Implementation of Traceability: Is the IVD Industry's Approach Really Fulfilling Obligations?

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What are Industry's Obligations for Implementation of Traceability?*

1. Comply with regulatory requirements (e.g., IVDD, FDA, etc.) and professional society guidelines (e.g., NACB, IFCC, IDF, NKDEP).
2. Provide metrological traceability/uncertainty information for calibrators (follow ISO 17511; unbroken chain from highest metrological order to kit calibrators).
3. Ensure patient test results are comparable [results from different methods/different labs/different times are equivalent (fit for purpose) for clinical diagnosis/management].
4. Maintain traceability, standardization/harmonization, & comparability of results continuously (e.g., through accuracy based EQA/PT programs).
5. Educate/train customers about how to use traceable & standardized products optimally for patient care.

*Who determines Industry's obligations and Industry's approach?

In Vitro Diagnostics Directive (7 Dec 03)

IVDD applies to European Economic Community (CE mark), but has global implications

Requires manufacturers to establish metrological traceability of kit calibrators & provide calibrator uncertainty (linkage between traceability and uncertainty)

Doesn't provide guidance for establishing traceability or estimating uncertainty

Traceability per ISO 17511, Metrological Traceability of Values Assigned to Calibrators and Control Materials*

- Establishes a metrology infrastructure for global assay standardization/harmonization in the clinical laboratory.
- Requires cooperation of national metrology institutes (NMIs), academia, industry, professional societies, & EQA/PT providers.

*Also ISO 15189, Medical laboratories- particular requirements for quality and competence (basis for laboratory accreditation)

EU IVD regulation: Something wicked this way comes? IVD Technology, Feb 2013

"Everybody welcomes the adoption of risk-based classification rules based on Global Harmonization Task Force (GHTF) guidelines, but still too few people realize that this will represent a fundamental change in the way that IVD products are regulated. Under the current IVD directive …, approximately 80% of IVD products are grouped in the self-certification class, while 20% require a premarket third-party intervention of some type, ... The new classification rules in the draft IVD regulation will completely reverse these percentages: …, only 20% of IVD products will remain in the self-certification category, while a form of third-party premarket intervention will be required for the remaining 80% of products. This is a fundamental change for the IVD industry that will dramatically raise compliance costs and workloads. For this reason, industry, led by Europe's diagnostics manufacturers association EDMA, has lobbied aggressively for a five-year transition period."

EU IVD regulation: Something wicked this way comes? IVD Technology, Feb 2013

"The requirement to show clinical evidence for IVDs is not new- it's in the current IVD directive-… manufacturers have only focused on proving and documenting the analytical performance of their tests. …, the proposed regulation has a strong focus on the need to prove and demonstrate clinical evidence of the various IVD assays. Clinical evidence is explained …: "The clinical evidence shall include all the information supporting the scientific validity of the analyte, the analytical performance and, where applicable, the clinical performance of the device, as described in Section 1 of Part A of Annex XII."
Manufacturers are required to summarize this data in a "clinical evidence report" referenced in Section 3, Part A, of Annex XII of the proposal.

Partial List of Organizations & Professional Societies Involved with Traceability & Assay Standardization/Global Harmonization

AACC	CLIA	FDA	IVDD	NIBSC
AdvaMed	DANAK	FINAS	JCTLM	NIST
BIPM	DGKL	IFCC	NATA	NMIs
BSI	EC4	ILAC	CLSI	RiliBÄK
CAP	ECCLS	IRMM	NEQAS	SWEDAC
CDC	EDMA	ISO	NFKK	WHO
RCPA	NKDEP	NGSP	QMP-LS	ACB

P Gillery, IS Young. Progress towards standaridization: an IFCC Scientific Division perspective. CCLM 2013; *in press*

List of Committees and Working Groups of the IFCC-SD in 2012.

- Committee on Nomenclature, Properties and Units (C-NPU)
- Committee on Molecular Diagnostics (C-MD)
- Committee on Reference Systems of Enzymes (C-RSE)
- Committee on Traceability in Laboratory Medicine (C-TLM)
- Committee on Reference Intervals and Decision Limits (C-RIDL)
- Committee on Standardization of Thyroid Function Tests (C-STFT)
- Working group on Standardization of Hemoglobin A 2 (WG-HbA 2)
- Working group on Standardization of Carbohydrate-Deficient Transferrin (WG-CDT)
- Working group on Standardization of Albumin Assays in Urine (WG-SAU)
- Working group on Standardization of Pregnancy-Associated Plasma Protein A (WG-PAPPA)
- Working group on Standardization of Insulin Assays (WG-SIA)
- Working group on Standardization of Troponin I (WG-TNI)
- Working group on Allowable Error for Traceable Results (WG-AETR)
- Working group on Harmonization of Autoantibody Tests (WG-HAT)
- Working group on Quality Specifications for Glucose POCT (WG-GPOCT)
- Working group on Clinical Quantitative Mass Spectrometry Proteomics (WG-cMSP)
- Working group on Serum Parathyroid Hormone (WG-sPTH)
- Working group on Cerebrospinal Fluid Proteins (WG-CSF)
- Working group on Standardization of Bone Marker Assays (WG-BMA)

Standarization Is a work in progress; manufacturers work with professional societies, but it's a challenge because there are so many initiatives under way.

Pillars of International Traceability & Standardization

JCTLM established the three pillars of traceability:

- **Reference measurement procedures (RMP)**
- **Reference materials (RM)**
- **Network of Reference Measurement Laboratories**

IFCC described a fourth pillar:

- **Universal reference intervals**

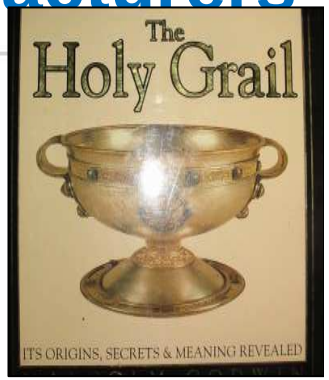
Fifth and sixth pillars:

- **Accuracy based grading EQA/PT to ensure and maintain international reference systems**
- **International standardization/harmonization of clinical laboratory practice using traceable assays (nomenclature/terminology/units, EBLM, etc.)**

Metrology & Clinical Chemistry/Clinical Laboratory Science: Comparison and Contrast

