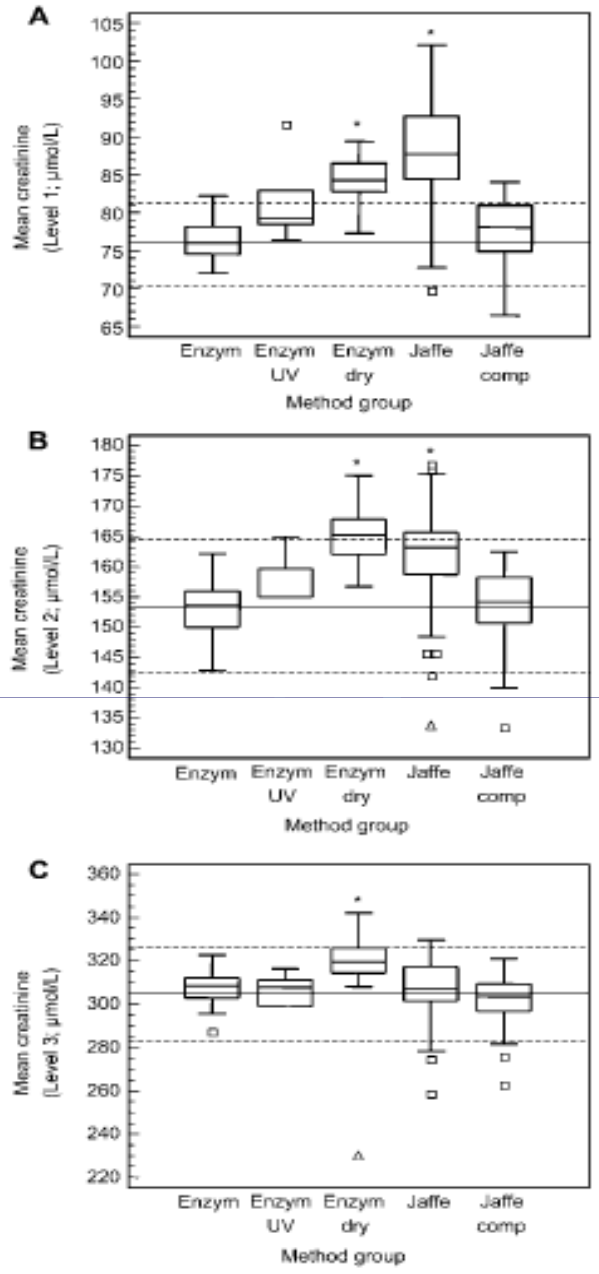


Figure 2 Creatinine results obtained for the various method groups in comparison with the target value (full line) and the total allowable error margins (dashed lines) at levels 1 (A), 2 (B), and 3 (C). *Result exceeding total allowable error.

Komenda P et al, J Am Soc Nephrol, 2008

Clin Chem Lab Med 2008;46(4):567–572 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.113

Enzymatic assays for creatinine: time for action[1),2)]

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[3)]

IFCC Scientific Division

Mauro Panteghini* on behalf of the IFCC Scientific Division

Centre for Metrological Traceability in Laboratory Medicine (CIRME) and Department of Clinical Sciences 'Luigi Sacco', University of Milan, Milan, Italy

Clin Chem Lab Med 2008;46(8):1127–1133 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.224

Determination of serum creatinine by Jaffe method and how to calibrate to eliminate matrix interference problems

Vratislav Chromý[1,*], Kateřina Rozkošná[2] and Pavel Sedlák[3]

[1] Institute of Chemistry, Faculty of Science, Masaryk University, Brno, Czech Republic
[2] Diagnostics Research Department, Pliva-Lachema Diagnostika, Brno, Czech Republic
[3] Department of Clinical Biochemistry, Municipal Hospital, Čáslav, Czech Republic

Clinical Chemistry 52:1
5–18 (2006)

Special Report

Recommendations for Improving Serum Creatinine Measurement: A Report from the Laboratory Working Group of the National Kidney Disease Education Program

Gary L. Myers,[1*] W. Greg Miller,[2] Josef Coresh,[3] James Fleming,[4] Neil Greenberg,[5] Tom Greene,[6] Thomas Hostetter,[7] Andrew S. Levey,[8] Mauro Panteghini,[9] Michael Welch,[10] and John H. Eckfeldt[11] for the National Kidney Disease Education Program Laboratory Working Group

IVD Manufacturers have to calibrate serum creatinine methods to be traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure in order to reduce the inter-laboratory bias in results and yield more accurate eGFR

Clin Chem Lab Med 2008;46(9):1319–1325 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.256

Trueness verification of actual creatinine assays in the European market demonstrates a disappointing variability that needs substantial improvement

An international study in the framework of the EC4 creatinine standardization working group

Clin Chem Lab Med 2007;45(4):549–552 © 2007 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2007.105

Short Communication

Implementing the Stockholm Conference hierarchy of objective quality criteria in a routine laboratory

Dhatt GS, Agarwal MM, Bishawi B and Gill J.

