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

Mauro Pantaghini
The issue: an absolute priority for public health

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

- CLINICAL
- ECONOMICAL
- ETHICAL
Standardization: clinical impact

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

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

Effective application of evidence-based medicine
Decision threshold

Non-diseased

Diseased

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

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

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

Impact of test accuracy (bias shifts and imprecision skews and broadens curves)
Growth Hormone in clinical guidelines

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

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

Eilat consensus
(childhood GHD, JCE&M 2000)

In a child with clinical criteria for GHD, a peak GH concentration below 10 μg/L has traditionally been used to support the diagnosis.
NOTA 39 AIFA Ormone della crescita (somatotropina)

ALLEGATO 1

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

Età evolutiva

II: Parametri di laboratorio:

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

Età adulta

E’ indicata la terapia con rGH in soggetti adulti, di età superiore a 25 anni, con livelli di GH allo stimolo con ipoglicemia insulinica <3 μg/L
• GH assays have been inaccurate in the past

• GH assays are inaccurate today

• “Estimates” of circulating GH concentrations vary by more than 300%

• Presence or absence of a disease mainly depends on which assay is (by chance?) chosen by the lab

• There was no significant improvement over the last 20 years

• It is waste of time to discuss about cut-off levels for clinical guidelines
Standardization: economic impact

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

Data from U.S. Government Accounting Office and College of American Pathologists
Standardization: economic impact

Source: NIST Planning Report 04-1, 2004

$60M/yr wasted

$199M/yr wasted
Effect of analytic inaccuracy in creatinine on the distribution of estimated GFR values

Klee GG et al., Clin Chem Lab Med 2007;45:737
The impact of the different HbA$_{1c}$ assays on position relative to other UK paediatric diabetes centres. The mean HbA$_{1c}$ of patients within a diabetes clinic or GP practice is being utilized by commissioners as a metric by which to assess the quality of diabetes care provided, which are likely to reach the public domain and used to determine remuneration.

All systems declared to be ‘DCCT-aligned’!

UK Paediatric Centres ranked by clinic mean HbA1C

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

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

Bossuyt X et al., Ann Rheum Dis 2008;67:1061
Ethical lag occurs when the speed of technological change (innovation) exceeds that of ethical development (standardization).

Hernandez JS X et al., Am J Clin Pathol 2010;133:8
To be accurate and comparable, results must be traceable: only traceability to high-order references can manage the issue and support evidence-based medicine in a global world.
Objective of traceability implementation

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

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

- Primary Ref. Procedure
- Secondary Ref. Procedure
- Manufacturer’s Internal Procedure
- End-user’s Routine Procedure
- Primary Reference Material (e.g. pure analyte)
- Secondary Ref. Material (matrix-based)
- Manufacturer’s Calibrator
- Routine Sample
- Test Result

SI Units

Traceability

CIRME

Reference System for Creatinine

- Primary reference material (pure substance)
  NIST SRM 914

- Secondary ref. material (creatinine in human serum)
  NIST SRM 967

- Measurement of clinical samples by commercial assays

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

Patient specimen correlation

Routine methods

Panteghini M et al., Clin Chem Lab Med 2006;44:1187
The line represents the limit of systematic bias and imprecision that produce a relative increase of <10% in the mean error when estimating GFR using the MDRD Study equation.

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Delanghe JR et al., Clin Chem Lab Med 2008;46:1319
Creatinine Accuracy Calibration
Verification/Linearity Survey LN24-B
Results from 2009 mailing

- **Abbott Systems**
- **Beckman Instruments**
- **Olympus AU**
- **Roche Instruments**
- **OCD**
- **Siemens Advia**
- **Siemens Dimension**
Reference System for γ-Glutamyltransferase

1. Primary reference material (IFCC): IRMM ERM-AD452
2. Reference measurement procedure (IFCC)
3. Secondary (“matrix”) reference material: e.g., JC ERM 406
4. Manufacturer’s product calibrator
5. Manufacturer’s standing measurement procedure
6. End user’s routine measurement procedure
7. Routine sample
8. Enzyme result

Traceability

Adapted from Infusino I et al., Clin Chem Lab Med 2010;48:301
Traceability investigation of γ-glutamyltransferase measurements in China

Xia C et al., Ann Clin Biochem 2010;47:189
Common reference intervals as fourth pillar of the reference measurement system

Until today

Method-dependent results

Method-dependent reference intervals

From today

Standardized methods that provide traceable results

Common reference intervals (at least within homogeneous ethnic groups)

Infusino I et al., Clin Chem Lab Med 2010;48:301
### Reference Intervals for Serum Creatinine Concentrations: Assessment of Available Data for Global Application

Ferruccio Ceriotti, James C. Boyd, Gerhard Klein, Joseph Henny, Josep Queraltó, Veli Kairisto, and Mauro Panteghini, on behalf of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL)