- "Pure science" of Metrology (science of measurement) vs. *gemisch* science of Clinical Chemistry/ Clinical Laboratory Science
- NMIs ("ivory towers") vs. clinical laboratories ("the trenches")
- Pure, well-defined analytes in simple matrices vs. complex, ill-defined analytes in challenging matrices (sometimes no RM or RMP)
- Expanded Uncertainty (bias eliminated) vs. Total Error Allowable (TEa = bias + imprecision); ongoing debate which is preferable
- "Absolute truth" by reference method analysis vs. "relative truth" by field method analysis
- Good metrology does not necessarily equal good clinical laboratory science; the clinical laboratory field needs to adapt concepts of Metrology and "translate" them for practical application in the clinical laboratory

Metrology/Assay Standardization & Manufacturers



Metrological Traceability and Its Implementation; A Report. CLSI X5R/C59

State of the art in trueness and interlaboratory harmonization for 10 analytes in general clinical chemistry.
Miller WG, Myers GL, Ashwood ER, et al. Arch Path Lab Med 2008;132:838-846.

The Joint Committee on Traceability in Laboratory Medicine (JCTLM): A Global Approach to Promote the Standardisation of Clinical Laboratory Test Results.
Armbruster D, Miller RR. Clin Biochem Rev 2007;28:105-113.

Measurement traceability and US IVD manufacturers: the impact of Metrology. Armbruster D. Accred Qual Assur 2009;14:393-398.

The IVD Directive and availability of reference systems for IFD medical devices: A view from industry. N Greenberg, IVD Technology 2001;2:18-27.

Why commutability matters. Miller WG, Myers GL, Rej R. Clin Chem 2006;52:553-554.

Paradigm Shift for IVD Manufacturers

Manufacturers traditionally seek to differentiate themselves from the competition (e.g., greater dynamic range, lower LoD, better precision, smaller sample size, etc.)- *not to produce comparable results* (clear from review of EQA/PT peer group data)

In era of IVDD & metrological traceability, results from different systems should be comparable! Manufacturers now provide traceability/uncertainty information, restandardize assays, address commutability, etc., and work with many professional organizations and each other- *but this is a new approach and a new challenge*

Manufacturers now have integral role in educating customers to standardize/harmonize practice of clinical laboratory science and to ensure continued comparability of test results

Where do manufacturers' obligations end and obligations of lab directors begin? Manufacturers are obligated to provide "fit for purpose" assays, but labs must use the assays properly and effectively. Assay failure- fault of manufacturer or the lab?

EQA/PT: One of the "Pillars"

GL Horowitz. Proficiency testing matters. Clin Chem 2013;59:335-337.

"Far too many laboratories consider proficiency testing just a necessary evil, little more than periodic pass–fail exercises we perform solely to meet regulatory requirements."

"Even for central-laboratory techniques, traditional PT suffers from 'matrix effects,' in that samples used for testing often react differently from native patient samples. Therefore, comparisons must be made only to peer groups, rather than to the 'true value.' What if the peer group as a whole is wrong?"

Miller WG, et al. State of the art in trueness and interlaboratory harmonization for 10 analytes in general clinical chemistry. Archive Pathol Lab Med 2008;132:838-846

"… peer group means from conventional PT results cannot be used to harmonize results … proficiency testing is typically used to measure a laboratory's proficiency at performing a test and not the trueness of the test method itself or its performance relative to other methods…. Traditional PT materials are not suitable for field-based postmarketing assessments of a method's trueness."

Harmonization/Standardization/Comparability of Results

Pathology Harmony; a pragmatic and scientific approach to unfounded variation in the clinical laboratory. Berg J, Lane V. Ann Clin Biochem 2011;48:195-197. "As we the move towards full electronic reporting of pathology results, we appreciate more fully that variations in things such as test names, reference intervals and units of measurement associated with our results is something that hinders progress."

ML Gantzer, WG Miller. Harmonisation of Measurement Procedures: how do we get it done? Clin Biochem Rev 2012,33:95-100. "Clinical laboratory measurement results must be comparable among different measurement procedures, different locations and different times in order to be used appropriately for identifying and managing disease conditions. Harmonisation … overall process of achieving comparability of results among clinical laboratory measurement procedures…standardisation is used when comparable results among measurement procedures are based on calibration traceability to SI using a reference measurement procedure of the highest available order.

"…, many of the currently available secondary RMs are not commutable with native clinical samples and they have failed to accomplish the intended goal of achieving harmonised results.

"Commutabilty is a property of a RM such that values measured for a RM and for the samples intended to be measured have the same relationship between two, or more, measurement procedures for the same measurand."

Defining acceptable limits for the metrological traceability of specific measurands

R Bais, D Armbruster, RTP Jansen, G Klee, M Panteghini, J Passarelli, KA Sikaris [IFCC Working Group on Allowable Error for Traceable Results (WG-AETR)] CCLM *in press*

"Although manufacturers are compelled by the European IVD Directive, 98/79/EC, to have traceability of the values assigned to their calibrators if suitable higher order reference materials and/or procedures are available, there is still no equivalence of results for many measurands determined in clinical laboratories".

"…for some measurands, it is possible for manufacturers to assign values to assay calibrators with a measurement uncertainty that allows the laboratory enough combined uncertainty for their routine measurements. However, for other measurands, e.g., plasma sodium, current assays are too imprecise to fulfill limits based on biological variation." (Impact of choice of TEa target)

"The aim of these efforts is to ensure equivalence of patient results .., laboratory results should be equivalent no matter where and on which platform they are generated. One important reason for adopting a traceable, metrological-based approach is that it will allow the use of common reference intervals and clinical decision limits."