IMPLEMENTING THE STOCKHOLM CONFERENCE HIERARCHY

The results show that the hierarchy model of the Stockholm Conference for the setting of objective quality specifications can be successfully implemented in routine laboratory. Furthermore, it can be inferred that the ***instrument, reagents, analytical methods and QC material are capable of meeting objective quality criteria*** consistently over a prolonged period.

Dhatt GS et al. Clin Chem Lab Med, 2007

What have we learned?

What have we learned?

- ✓ Clinical goals not often are identified or available
- ✓ Difficulties in evaluating laboratories performances when clinically plausible abnormal values coincide with values at one extreme or other of the usual operating range of the instruments
- ✓ Several studies on Biological Variability provides different data, consequently there is a continuous change/update of CVw e CVg (are they evidence-based???).

What have we learned?

- ✓ Imprecision is often different at different concentration of analytes, and therefore, the percentage of laboratories that achieves the ETa goals is different at different concentrations.

- ✓ Standardization problems can affect the applicability of suitable goals.

EQAS and progress in standardization

- Use of commutable control materials with target values assigned using the reference method to assess the performance of clinical laboratories and the success of their accuracy transfer processes.

EQAS and progress in standardization

- Objective evaluation and post-market surveillance of the performance of IVD medical devices with an accuracy-based (instead of inferior consensus-group) grading

- International cooperation among IVD manufacturers, clinical laboratories, professional organizations and EQAS/PT providers in order to establishing measurement traceability

CONUNDRUM

Is it possible to set

Quality Specifications

based on the Hierarchy of Models

to evaluate the laboratory

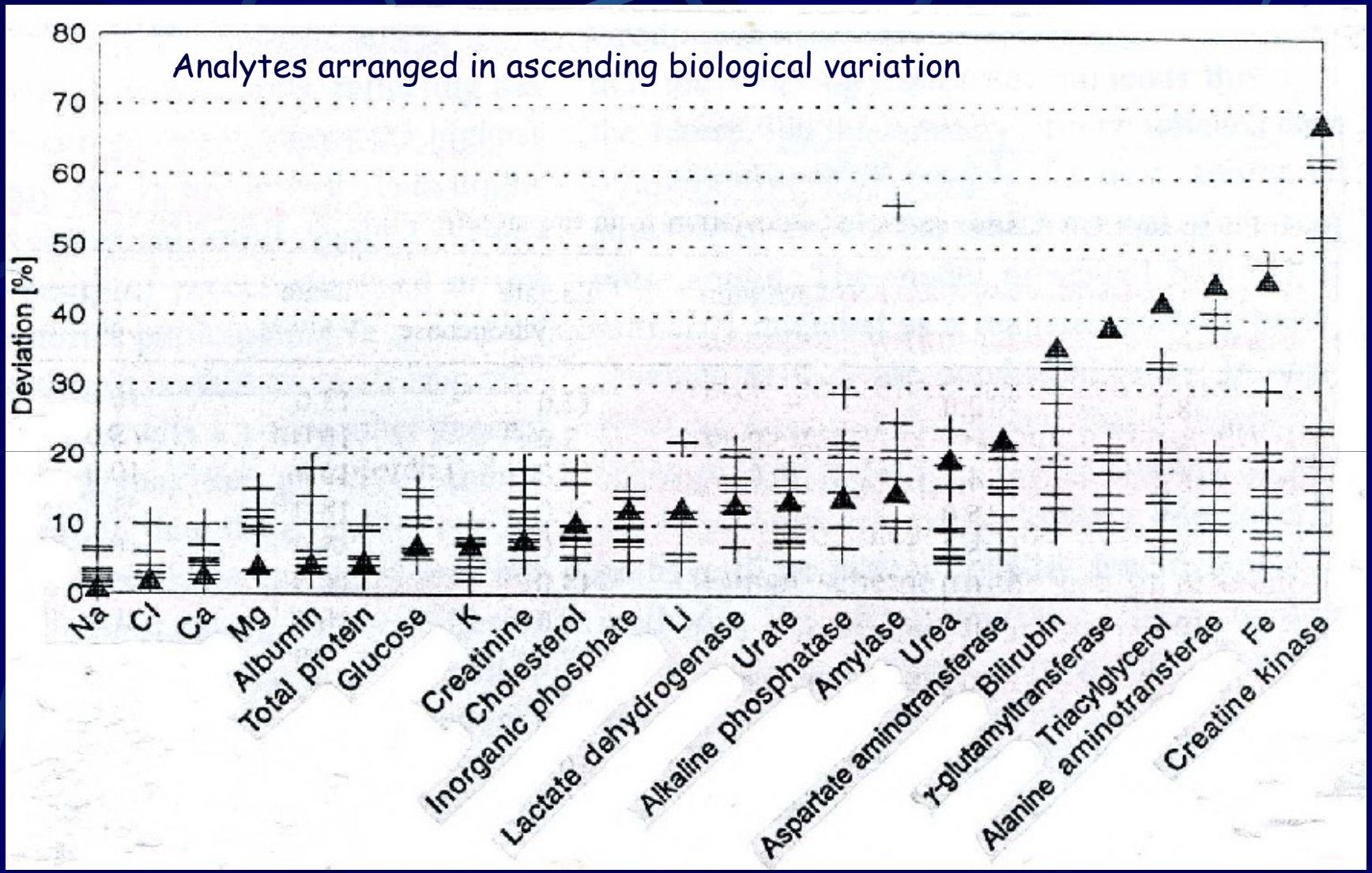
performances in the EQA Schemes ?

