11th Asian Pacific Congress of Clinical Biochemistry

IFCC Scientific Division activities on standardization and traceability

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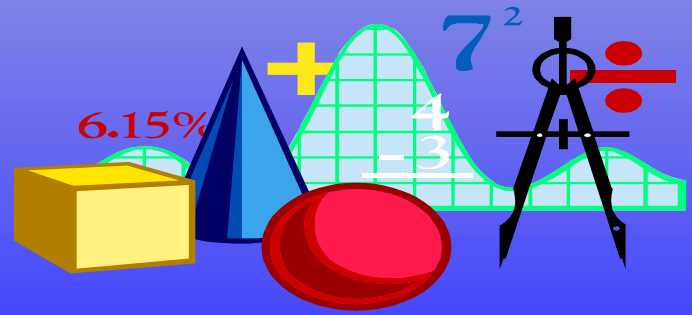
International Federation Of Clinical Chemistry And Laboratory Medicine

Scientific Division

- Mission: To advance the science of Clinical Chemistry and Laboratory Medicine and to apply it to the clinical practice
- Transfer of research results to the clinical laboratory
- Analytical standardization: reference systems, new techniques
- Post-analytical standardization: establish diagnostic strategies for new biomarkers
- Standards for good laboratory practice
- Collaborations: BIPM, CLSI, ILAC, IRMM, IUPAC, NIST, WHO, ADA, NKDEP



Clin Chem Lab Med 2001; 39(2):174–178 © 2001 by Walter de Gruyter · Berlin · New York

Standards for good laboratory practice

Quality Specifications for Cardiac Troponin Assa

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[1) 2)]

IFCC Scientific Division
Committee on Standardization of Markers of Cardiac Damage[3)]

Prepared for publication[4)] by

Mauro Panteghini[1, 5)], Willie Gerhardt[2], Fred S. Apple[3], Francesco Dati[4], Jan Ravkilde[5] and Alan H. Wu[6]

Clin Chem Lab Med 2006;44(12):1486–1490 © 2006 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2006.275

Approved IFCC recommendation on reporting results for blood glucose[1)]

International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division[2),3)]

Clinical Chemistry 51:3
486–493 (2005)

Abstract

Special Report

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

National Academy of Clinical Biochemistry and IFCC mmittee for Standardization of Markers of Cardiac Damage boratory Medicine Practice Guidelines: Analytical Issues for Biochemical Markers of Acute Coronary Syndromes

NACB WRITING [illegible]
[illegible] Alan H.B. [illegible] and Robert H. Christenson[5*]
Ro

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

MMITTEE ON STANDARDIZATION OF MARKERS OF CARDIAC DAMAGE (C-SMCD) MEMBERS

ed S. Apple, *Chair*; Robert H. Christenson; Allan S. Jaffe, Rochester, MN; ohannes Mair, Innsbruck, Austria; Jordi Ordonez-Llanos, Barcelona, Spain; ni, Brecia, Italy; Mauro Panteghini, Milan, Italy; Jillian Tate, Brisbane, Australia; and

Clin Chem Lab Med 2006;44(3):346–352 © 2006 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2006.060

Quality Specifications for B-Type Natriuretic Peptide Assays

Fred S. Apple,[1*] Mauro Panteghini,[2] Jan Ravkilde,[3] Johannes Mair,[4] Alan H.B. Wu, Jillian Tate,[6] Franca Pagani,[2] Robert H. Christenson,[7] and Allan S. Jaffe,[8] on Behalf of the Committee on Standardization of Markers of Cardiac Damage of the IFCC

Recommendation for measuring and reporting chloride by ISEs in undiluted serum, plasma or blood

STANDARDS IN COOPERATION WITH CLSI:

- Analysis of Body Fluids in Clinical Chemistry; Proposed Guideline (C49-P)
- Body Fluid Analysis for Cellular Composition; Approved Guideline (H56-A)
- Point-of-Care Connectivity; Approved Standard (POCT1-A2)
- Metrological Traceability and Its Implementation; A Report (X05-R)
- Measurement of Free Thyroid Hormones; Approved Guideline (C45-A)
- Application of Biochemical Markers of Bone Turnover in the Assessment and Monitoring of Bone Diseases; Approved Guideline (C48-A)
- Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (EP17-A)
- Performance of Single Cell Immune Response Assays; Approved Guideline (I/LA26-A)
- Diagnostic Nucleic Acid Microarrays; Approved Guideline (MM12-A)
- Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline (MM13-A)
- Proficiency Testing (External Quality Assessment) for Molecular Methods; Approved Guideline (MM14-A)
- Use of External RNA Controls in Gene Expression Assays; Approved Guideline (MM16-A)