Due to cost and limited resources, IVD manufacturers, however, do not perform the full traceable series of steps to value assign every new lot of assay calibrator. They often rely on value transfer from their internally stored (" master ") calibrator material. In most cases, this procedure is probably valid, …

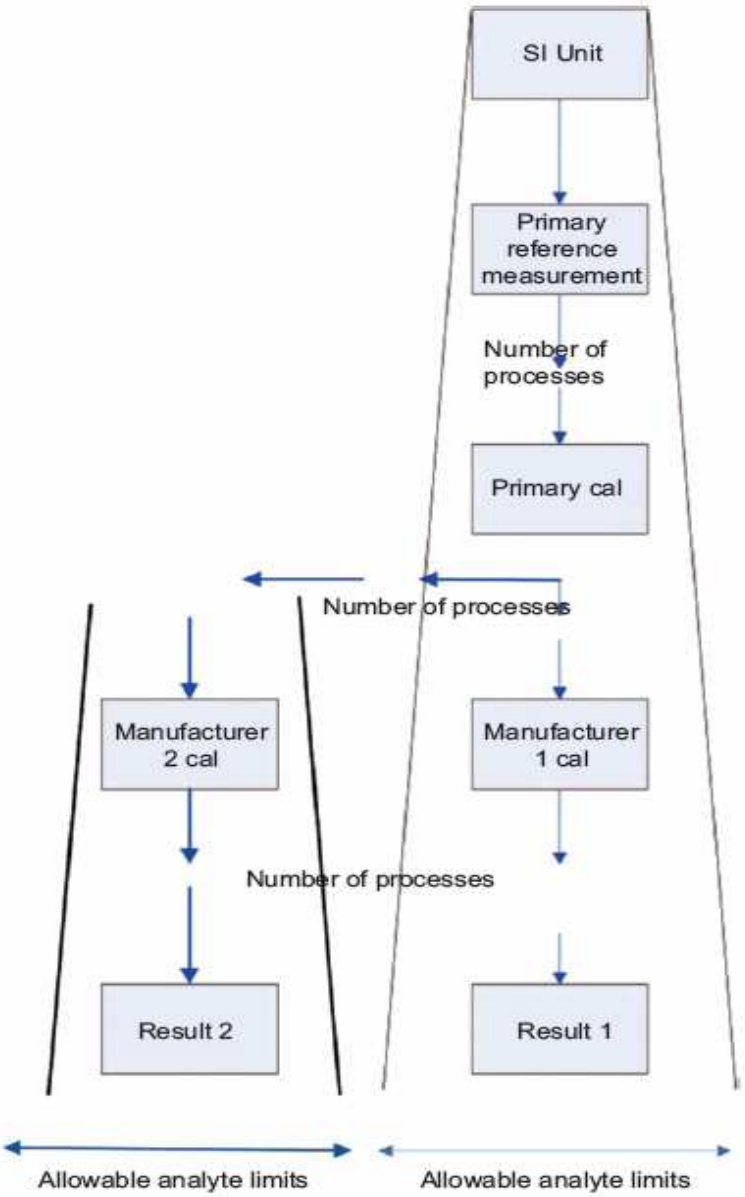
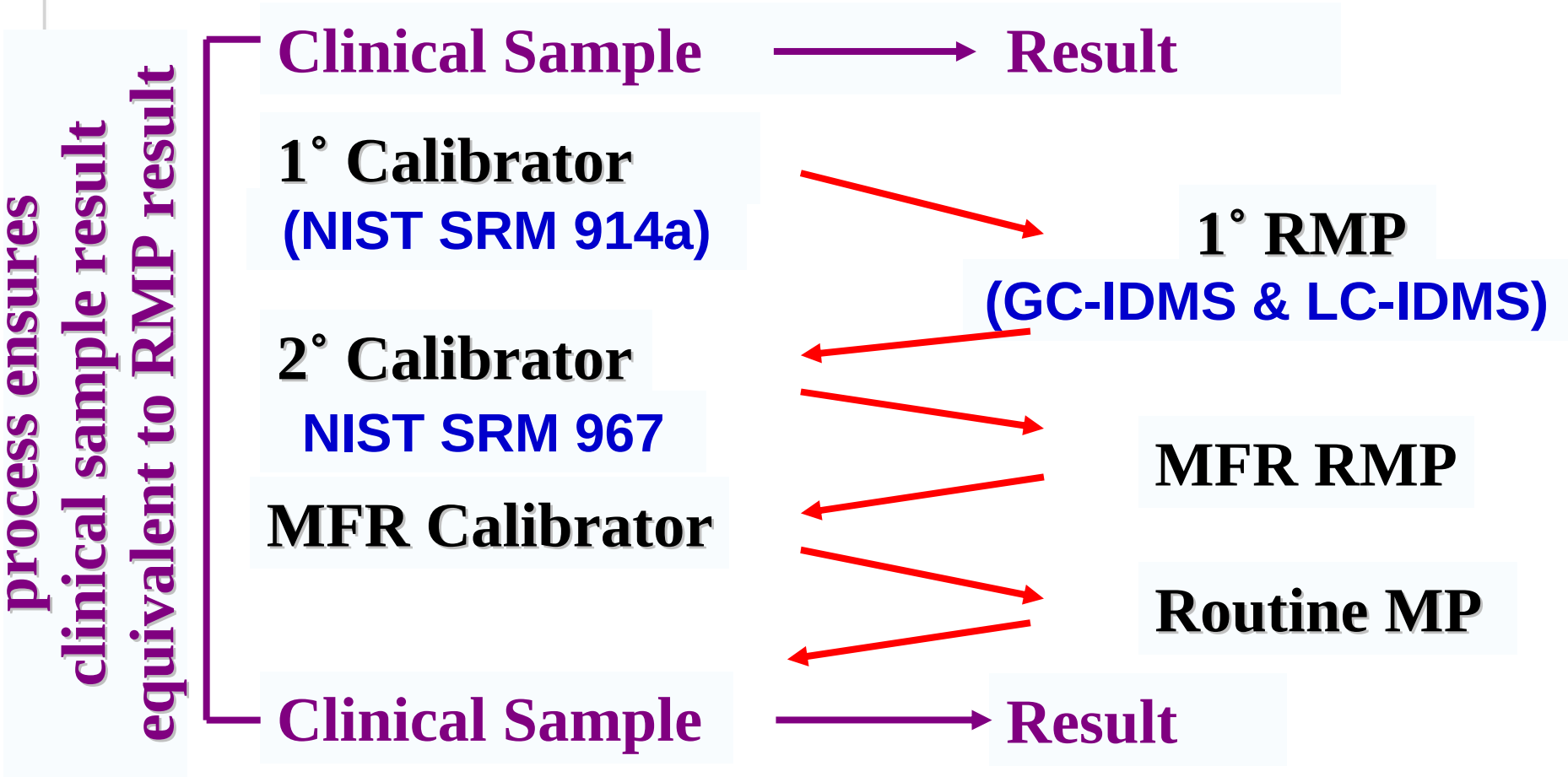


Figure 2 Two schematic traceability processes which are both metrological acceptable.
In both cases, the final product is traceable to the measurand definition but the divergence would result in significantly different patient results. Note that both processes could have the same allowable measurand limit.