<table>
<thead>
<tr>
<th>Age (gender) group</th>
<th>2.5th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>0.52</td>
<td>0.97</td>
</tr>
<tr>
<td>Preterm neonates 0–21 d</td>
<td>0.32</td>
<td>0.98</td>
</tr>
<tr>
<td>Term neonates 0–14 d</td>
<td>0.31</td>
<td>0.92</td>
</tr>
<tr>
<td>2 m–&lt;1 y</td>
<td>0.16</td>
<td>0.39</td>
</tr>
<tr>
<td>1 y–&lt;3 y</td>
<td>0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>3 y–&lt;5 y</td>
<td>0.26</td>
<td>0.42</td>
</tr>
<tr>
<td>5 y–&lt;7 y</td>
<td>0.29</td>
<td>0.48</td>
</tr>
<tr>
<td>7 y–&lt;9 y</td>
<td>0.34</td>
<td>0.55</td>
</tr>
<tr>
<td>9 y–&lt;11 y</td>
<td>0.32</td>
<td>0.64</td>
</tr>
<tr>
<td>11 y–&lt;13 y</td>
<td>0.42</td>
<td>0.71</td>
</tr>
<tr>
<td>13 y–&lt;15 y</td>
<td>0.46</td>
<td>0.81</td>
</tr>
<tr>
<td>Adult (males)</td>
<td>0.72</td>
<td>1.18</td>
</tr>
<tr>
<td>Adult (females)</td>
<td>0.55</td>
<td>1.02</td>
</tr>
</tbody>
</table>

*To express creatinine values in μmol/L, multiply the values by 88.4.

**Clin Chem 2008;54:559-66**
Common reference intervals for γ-GT in adults

Ceriotti F et al., Clin Chem Lab Med 2010;48:1593
Profession (e.g., IFCC, JCTLM):

- Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)

Diagnostic manufacturers:

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

End users (clinical laboratories):

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

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

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

L Thienpont et al., Clin Chem Lab Med 2004;42:842
Serum albumin: Metrological traceability chain

U.S. National Reference Preparation no. 12-0575C

Combined Standard Uncertainty ($u_c$)

- $u_c$ 1.01%
- $u_c$ 1.61%
- $u_c$ 1.74%
- $u_c$ >2.5%

Note: Minimum imprecision goal ≤2.33%

Uncertainty of measurement that fits for purpose must be defined across the entire traceability chain, starting with the provider of RMs, extending through the IVD manufacturers and their processes for assignment of calibrator values, and ultimately to the final result reported to clinicians by end users.
Profession (e.g., IFCC, JCTLM): Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)

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

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

Fulfillment of the Requirements of the EU IVD Directive by Manufacturers

- Preparation of the necessary technical documentation
- All data that characterize the product
- Testing protocols
- Labels and instruction for use
- Assigned values and metrological traceability
  - Traceability chain and calibration hierarchy
  - Transfer protocols
  - Commutability testing
  - Determination of uncertainty (fitness for purpose)
- Stability testing
Thus, the laboratory needs to rely on the manufacturers who must ensure traceability of their analytical system to the highest available level.
In turn, clinical laboratories must verify the consistency of declared performance during routine operations performed in accordance with the manufacturer’s instructions, by analyzing the system control materials and confirming that current measurements are in control, with no clinically significant changes in the assumed unbiased results.
Profession (e.g., IFCC, JCTLM): Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)

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

External Quality Assessment
[Analytical quality of measurement]

Measurement uncertainty

Check trueness

Imprecision

Internal Quality Control
[Reliability of the analytical system]


Università degli Studi di Milano

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

Alberto Dolci1, Luisa Scapellato2, Roberta Mozzi1 and Mauro Panteghini1,2

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

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

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

Results: Biomarkers concentration means and average yearly CVs (desirable goals in parentheses) were as follows: α-fetoprotein, 9.6 μg/L, 3.9% (6.0%); CA125, 41.2 U/L, 2.8% (12.4%); CA15-3, 32.7 U/L, 3.1% (3.1%); CA19.9, 25.1 U/L, 2.8% (8.0%); CEA, 7.7 μg/L, 4.3% (6.4%); prostate-specific antigen (PSA), 4.1 μg/L, 4.3% (8.1%); CYFRA 21.1, 2.4 μg/L, 5.7% (11.3%); and ferritin, 64.5 μg/L, 4.0% (7.1%).

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

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

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

End users (clinical laboratories): Survey assay and laboratory performance through
- IQC: testing system controls to confirm and verify manufacturer’s declared performance (CE marked – virtually unbiased)
- EQA (true value in commutable materials): defining uncertainty of laboratory measurements
### Requirements for the applicability of EQA results to evaluation of the performance of individual laboratories

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

Important issue to be considered

• To ensure reliability in the estimate of end user uncertainty alone, the uncertainty of the values assigned by the reference laboratory to EQAS materials should be maintained at a minimum.