SD Activities

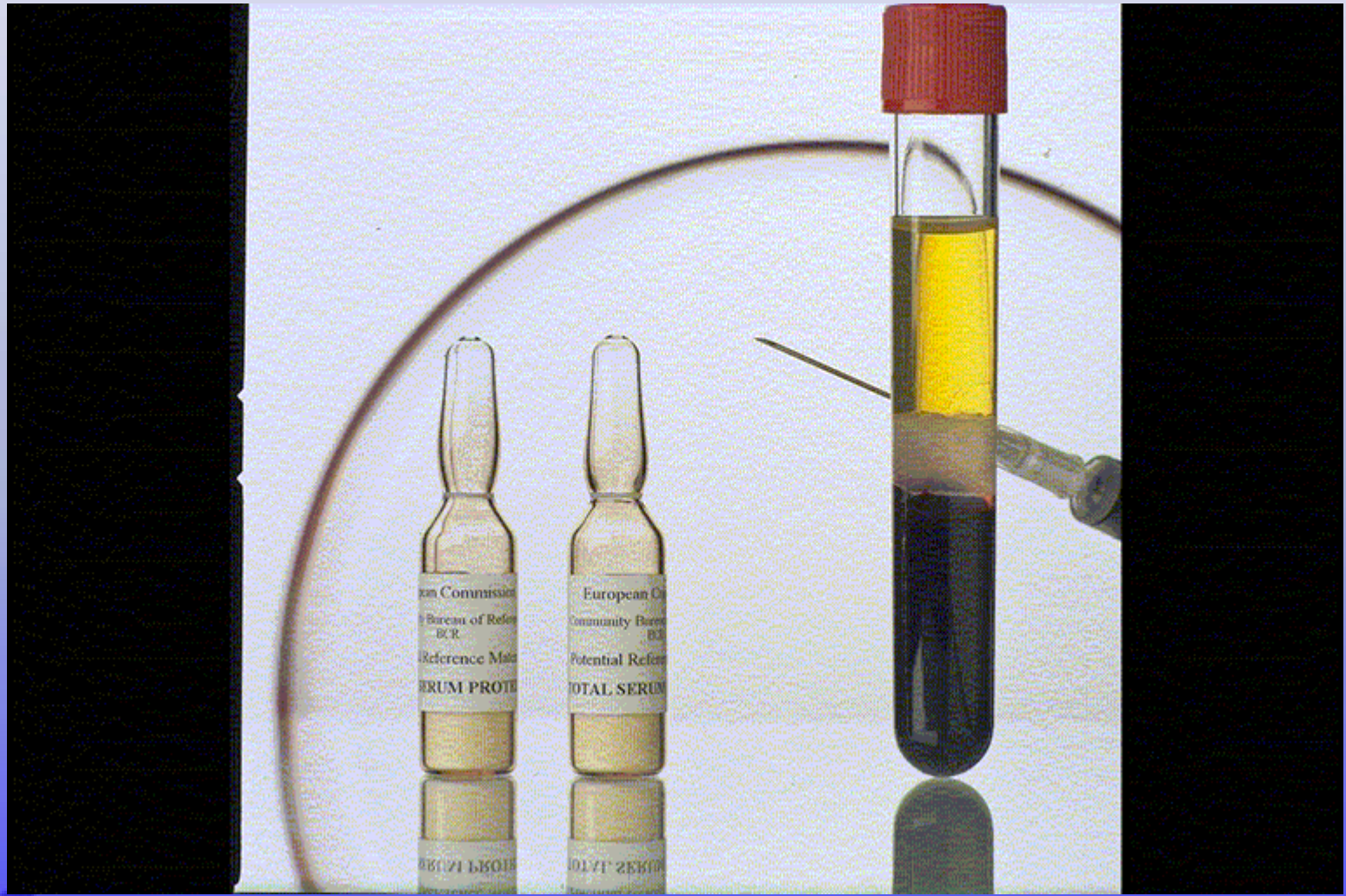
- IMPLEMENTATION OF STANDARDIZATION IN LABORATORY MEDICINE
  - Reference Materials
  - Reference Measurement Systems
  - [illegible] Reference Laboratories
  - Reference Intervals & Decision Limits
- PUBLICATIONS
- COLLABORATIONS

Reference Measurement Systems

Scientific Division

IFCC standardisation activities are currently accomplished by 8 Committees (theme-oriented) and 13 Working Groups (task-oriented)

CRM 470 - Human Serum Proteins

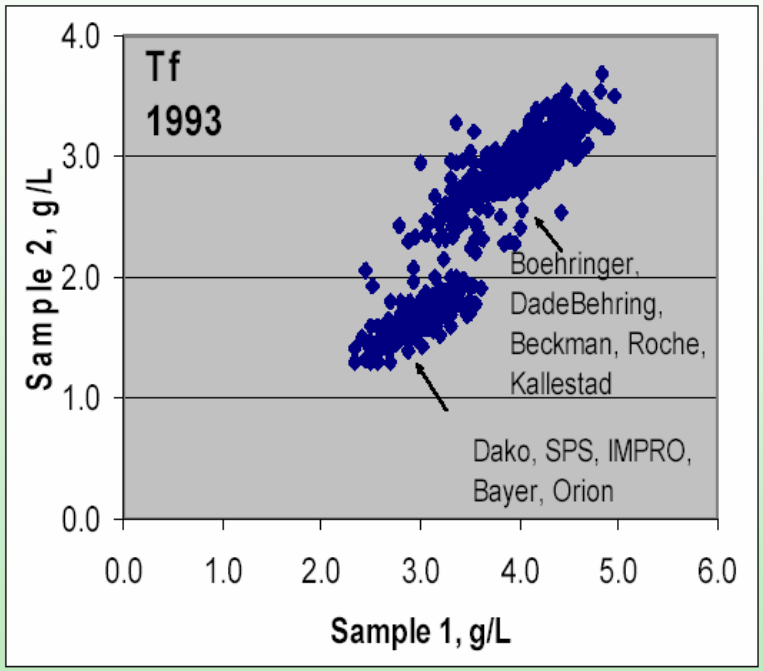


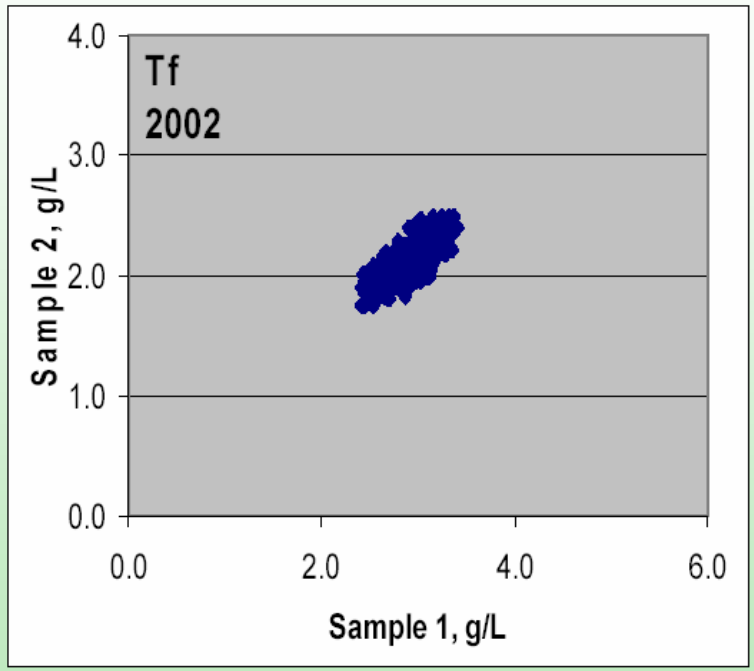
Effect of CRM 470 on plasma protein results

- **Very Good but Could be Better!**
  - α_1-Antitrypsin
  - Haptoglobin
  - Transferrin
  - IgA, G, and M
- **Fair**
  - C3
  - C4
- **Not Good**
  - Ceruloplasmin
  - C-Reactive Protein
- **Too Few Labs**
  - α_1-Acid Glycoprotein
  - α_2-Macroglobulin
- **Not Evaluated Yet**
  - α_1-Antichymotrypsin