Defining acceptable limits for the metrological traceability of specific measurands

" We have illustrated this in Fig. 2 in which there are two traceability paths for a measurand, say from two different manufacturers … The assigned values for the two calibrators are both derived from valid traceability chains, but produce results that would not be equivalent. For these two systems to produce equivalent laboratory results for a measurand would require the use of a correction factor determined by a correlation study at the steps where there is a divergence … This scenario is commonly seen in immunoassays when manufacturers use proprietary antibodies to measure products. Obviously, this also means that clinical decision limits or reference intervals would be quite different for the two assays unless the bias is removed."

Traceability Chain for Serum Creatinine Calibrators



RMP = Reference Measurement Procedure
MFR = Manufacturer
MP = Measurement Procedure

NIST =National Institute of Standards and Technology
SRM = Standard Reference Material

Source: National Kidney Disease Education Program (NKDEP)

CAP LN24-A Creatinine Accuracy Calibration Verfication/Linearity PT Survey (2012)

The Creatinine Accuracy Calibration Verification/Linearity Survey (LN24) is designed to provide an accuracy based assessment of a clinical laboratory's serum creatinine measurements in the normal and slightly elevated range, which is important for accurate estimation of glomerular filtration rate (eGFR). In addition, LN24 allows participants to determine if the eGFR calculation is performed correctly, accounting for sex and race.

Sample	Creatinine
LN24-01	0.707 mg/dL*
LN24-02	1.368 mg/dL
LN24-03	2.030 mg/dL
LN24-04	2.692 mg/dL*
LN24-05	3.352 mg/dL
LN24-06	4.012 mg/dL*

* Indicates values that were measured by LC IDMS; other creatinine concentrations were calculated from admixture ratios.

Analyte	Units	Calibration Verification Error Limits	Linearity Goal for Total Error
Creatinine	mg/dL	±5% or 0.1 mg/dL	10%
Abbott Architect		LN24-01 0.688 mg/dL	% Error: - 2.6%
(kinetic alk picrate		LN24-04 2.620 mg/dL	% Error: - 2.7%
Jaffe; 36 labs)		LN24-06 3.962 mg/dL	% Error: -1.3%

CAP LN24-A Creatinine Accuracy Calibration Verfication/Linearity PT Survey (2012) eGFR

Most major commercial manufacturers are using calibrators that are now traceable to IDMS …

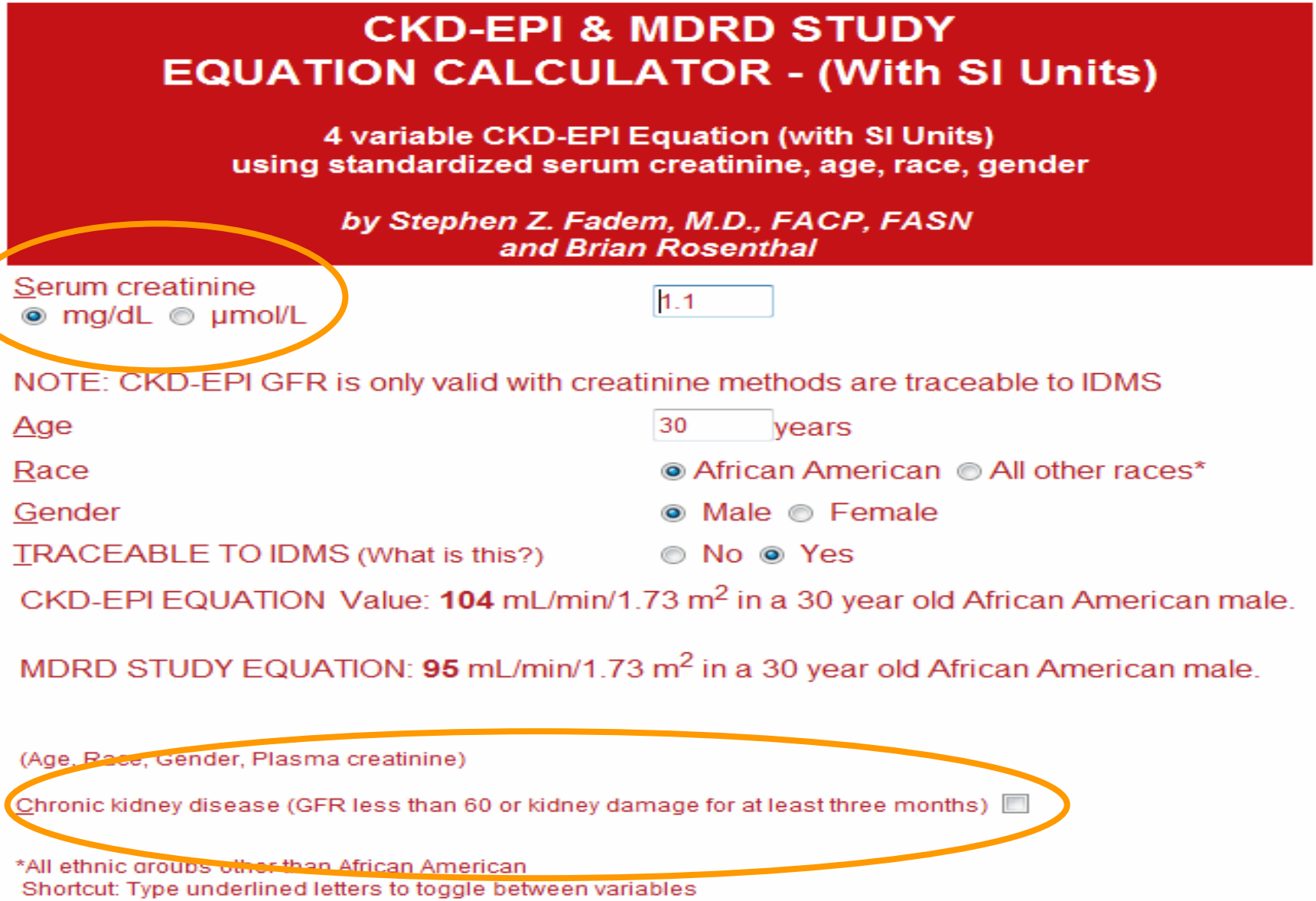
Participants were asked to identify their calibration type (traditional or IDMS). Some participants are continuing to use the traditional MDRD equation, which will produce eGFR values that are 5 to 10% too high when using IDMS-traceable calibrators. This occurs because the traditional calibration method that was used to derive the MDRD equation was biased high. The Laboratory Working Group of the National Kidney Disease Education Program recommends that laboratories implement the MDRD equation to estimate GFR.