• To achieve this, Stöckl and Reinauer [Scan J Clin Lab Invest 1993;53(suppl 212):16] have proposed that the uncertainty of the target should be <0.2 times the EQAS maximal tolerated limit, i.e. the clinically allowable uncertainty of measurements.
http://www.bipm.org/en/committees/jc/jctlm/
## List of reference measurement services

This file was created on 04 November 2010 from the JCTLM-DB website ([http://www.bipm.org/jctlm/](http://www.bipm.org/jctlm/))

Your search criteria: Reference measurement services; Analyte: ALT; Analyte category: Enzymes; Matrix category: Blood serum

<table>
<thead>
<tr>
<th>CIRME, Italy</th>
<th>Contact person</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone: +39 02 3904 2806</td>
<td>Prof. Mauro Panteghini</td>
<td><a href="mailto:mauro.panteghini@unimi.it">mauro.panteghini@unimi.it</a></td>
</tr>
<tr>
<td>Fax: +39 02 5031 9535</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analyte</th>
<th>alanine aminotransferase (ALT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material or matrix</td>
<td>blood serum, blood plasma</td>
</tr>
<tr>
<td>Applicable material or matrix</td>
<td>human serum or plasma (heparin), lyophilized, fresh, or frozen</td>
</tr>
<tr>
<td>Quantity</td>
<td>Catalytic activity concentration</td>
</tr>
<tr>
<td>Service measurement range</td>
<td>0.063 µkat/L to 4.17 µkat/L</td>
</tr>
<tr>
<td></td>
<td>The conversion factor for enzyme catalytic activity concentrations: 1 U/L = 0.01667 µkat/L</td>
</tr>
<tr>
<td>Expanded uncertainty</td>
<td>(not available) to 2.3%</td>
</tr>
<tr>
<td>(level of confidence 95%)</td>
<td>The uncertainty of the lower limit of the measurement range is not available as this enzyme value is clinically irrelevant</td>
</tr>
</tbody>
</table>

**Interlaboratory comparison results**


**Measurement principle**

- Kinetic spectrophotometry

**JCTLM reference measurement method/procedure**

- IFCC reference measurement procedure (37 °C) for ALT
### Risultati utilizzati per il calcolo dell’incertezza estesa secondo GUM nella misurazione dell’attività catalitica dell’alanina aminotransferasi (ALT) con procedura di riferimento

La tabella riporta i risultati per l’incertezza massima accettabile, lo scarto tipo, il coefficiente di sensibilità e l’incertezza standard relativa per varie grandezze.

#### Tabella di Accreditamento SIT

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

Totale 1,393%
EQAS for quantities where no high-order reference is available

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

HOWEVER

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

Accuracy verification in EQAS: time to care about the quality of the samples!

Allowable Limits

IFCC-IUPAC Stockholm Conference 1999

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings (e.g. misclassification in diagnosis)

2. Evaluation of the effect of analytical performance on clinical decisions in general
   a. Data based on components of biological variation
   b. Data based on analysis of clinicians opinions

3. Published professional recommendations from national and international expert bodies

4. Performance goals set by
   a. Regulatory bodies
   b. EQAS organizers

5. Goals based on the current state of the art (e.g. as demonstrated by data from EQAS)
Is available information on biological variability reliable?

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

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Method specificity as per HbA$_{1c}$ measurand definition</th>
<th>Recruitment of healthy subjects</th>
<th>Optimal study duration</th>
<th>Optimal protocol of sample analysis</th>
<th>Statistical analysis described</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>±</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>5</td>
<td>±</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>±</td>
<td>Yes (F only)</td>
<td>Yes</td>
<td>±</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>Yes (M only)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>±</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Braga F et al, Chim Clin Acta 2010;411:1606
Traceability as Copernican Revolution in Laboratory Medicine (and in Analytical Quality Control)

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

In the Quality Control setting, the objective laboratory world producing experimental data does not change, but our ‘a priori’ concept of it is turned inside out.
What COPERNICUS did was take the existing ‘a priori’ concept of the world and pose an alternative ‘a priori’ concept.

The earth is flat and fixed in space vs. The earth is spherical and moves around the sun.

Equivalency-based grading vs. Accuracy-based grading.

What TRACEABILITY does is take the existing ‘a priori’ concept of the QC and pose an alternative ‘a priori’ concept.
The effect was overwhelming.

It was the acceptance of the Copernican revolution that distinguishes modern man from his medieval predecessors.

Robert M. Pirsig – *Zen and the Art of Motorcycle Maintenance*, 1974