Effect of CRM 470 on plasma protein results

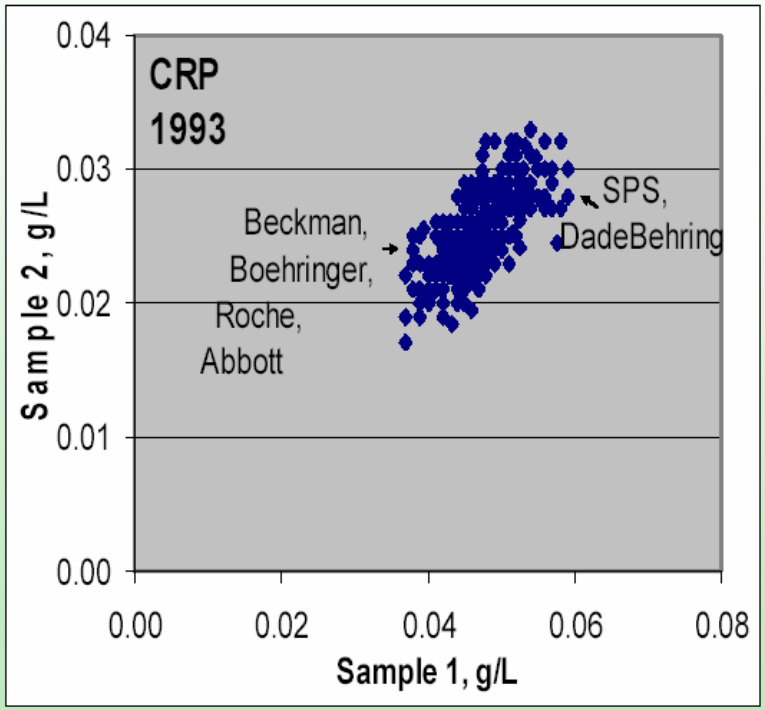
Transferrin

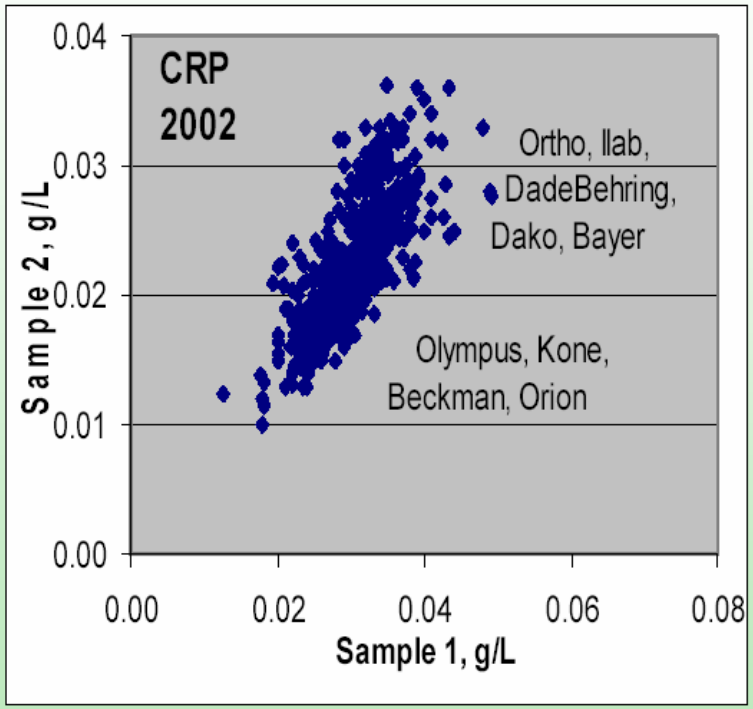




Effect of CRM 470 on plasma protein results

C-Reactive Protein





Main reasons for remaining variability

- Inadequate transfer of values by manufacturers from CRM 470 to working calibrators
- Commutability problems (CRM 470 is based on a delipidated and lyophilized serum pool)

COMMITTEE ON PLASMA PROTEINS

ONGOING ACTIVITIES

- standardization of protein measurement in biological fluids:
  - scientific and technical support to IRMM for the preparation of the new reference material for plasma proteins [ERM-DA470]
  - serum collection, completed;
  - selection of laboratories participating in the value transfer, completed;
  - feasibility study, completed;
  - value transfer campaign (Autumn 2007);
  - assignment of values for additional proteins:
    → β2-microglobulin

COMMITTEE ON PLASMA PROTEINS

ONGOING ACTIVITIES

- standardization of protein measurement in biological fluids:
  - scientific and technical support for the preparation of the new ERM
  - value transfer protocol for serum proteins

Protocol for Transfer of Values from CRM 470 to Manufacturers' Reference Materials

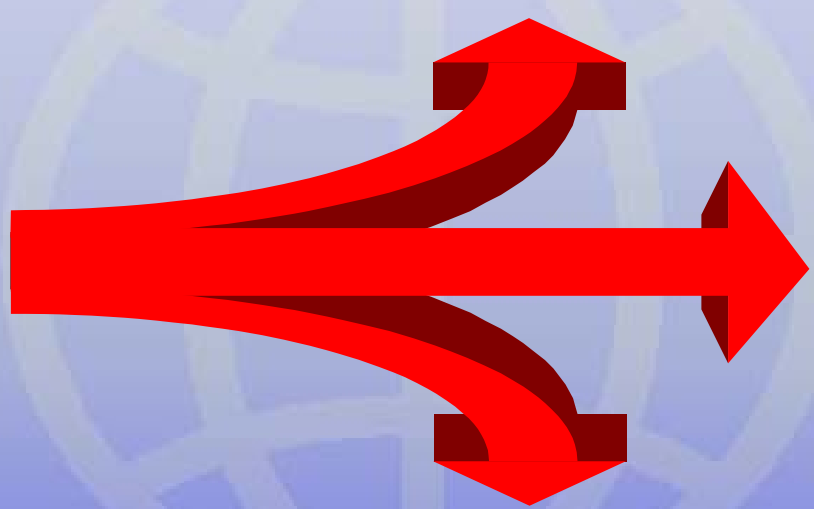
A. Myron Johnson, M.D.*; University of North Carolina School of Medicine, Chapel Hill, NC USA 27599-7516, and
Soren Blirup-Jensen, DVM, PhD*; DakoCytomation a/s, Productionsvej 42, DK-2600 Glostrup, Copenhagen, Denmark