Some participants may be using a more recently reported equation, CKD-EPI …The CKD-EPI equation provides improved estimates of GFR in patients with higher GFRs than does the MDRD equation.

Participants calculated the eGFR using their first result for specimens LN24-01 and LN24-03. The following table shows the percentage of laboratories that reported an eGFR that was within the acceptable range. Calculations of eGFR within ±1 mL/min/1.73 m2 were deemed acceptable.

LN24-01			
Equation	Calibration Type	Acceptable	Unacceptable
MDRD	IDMS	176	3
	Traditional	36	2
CKD-EPI	IDMS	12	7
LN24-03			
Equation	Calibration Type	Acceptable	Unacceptable
MDRD	IDMS	201	25
	Traditional	34	15
CKD-EPI	IDMS	16	1

MDRD.com


CKD-EPI & MDRD STUDY
EQUATION CALCULATOR - (With SI Units)
4 variable CKD-EPI Equation (with SI Units)
using standardized serum creatinine, age, race, gender
by Stephen Z. Fadem, M.D., FACP, FASN
and Brian Rosenthal
Serum creatinine
mg/dL µmol/L
1.1
NOTE: CKD-EPI GFR is only valid with creatinine methods are traceable to IDMS
Age
30
years
Race
African American All other races*
Gender
Male Female
TRACEABLE TO IDMS (What is this?)
No Yes
CKD-EPI EQUATION Value: 104 mL/min/1.73 m2 in a 30 year old African American male.
MDRD STUDY EQUATION: 95 mL/min/1.73 m2 in a 30 year old African American male.
(Age, Race, Gender, Plasma creatinine)
Chronic kidney disease (GFR less than 60 or kidney damage for at least three months)
*All ethnic groups other than African American
Shortcut: Type underlined letters to toggle between variables

The new ERM-DA471/IFCC Cystatin C calibrator was released June 2010

ERM
European Reference Materials

CERTIFICATION REPORT

Certification of cystatin C in the human serum reference material ERM®-DA471/IFCC

Certified Reference Material ERM®-DA471/IFCC

I. Zegers, G. Auclair, H. Schimmel, H. Emons

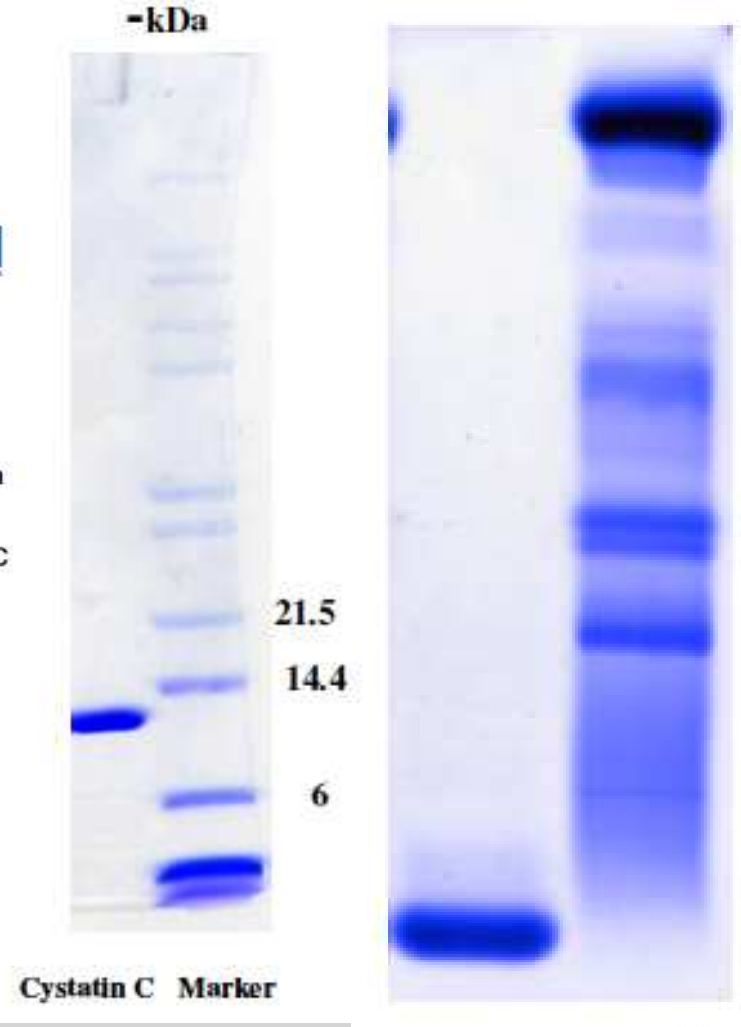
European Commission, Joint Research Centre
Institute for Reference Materials and Measurements (IRMM),
B-2440 Geel (Belgium)

S. Blirup-Jensen, C. Schmidt, V. Lindström, A. Grubb

Department of Clinical Chemistry, University Hospital, Lund (Sweden)

H. Althaus

Siemens Healthcare Diagnostics Products GmbH,Marburg (Germany)



First certified reference material for cystatin C in human serum ERM-DA471/IFCC

Anders Grubb et al., on behalf of the IFCC Working Group on Standardisation of Cystatin C (WG-SCC). Clin Chem Lab Med 2010;48(11):1619–1621

ERM-DA471/IFCC, 5.48 mg/L, expanded uncertainty (*k*s2) +/- 0.15 mg/L.

"However, the problem today is that a large number of different cystatin C-based GFR prediction equations have been proposed. This is due to variations in the cystatin C calibrators that are used, as well as to the use of different non-harmonised methods for determination of cystatin C concentrations."