Yes

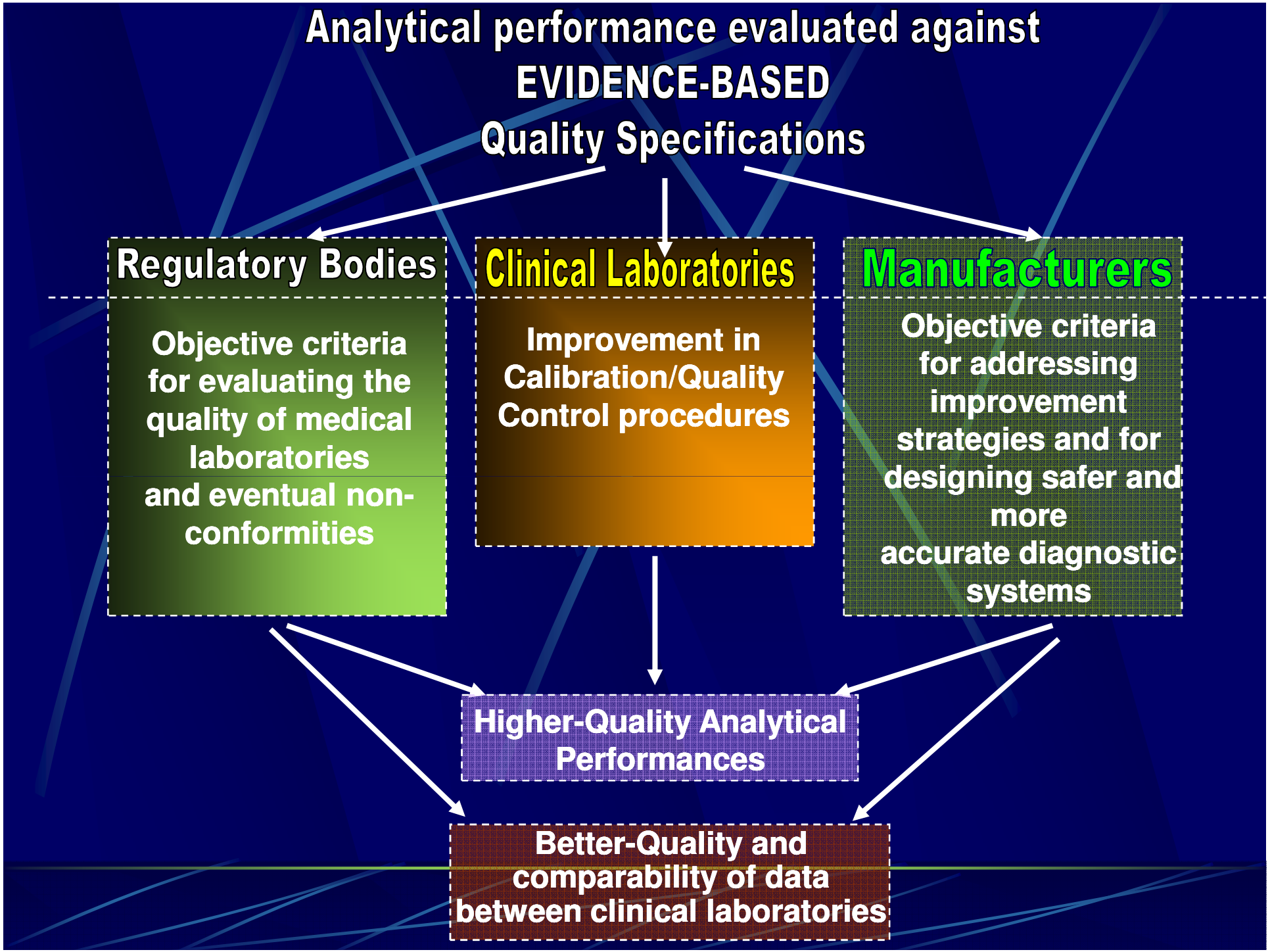
but

criteria and goals have to be defined in order to harmonize the approach to evaluate the laboratories' EQA results.

Current European EQA limits (1996)



EQAS Organizers WG on Quality Goals. Eur J Clin Chem Clin Biochem 1996;34:159-65


Analytical performance evaluated against
EVIDENCE-BASED
Quality Specifications
Regulatory Bodies
Objective criteria for evaluating the quality of medical laboratories and eventual non-conformities
Clinical Laboratories
Improvement in Calibration/Quality Control procedures
Manufacturers
Objective criteria for addressing improvement strategies and for designing safer and more accurate diagnostic systems
Higher-Quality Analytical Performances
Better-Quality and comparability of data between clinical laboratories