Committee on Reference Systems for Enzymes

- ✓ ALT
- ✓ CK
- ✓ LDH
- ✓ GGT
- ✓ Amylase
- ✓ AST*

*Reference material under certification

Reference Measurement Procedure



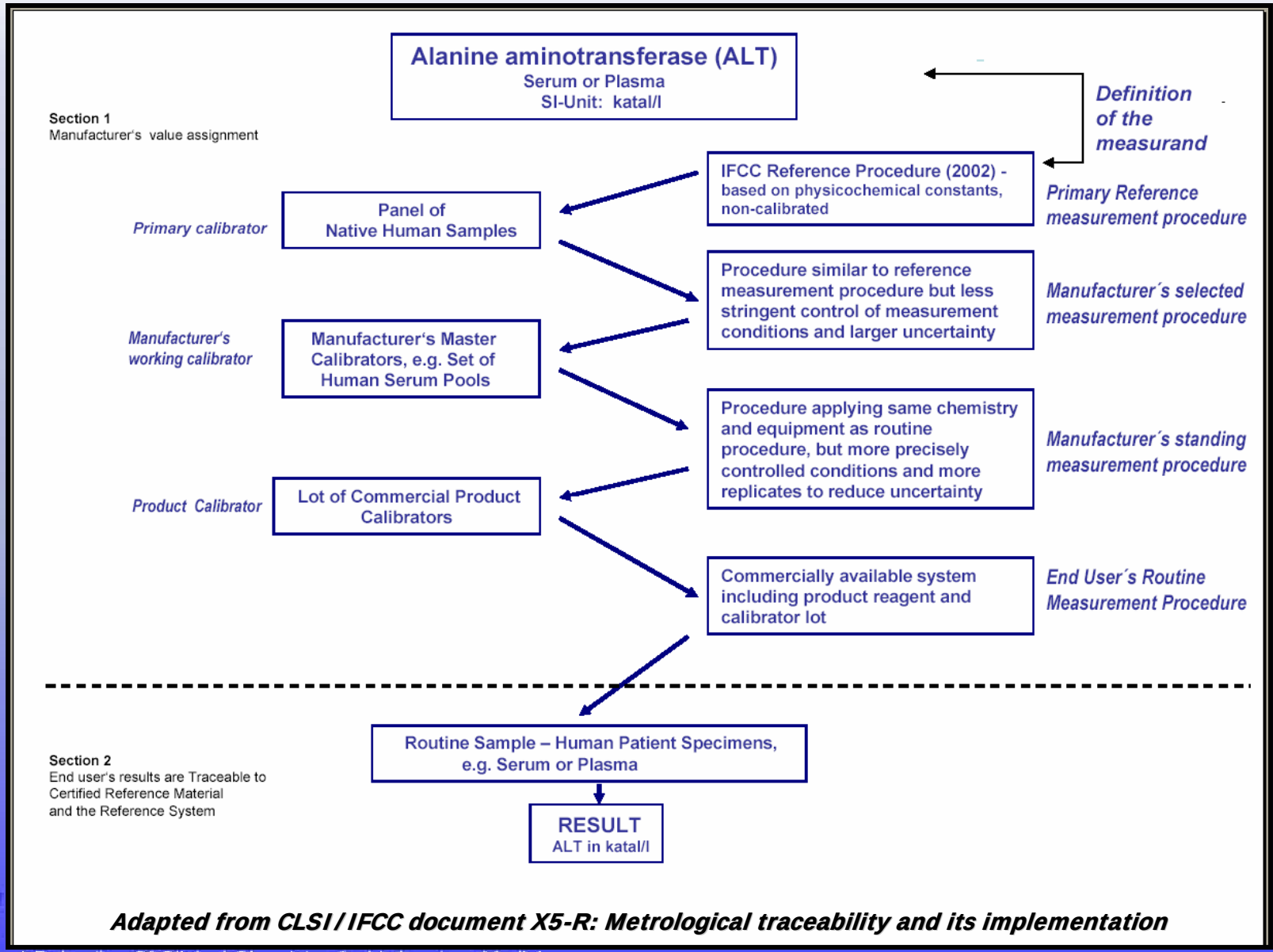
Reference Materials

Reference Laboratories

Evaluation of transferability of ref meas procedure: *Alkaline phosphatase*

Under discussion: *Pancreatic lipase*

Establishing Traceability of ALT Results



Adapted from CLSI / IFCC document X5-R: Metrological traceability and its implementation

C-TLM
Traceability in Laboratory Medicine

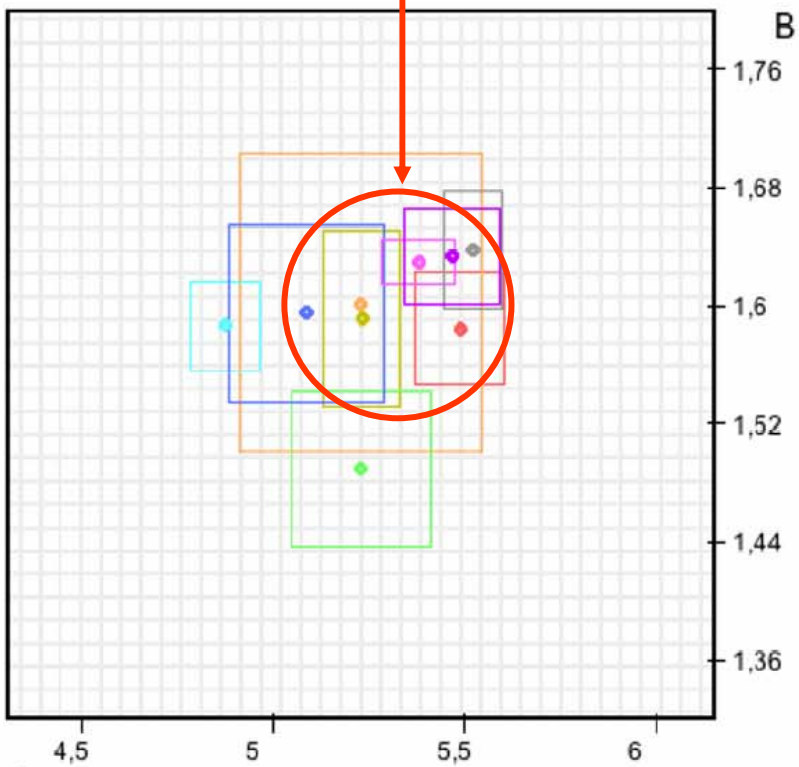
To support reference laboratories in the context of complete reference systems by establishing an EQAS (ring trials) for reference laboratories in order to monitor their competence

C-TLM
Traceability in Laboratory Medicine

RELA 2005

AST [ukat/l]

Results from IFCC laboratory network



Lab	A	p.e.u.	B	p.e.u.	method
03	5,485	0,115	1,584	0,036	kinetic spectrophotometry (IFCC)
04	5,227	0,316	1,601	0,101	kinetic spectrophotometry (IFCC)
06	5,230	0,100	1,591	0,059	kinetic spectrophotometry (IFCC)
12	5,228	0,182	1,489	0,052	kinetic spectrophotometry (IFCC)
19	4,873	0,092	1,586	0,030	kinetic spectrophotometry (IFCC)
23	5,085	0,200	1,594	0,060	kinetic spectrophotometry (IFCC)
27	5,377	0,094	1,629	0,015	kinetic spectrophotometry (IFCC)
38	5,521	0,073	1,637	0,039	kinetic spectrophotometry (IFCC)
41	5,467	0,125	1,633	0,032	kinetic spectrophotometry (IFCC)

Results of IFCC ring trials are available at:
http://www.dgkl-rfb.de:81

C-RIDL
Reference Intervals and Decision Limits

- Preparation of a protocol for collaborative experiments on the establishment of reference values using assays traceable to reference systems
- Production of “standardized” reference intervals for AST, ALT, and γGT

C-RIDL

Reference Intervals and Decision Limits

Multicenter Reference Interval study for AST, ALT & GGT

Three phases

1. Distribution of commutable trueness materials, collection of information on methods characteristics and on the analytical quality of the group of participants [completed]
2. Collection of reference samples according to a well defined protocol established for each analyte following the principles indicated in CLSI C28 standard [ongoing]
3. Centralized data reduction according to C28.