Characterized using methods whose analytical principles are recognized as reference methods by the JCTLM. Commutable with Siemens, Sentinel & Gentian on Architect, and Roche

Manufacturers' Cystatin C assays can be metrologically traceable to the same SRM

But …

Identical metrological traceability doesn't guarantee equivalent patient results so commutability of ERM-DA471 needs to be proven for as many field methods as feasible

Standardization of Cystatin C assays ideally follows a similar process as used for Creatinine assays with SRM 972

Example: Abbott Architect Cystatin C Restandardization

ERM-DA471/IFCC SRM available in 2010; Sentinel (third party manufacturer for Abbott) restandardizes Cystatin C assay

Abbott sends product information- results shift upward approximately 11% (actual shifts a lab observes may differ and must be evaluated according to lab's procedures)

eGFR equation factor changes from 71 to 81.8

	New Ref Range		Previous Ref Range	
Gender	Age < 50 (mg/L)	Age ≥ 50 (mg/L)	Age < 50 (mg/L)	Age ≥ 50 (mg/L)
Male	0.31 – 0.79	0.41 – 0.99	0.45 – 0.74	0.44 – 0.93
Female	0.40 - 0.99	0.40 – 0.99	0.44 – 0.76	0.47 – 0.88

EQA/PT concerns: switch over period with old and new assays used by labs; bimodal distribution of results (peer group grading)

Time to restandardize (about 18 – 24 months)

Multiple Cystatin C eGFR Formulae

- eGFR = 84.69 X Cystatin C (mg/L)$^{-1.680}$ X 1.384 (if a child < 14 years old) [Grubb et al., Clin Chem 2005;51:1420-1431; turbidimetry]
- eGFR = 66.88 x Cystatin C (mg/L)$^{-1.360}$ [Rule et al., Kidney International 2006;69:399-405; nephelometry]
- eGFR = 76.7 X Cystatin C (mg/L)$^{-1.18}$

  [American Society of Nephrology presentations 2005 & 2006]
- eGFR = 81.8 X Cystatin C (mg/L) $^{-1.28}$ [Sentinel/Architect; turbidimetry]
- eGFR = 127.7 X (-0.105 + 1.13 x Cystatin C) $^{-1.17}$ X (-0.13 age) X (0.91 if female) X (1.06 if black)
  [Inker, Eckfeldt, et al., Am J Kid Dis 2011;58:682-684]
- eGFR = 77.239 X (Cystatin C)
  [Larsson, Malm, Grubb, Hansson, Scand J Clin Lab Invest 2004;64:25-30; turbidimetry]

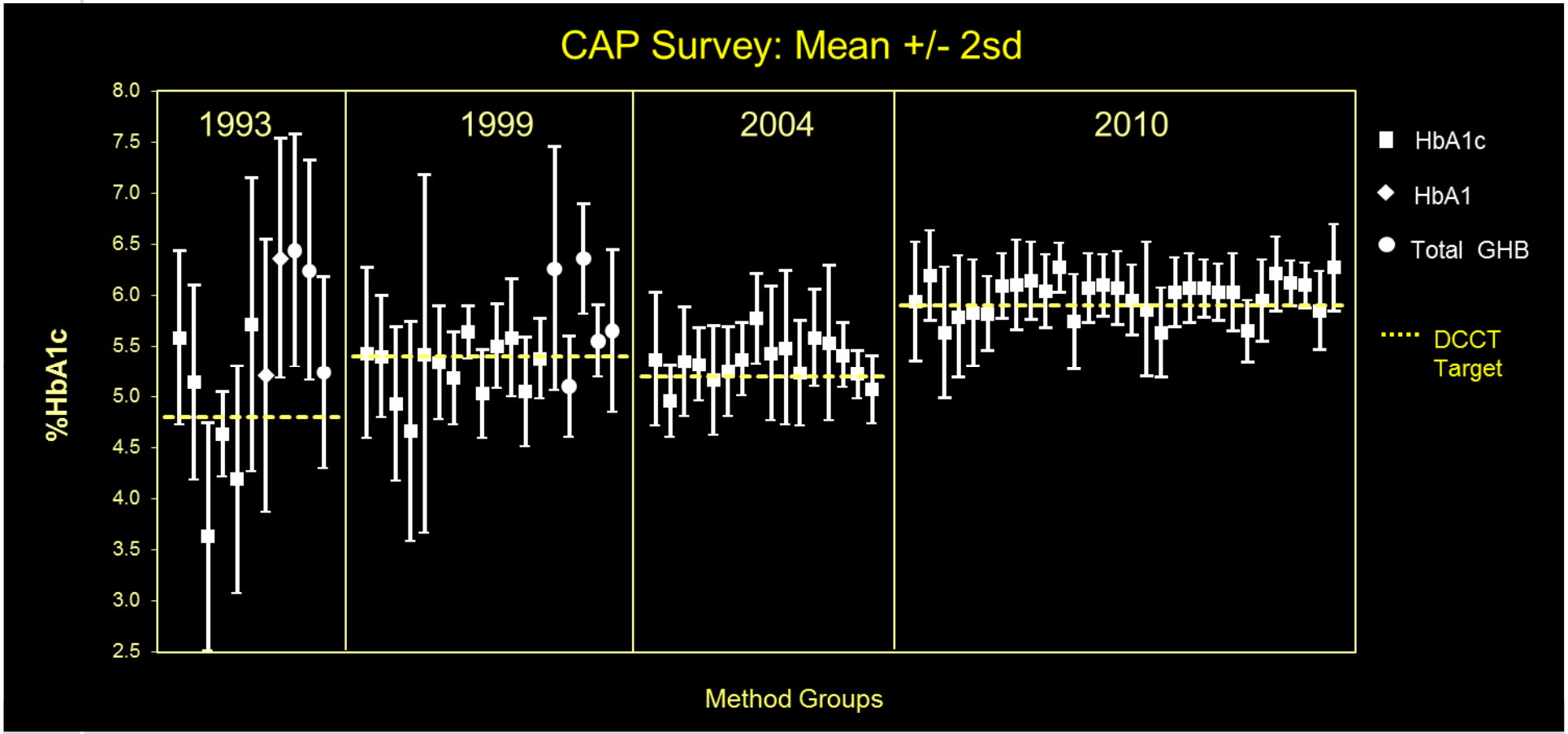
Challenge for clinical laboratories & manufacturers to remain current and know which formula is best for Cystatin C eGFR

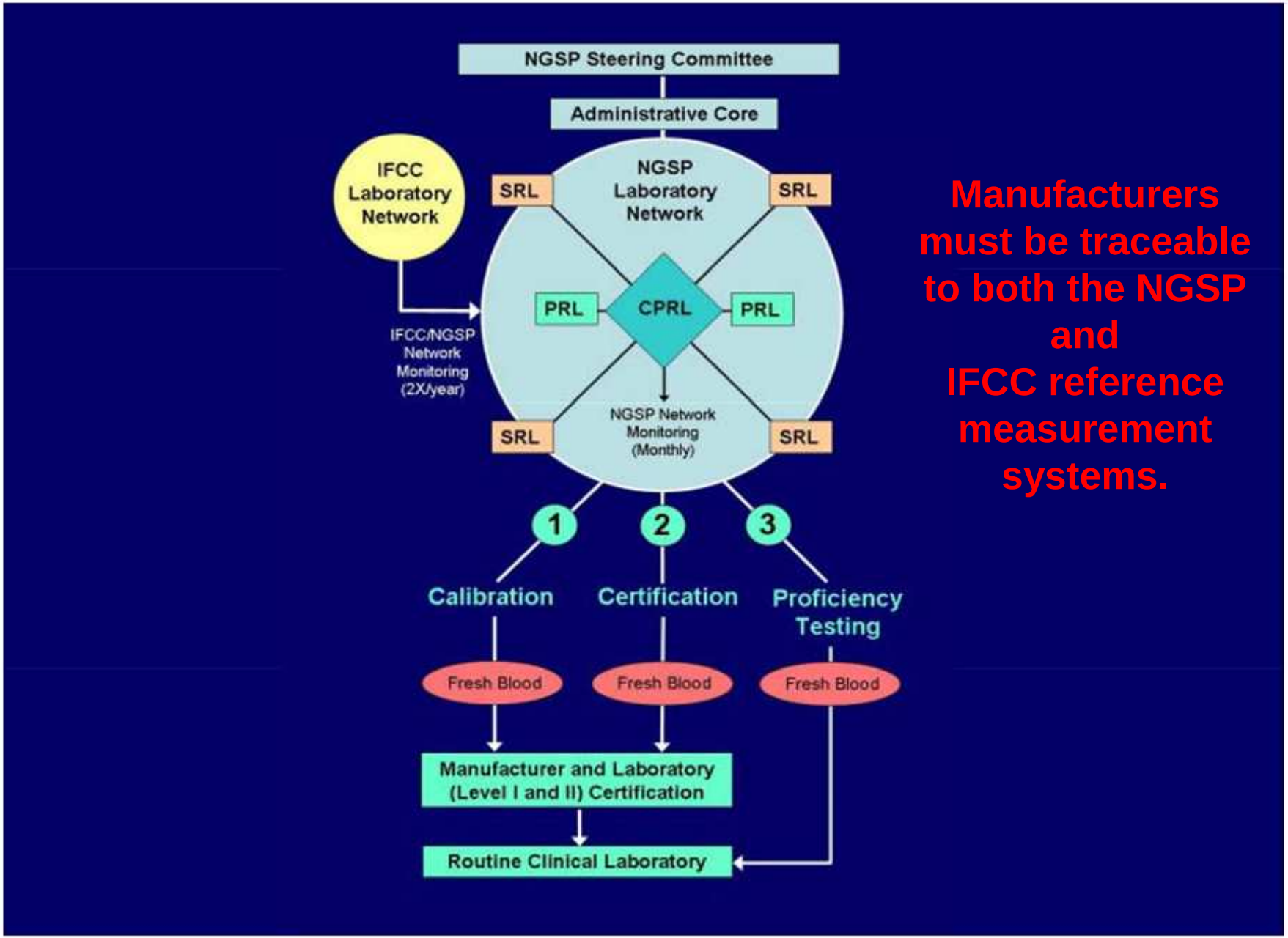
P Gillery. A history of Hb A1c through Clinical Chemistry and Laboratory Medicine. CCLM 2013;51:65-74.

- NGSP HPLC not specific enough to support international standardization of Hb A_{1c}.
- IFCC WG produced purified Hb A_{1c} and Hb A_0 reference materials and LC/MS and LC/CE reference methods.
- "Owing to the different specificities of the methods, the results of Hb A_{1c} expressed in percentages of total hemoglobin were different, being approximately lower by 2% in absolute value with the IFCC system compared to the NGSP system." **(Addressed partially by master equation)**
- Recommended to express results as molar ratio of Hb A_{1c} to Hb A_0 in mmol/mol instead of % Hb A_{1c}
- ADA, EASD, & IDF recognized IFCC reference system as only valid anchor for international standardization of Hb A_{1c} and to report results in both mmol/mol and % Hb A_{1c}.

From Chaos to Order

Evidence that manufacturers have successfully implemented traceability





Manufacturers must be traceable to both the NGSP and IFCC reference measurement systems.

R Hanas, WG John. 2013 update on the worldwide standardization of the Hb A1c measurement. CCLM 2013

1. HbA 1c results are to be reported by clinical laboratories worldwide in SI (Système Internationale) units (mmol/mol – no decimals) and derived NGSP units (% – 1 decimal), using the IFCC-NGSP master equation (DCCT units).

2. HbA 1c conversion tables including both SI (IFCC) and NGSP units should be easily accessible for the diabetes community.

3. Journals are strongly recommended to require that submitted manuscripts report HbA 1c in both SI (IFCC) and NGSP/DCCT units.

2011: "Laboratories in the US continue to report HbA 1c results in % only (NGSP values), and clinicians are mostly unaware of SI (IFCC) units... Across Europe most countries have adopted dual reporting, whereas some European countries following different time periods of dual reporting are now reporting SI units (mmol/mol) only. No new consensus was reached, but participants agreed to the following: The original consensus where results are reported in both SI units (mmol/mol) and in derived NGSP/DCCT percent units remains the ideal to achieve global standardization."

Hb A1c reporting still evolving: a challenge to manufacturers who must address both the NGSP and IFCC reference measurement systems and reporting units; does reporting in both SI and NGSP represent "standardization?"

CAP GH2-A Hb A1c PT Survey, 2012

GH2-01, GH2-02, and GH2-03 samples were prepared from **pooled whole blood** obtained from healthy or diabetic individuals. The target values were determined from the means of all results from seven … (NGSP) Secondary Reference Laboratories (SRLs)… traceable to the method used in the Diabetes Control and Complications Trial (DCCT).