International assessment of IVD devices for enzyme measurements

- A commutable Trueness Control Material (TCM) was developed in the Calibration 2000 project of The Netherlands
- This TCM was targeted by 3 IFCC reference labs for ALT, AST, CK, GGT, LDH, and amylase
- 70 European laboratories employing the 6 most commonly used instruments/companies (all CE marked) were requested to measure TCM and their results evaluated

Jansen R et al., Clin Chim Acta 2006

International assessment of IVD devices for enzyme measurements

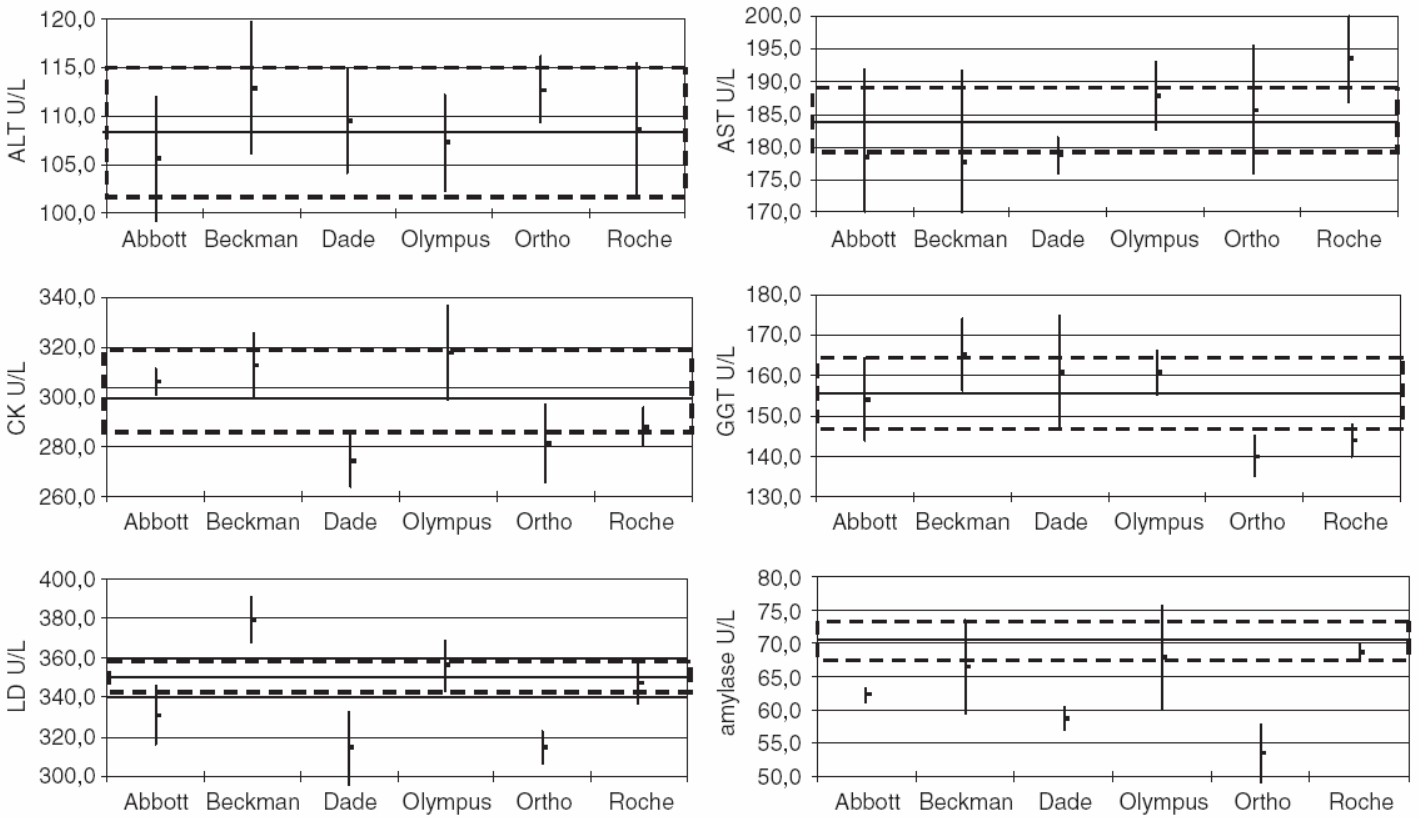


Fig. 1. Target value (fat line), means ± SD_{bl} (U/L) for each company system, and the area (dashed) of maximum allowable SD_{bl} in absence of significant bias.

Apolipoprotein B survey

Method	No. labs	Survey CHM-01		Survey CHM-02	
		Mean	CV	Mean	CV
Beckman INA	20	73.0	3.8%	68.0	4.3%
Dade INA	31	71.0	5.6%	64.9	5.7%
IT assays	53	70.6	7.6%	64.1	7.0%
All	122	71.1	7.7%	65.0	8.8%

LDL cholesterol survey

Method	# Labs	LP-01	LP-02	LP-03	LP-04	LP-05
"Direct"						
All	**1605**	**108.2 (14.7)**	**82.0 (17.3)**	**161.4 (13)**	**137.6 (15.4)**	**91.5 (15.8)**
Surfactant	301	134.5 (5)	105.3 (5.8)	191.2 (6.1)	173.6 (4.5)	117.5 (4.6)
Deterg/Selec	219	105.6 (7.6)	77.9 (9.5)	165.2 (7.5)	133.7 (7.2)	86.3 (7.3)
Liquid Select	992	99.9 (6.6)	75.0 (8.8)	149.8 (5.7)	126.5 (6.2)	84.2 (6.2)
Calculated*	**2931**	**134.4 (4.7)**	**106.6 (4.4)**	**194.3 (7.9)**	**173.4 (4.3)**	**115.8 (5.8)**
CDC 'target' value		**136.9**	**108.8**	**185.8**	**174.1**	**121.0**