The Survey uses an **accuracy based evaluation against the NGSP reference method targets with an acceptable limit equal to ±7% of the target value**. Because the Proficiency Testing (PT) samples are prepared from human whole blood, the bias observed for the PT samples is expected to reliably reflect the bias that exists for patient samples analyzed with the same method.

Specimen	NGSP Target (%HbA1c)	Acceptable Range	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH2-01	5.6	5.2-6.0	72.7/100	95.6
GH2-02	9.4	8.7-10.1	81.8/100	94.9
GH2-03	7.2	6.6-7.8	89.4/100	96.2

	2007	2008	2009	2010	2011-2012	2013
Passing limits based on target NGSP reference value	±15%	±12%	±10%	±8%	±7%	±6%

CAP ABL-B, 2009, Accuracy Based Lipid PT Survey

"…, the ABL Survey is a new CAP product designed to minimize, if not eliminate, matrix effects present in typical proficiency testing materials and thereby allow laboratories to assess the accuracy and harmonization of lipid and lipoprotein tests."

"However, we remain concerned that, for LDL cholesterol in particular, the material is not fully commutable. We have had extensive discussions with the CDC, who confirmed that they have experienced the same problem for many years with this analyte. As a result, we have decided to continue to grade LDL cholesterol by peer group. In addition, since we were not able to get reference values for triglycerides, we used peer group values for this analyte as well."

In summary, here are the evaluation criteria used in this mailing. In each case, the allowable deviation from the target value represents the total error requirements (bias plus imprecision) from the National Cholesterol Education Program (NCEP):

Total Cholesterol Reference Value +/- 9%

HDL Cholesterol Reference Value +/- 13%

LDL Cholesterol Peer Group Mean +/- 12%

Triglycerides Peer Group Mean +/- 15%.

CAP ABL-B, 2009, Accuracy Based Lipid PT Survey

Percentage of Labs Meeting NCEP Guidelines

Cholesterol (within 9% of target)						
	ABL-01	ABL-02	ABL-03	ABL-04	ABL-05	ABL-06
Target	152.6 mg/dL	180.0 mg/dL	244.2 mg/dL	219.4 mg/dL	220.5 mg/dL	211.0 mg/dL
Peer Group 1	100.0	100.0	100.0	100.0	100.0	100.0
Peer Group 2	100.0	100.0	100.0	100.0	100.0	95.3
Peer Group 3	100.0	100.0	100.0	100.0	100.0	100.0
Peer Group 4	100.0	100.0	100.0	100.0	100.0	100.0
Peer Group 5	100.0	100.0	100.0	100.0	91.7	100.0
Peer Group 6	93.3	100.0	100.0	100.0	100.0	18.8
Peer Group 7	100.0	100.0	100.0	100.0	100.0	100.0
Peer Group 8	87.5	100.0	87.5	100.0	100.0	100.0
Total	98.6	100.0	99.3	100.0	99.4	88.5

HDL Cholesterol (within 13% of target)						
	ABL-01	ABL-02	ABL-03	ABL-04	ABL-05	ABL-06
Target	33.9 mg/dL	56.8 mg/dL	49.3 mg/dL	64.1 mg/dL	40.4 mg/dL	40.6 mg/dL
Peer Group 1	93.8	87.5	50.0	93.8	0.0	12.5
Peer Group 2	100.0	100.0	100.0	100.0	100.0	100.0
Peer Group 3	87.5	87.5	87.5	100.0	100.0	100.0
Peer Group 4	100.0	96.2	100.0	100.0	100.0	96.2
Peer Group 5	87.5	87.5	100.0	100.0	70.0	90.0
Peer Group 6	100.0	100.0	75.0	100.0	80.0	100.0
Peer Group 7	49.0	100.0	96.1	100.0	83.7	81.6
Peer Group 8	42.9	100.0	100.0	100.0	87.5	87.5
Total	77.4	96.6	91.8	99.3	80.1	82.7

Global Harmonization

"The World is Flat"- Thomas Friedman

CDs 

Fast Food 

Cars 

PCs

English Language

Travel 

Internet 

Fashion

Movies

Music

Television 

Mobile Phones

SI System 

Business

Money 

"It has been said that arguing against globalization is like arguing against the laws of gravity." Kofi Annan [Secretary General of the United Nations; 1997 – 2006]

Global Harmonization in the Clinical Laboratory- or not!

Analyte	"Conventional Units" (Mass concentration)	SI Units* (Substance Concentration)
ALT	U/L	μkat/L
Bilirubin	mg/dL	μmol/L
Cl	mEq/L	mmol/L
Glucose	mg/dL	mmol/L
Creatinine	mg/dL	μmol/L
Hb A1c	% Hb A1c	mmol/mol

SI = International System of Units (abbreviated SI from the French *le Système International d'unités*) is the modern form of the metric system

The Metric System (SI) in the U.S.

1999- Metric mishap caused loss of NASA orbiter

NASA lost a $125 million Mars orbiter because a Lockheed Martin engineering team used English units (pounds-seconds) while NASA's team used SI units (Newton-seconds) resulting in a navigation error (satellite altitude too low-disintegration). U.S. Metric Association stated "In this day and age when the metric system is the measurement language of all sophisticated science, two measurement systems should not be used." and "Only the metric system should be used because that is the system science uses."

Implementation of Traceability: Is the IVD Industry's Approach Really Fulfilling Obligations? Yes and No!

Creatinine- Yes: most creatinine assays restandardized (but not all) & accuracy based EQA/PT is available- but related analyte, Cystatin C, still undergoing standardization/harmonization and will need accuracy based EQA/PT

Hb A1c- Yes: performance improved markedly due to traceability & standardization, but still issues because of dual traceability systems and reporting units

Lipids- Yes for cholesterol & HDL cholesterol (reference materials & methods), No for LDL cholesterol (lack of commutability) and triglycerides (no reference method target values)

Failure example: Prolactin IA traceable to WHO 3rd International Standard 84/500; manufacturer's internal measurement standard (IMS) depleted; assay not re-standardized but new IMS prepared; results now about 20% (22% by NEQAS) lower than previously; calibrator lots had "drifted" with old IMS; calibrators properly traceable but manufacturing process not adequately controlled.

We still have a long way to go! Manufacturers "get it"- metrological traceability, assay standardization/harmonization- but can't do it alone and must work with professional societies, key opinion leaders, metrology institutes, and each other.