Apolipoprotein A-I survey

Method	No. labs	Survey CHM-01		Survey CHM-02	
		Mean	CV	Mean	CV
Beckman INA	19	129.2	5.0%	121.1	6.4%
Dade INA	26	134.9	5.4%	123.2	5.2%
IT assays	52	124.5	5.8%	113.4	5.7%
All	115	128.0	6.6%	117.4	6.7%

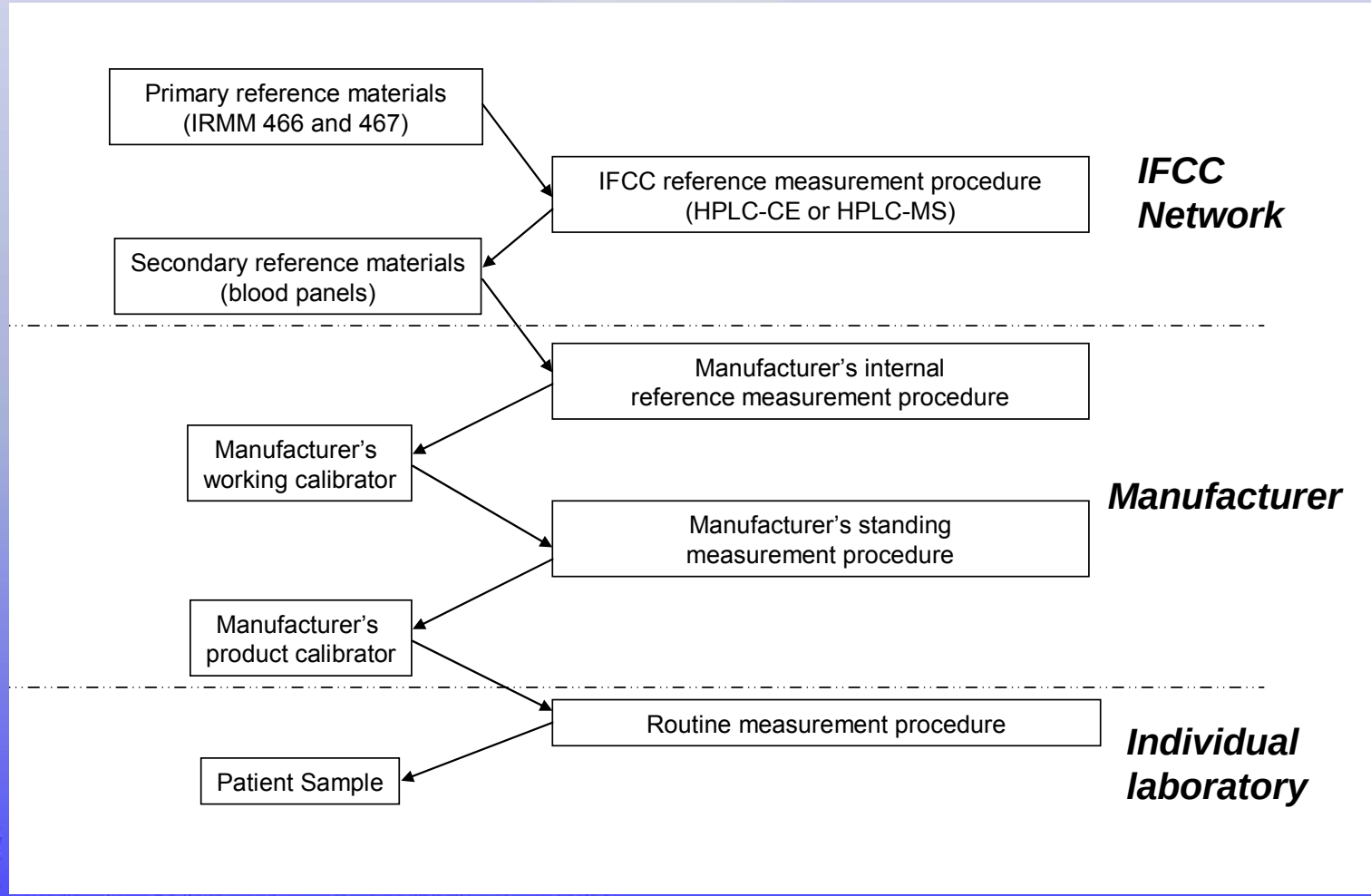
HDL cholesterol survey

Method	# Labs	LP-01	LP-02	LP-03	LP-04	LP-05
"Homogeneous"						
All	**3954**	**52.4 (8.9)**	**38.3 (8.1)**	**59.2 (16.2)**	**61.8 (8.7)**	**79.1 (8.0)**
Accel Select Deter	616	57.7 (3.9)	41.5 (4.9)	69.4 (4.7)	67.5 (3.9)	85.5 (4.1)
Liqu Deterg/Selec	1607	53.2 (8.0)	38.5 (7.3)	62.3 (11.4)	63.1 (7.2)	80.8 (6.4)
Modif Enzymatic	890	49.8 (5.1)	37.1 (4.9)	50.2 (15.8)	58.7 (5.7)	76.0 (4.0)
"Preciptation"						
Dex $S0_4$ 50K	171	48.9 (6.0)	35.7 (5.9)	53.1 (9.4)	56.8 (7.0)	73.4 (6.9)
Magnet Dex $S0_4$	213	48.1 (6.4)	35.3 (6.2)	50.7 (11.1)	54.9 (7.3)	70.9 (6.6)
CDC 'target' value		**49.3**	**35.7**	**55.6**	**56.9**	**74.7**

Standardization of apolipoprotein measurements

- PT data provide very good assessment of state of accuracy and allows direct comparisons of the lipoprotein and apolipoprotein measurement reliability in “real” life.
- CAP survey data indicates Apos performance is clearly better than for direct LDL & HDL cholesterol measurements.
- Apolipoprotein B & A-I standardization is now available and achievable.

Reference System for HbA1c



C-NPU
Nomenclature, Properties and Units

Recommendations on the unit and nomenclature for HbA1c:

- *Systematic name → Haemoglobin beta chain(Blood) — N-(1-deoxyfructos-1-yl)haemoglobin beta chain; substance fraction*
- *Trivial name → Hemoglobin A1c (HbA1c)*
- *SI unit → mmol/mol*

Metrological vs. “Clinical” Traceability

- The knowledge about the clinical validity of HbA1c and the decision-making criteria used by physicians in different parts of the world are based on data which are generated with routine tests which are not standardized.
- Tracing back the calibration of these routine tests to the IFCC reference system may then invalidate the clinical decision-making criteria currently used.
- In order to maintain the clinical experience, the quantitative relationship to the previous calibration system should be established and, if necessary, the clinical decision-making criteria should be adjusted accordingly.

In the case of HbA1c, reliable linear relationships between results traceable to the IFCC reference system for HbA1c and previous national and regional recommended methods have been demonstrated, allowing the conversion of analytical and clinical data from one system to another.

IFCC HbA1c concentration = 53 mmol/mol

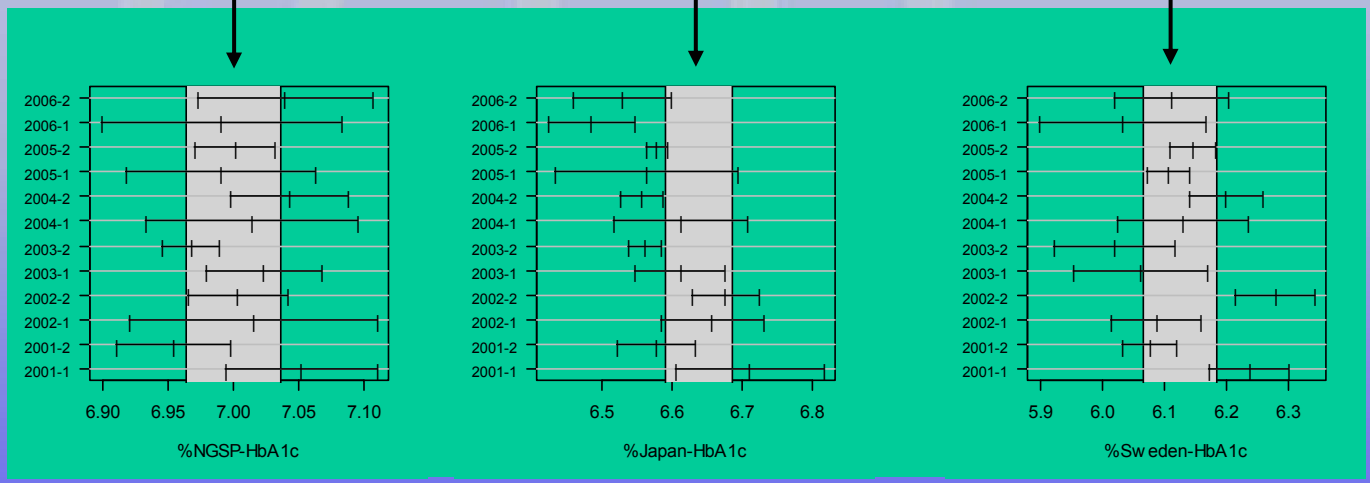
Relationship:

The grey zones are the 95% confidence intervals of the equations

y=0.0915x+2.152

y=0.0927x+1.724

y=0.0989x+0.884



NGSP (USA)

JDS (Japan)

Mono-S (Scand)

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 U.S. National Glycohemoglobin Standardization Program.
[b] as recommended by American Diabetes Association.

Panteghini M & John G, CCLM 2007;45:942

Advantages

- The use of a completely different unit (mmol/mol instead of %) avoids confusion when recalculating old HbA1c targets to the new IFCC standardized values if clinical laboratories wish to implement HbA1c results traceable to the IFCC reference system.
- A positive impact of changing of scale of reported HbA1c results is expected, allowing clinicians and diabetic patients to better understand the marker changes (currently they may perceive small changes in percentage values – although linked to large health effects – as unimportant).
- Supposed increased potential for future use of HbA1c as diagnostic tool.

Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement

The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation

1. The HbA1c results should be standardized worldwide, including the reference system and results reporting.
2. The IFCC reference system for HbA1c represents the only valid anchor to implement standardization of the measurement.
3. The HbA1c assay results are to be reported worldwide in IFCC units (mmol/mol) *and* derived NGSP units (%), using the IFCC-NGSP master equation.
4. If the ongoing "average plasma glucose study" fulfills its *a priori* specified criteria, an HbA1c-derived average glucose (ADAG) value will also be reported as an interpretation of the HbA1c result.
5. Glycemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units, and as ADAG.

NKDEP

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

EC4

Standardization of GFR assessment International Initiatives

- Program to standardize and improve serum creatinine measurements
- Development of a modified MDRD-like equation that is appropriate for standardized creatinine
- Routinely report estimated GFR

The Reference Measurement System for Creatinine

Primary reference material
(pure substance)
NIST SRM 914

calibrate

Ref. procedure
(GC-IDMS or LC-IDMS)
Reference laboratories

certify

Sec…terial
(creat… serum)

calibrate

Routine methods

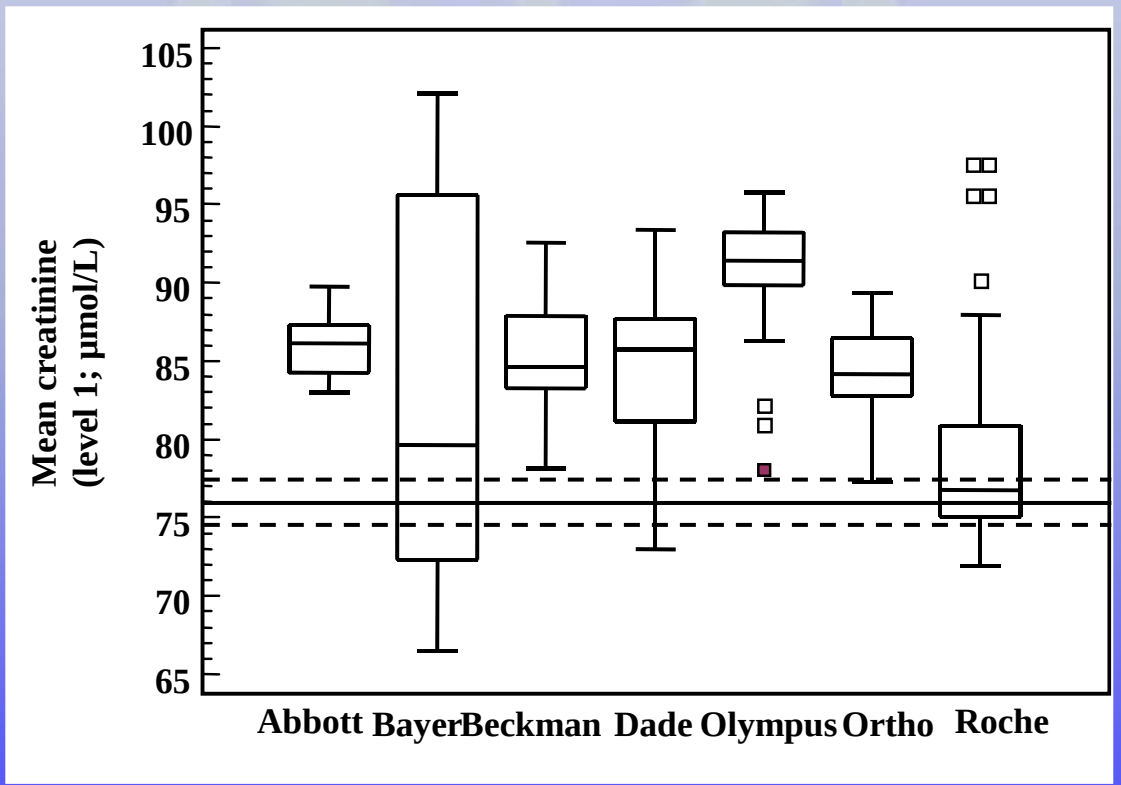
Measurement of clinical samples by commercial assays

International Federation Of Clinical Chemistry And Laboratory Medicine

Panteghini M et al., Clin Chem Lab Med 2006

Trueness verification study of creatinine measurements

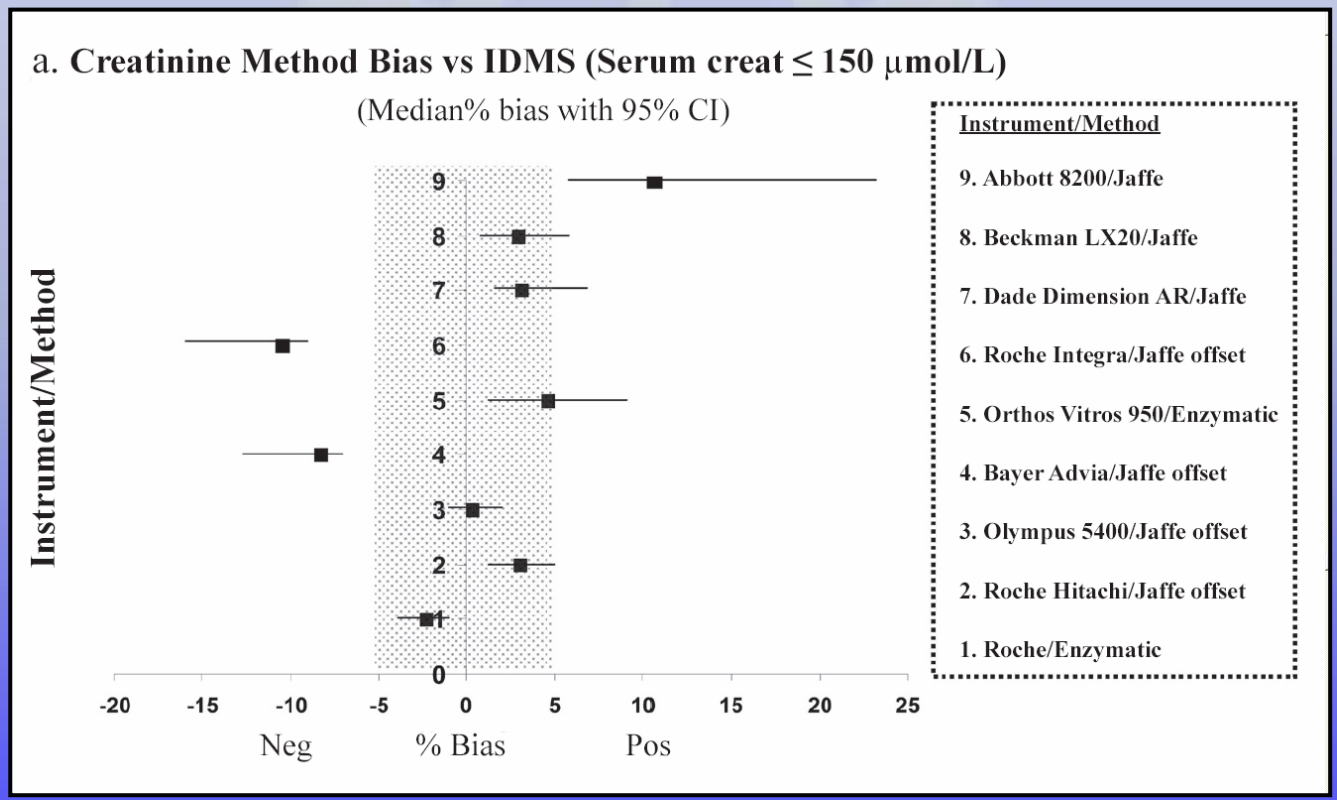
- 172 laboratories from Belgium, Finland, France, Germany, Italy & The Netherlands



Delanghe J et al., 2007

2006 trueness verification study of creatinine measurements in the Australasian region

- 16 serum samples analysed by 9 instrument/methods in 6 different laboratories



Peake M & Whiting M, Clin Biochem Rev 2006

IDMS-traceable MDRD Study
4-Variable Equation for Estimating GFR

(Levey AS et al., Clin Chem 2007)

GFR (ml/min 1.73 m^2) =

175 x $(s\text{-}Cr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if Female)

x (1.210 if African American)

By using this equation and a standardized creatinine assay, clinical laboratories can report estimated GFR more uniformly and accurately.

Reference System for Troponin I

International Federation of Clinical Chemistry and Laboratory Medicine

Prim 
National Institute of Standards & Technology

Certificate of Analysis

Standard Reference Material® 2921

Human Cardiac Troponin Complex

terial

Ref. procedure
(high level consensus method)

Secondary ref. material
(cTnI in human serum)

Calibration of routine methods

Measurement of clinical samples by immunoassays

M. Panteghini, Clin Chem 2005

Designated Higher-Order Reference Procedures for Cardiac Troponin I

- Not commercial cTnI immunoassay based on monoclonal antibodies (1x1 or 2x2 MAbs)
  - directed to an invariant part of the molecule
  - comparable antibody specificity with the last-generation commercial assays
  - calibrated with NIST SRM 2921
- Thorough definition of assay characteristics including:
  - Antibody specificity
  - Immunoreactivity to cTnI forms present in plasma
  - Detection limit and imprecision

Candidate cTnI Commutable Secondary Reference Materials

Panel consisting of:

- Three (3) pools of positive cTnI serum samples from MI subjects with clinically relevant cTnI concentrations
- Production of at least an estimated 5-year supply for each level.

New IFCC Reference Systems in Development

a) Enzymes: ALP, Lipase
b) Proteins: Cystatin C, Carbohydrate-Deficient Transferrin (CDT), Albumin (urine), HbA2, Myoglobin
c) Hormones: freeT4 & totalT4, hCG, GH, Insulin

Thanks to more than 500 specialists in Laboratory Medicine, coming from diverse organisations around the world (Hospitals, Universities, Manufacturers, Regulatory and Governmental Bodies) who contribute to the IFCC SD activities.