Traceability in laboratory medicine: why is it important?

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On behalf of the Joint Committee for Traceability in Laboratory Medicine
Outline

• Background
• Traceability in laboratory medicine
• JCTLM
• Example
• Relevance to EQALM
Everyday examples of traceable measurements

Weight (mass)

Length

Time

Temperature
“The Kilogram”
BIPM, Paris

Traceable results are comparable
Local weights and measures: Falkirk, Scotland
Système Internationale (SI) units

- Mass: kilogram (kg)
- Length: metre (m)
- Time: second (s)
- Electric current: Ampere (A)
- Temperature: Kelvin (K)
- Amount of substance: mole (mol)
- Luminosity: candela (cd)

SI units underpin our scientific, manufacturing & technological civilisation
So what about laboratory medicine?

Patients assume and expect that all methods will give the same result for a single test!
HbA2 and clinical practice guidelines

Many clinical practice guidelines exist for thalassaemia that link diagnosis to target HbA2 levels.

For example UK NHS sickle cell and thalassaemia screening programme:

“A national recommended cut-off for HbA2 of 3.5% has been set as the action point in the diagnosis of carriers of beta thalassaemia.”
Current HbA2 EQA performance

Figure from UK NEQAS with permission
Why should different methods give the same result?

Adapted from Plebani, *Clin Chem Lab Med* 2013; 51: 741-51
What can we standardise / harmonise in laboratory medicine?

- Standardise / Harmonise
  - Laboratory Protocols
  - Laboratory Parameters
  - Laboratory Methods
  - Test requesting
  - Sample handling
  - Reporting
  - Test names and units
  - Reference intervals
  - Critical values
  - Technology
  - Traceability
  - Commutability
  - Local
  - Local / National
  - Local / International

Adapted from Plebani, *Clin Chem Lab Med* 2013; 51: 741-51
Reducing between method variability

Comparable results

Monitoring
Consistent performance maintained via PT, EQA etc

Design
Calibration and traceability to a common reference system

Standardisation Harmonisation
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What is traceability in laboratory medicine?

- Metrological traceability is the property of a measurement result, which can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.
- Traceability requires both (certified) reference materials and the reference measurement procedures (methods) in which they are used.
- For structurally simple measurands (analytes) it is possible to get pure substance primary reference materials. For more complex measurands pure substance may not be available.
- Primary reference measurement procedures are based on physical methods (e.g. ID-MS).

### Reference materials (calibrators)
- Primary reference material (pure substance)
- Primary calibrator (SI traceable)
- Secondary calibrator
- Product calibrator

### Reference measurement procedures
- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected procedure
- Routine laboratory procedure

Hierarchy
The metrological traceability chain

- Definition of measurand: Concentration in SI units

- Primary reference material
- Primary calibrator
- Secondary calibrator
- Manufacturer master calibrator
- Product calibrator
- Patient result

- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected measurement procedure
- Manufacturer standing measurement procedure
- Routine laboratory method

- Metrology institute / Reference lab
- IVD method manufacturer
- Routine lab

Adapted from EN ISO 17511 2003
‘Higher order’ materials and procedures

1. Primary reference material
   - Primary RMP
     - Primary calibrator (SI traceable)
       - Secondary RMP
         - Secondary calibrator

2. Higher order
   - International CC (non-SI)
     - International conventional RMP
       - Calibration materials

3. Metrological traceability
   - International CC (non-SI)
     - International conventional RMP
       - Calibration materials

4. Lower order
   - International CC (non-SI)

5. Manufacturer’s selected method

RMP = reference measurement procedure
CC = conventional calibrator

Adapted from White GH Ann Clin Biochem 2011; 48: 393-408
Requirements for traceability in laboratory medicine

European Union In-Vitro Diagnostic Directive (IVDD): 98/79/EC

“The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.”

EU In-Vitro Diagnostic Device Regulation (IVDR): EU/2017/746

“9.3. Where the performance of devices depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order.”
Who are the stakeholders in achieving traceability?

- Define clinical decision values and analytical requirements
- Provide reference materials and higher-order reference methods
- Raise analytical and clinical quality targets
- Lists available materials and methods. Promotes traceability
- Use commutable materials to monitor method performance
- Produce methods that are traceable to a reference system, when available
- Select methods based on quality performance

Routine lab
EQA provider
IVD method manufacturer
Standards institutes Accreditation bodies
Global database of reference materials & methods
National metrology institutes Professional bodies / societies
Internationally recognised expert clinical / laboratory committees

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Joint Committee for Traceability in Laboratory Medicine

Formed in 2002 to enable a global response to the IVD Directive

- Intergovernmental treaty organisation for measurement standards
- International NGO for professionals in laboratory medicine
- International NGO for accreditation bodies

Now has 49 members from 19 countries
NMIs, EQA providers, professional bodies, IVD manufacturers
What does JCTLM do?

- Maintains a global database of:
  - Reference materials
  - Reference methods
  - Reference laboratories
  - [www.bipm.org/jctlm](http://www.bipm.org/jctlm)

- Co-ordinates the nomination and review process for database entries
  - [www.bipm.org/jctlm](http://www.bipm.org/jctlm)

- Contributes to ISO Working Groups on reference systems, which are responsible for global standards

- Provides news and freely available resources on traceability in laboratory medicine:
  - Webinars; publication lists
  - [www.jctlm.org](http://www.jctlm.org)

- Hosts a biennial scientific meeting
JCTLM Database: Laboratory medicine and *in vitro* diagnostics

**Type an analyte name** in part or full, e.g. cholesterol

**Please select your requirement:**
- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

[Search]
JCTLM database entries: October 2018

- **Vitamins and Micronutrients**: 11 (Materials), 10 (Methods), 2 (Services)
- **Non-Electrolyte Metals**: 30 (Materials), 56 (Methods), 21 (Services)
- **Electrolytes**: 32 (Materials), 41 (Methods), 26 (Services)
- **Non-Peptide Hormones**: 91 (Materials), 49 (Methods), 46 (Services)
- **Metabolites and Substrates**: 32 (Materials), 15 (Methods), 5 (Services)
- **Drugs**: 31 (Materials), 23 (Methods), 8 (Services)
- **Proteins**: 7 (Materials), 7 (Methods), 8 (Services)
- **Nucleic Acids**: 1 (Materials), 1 (Methods), 68 (Services)
- **Enzymes**: 3 (Materials), 3 (Methods), 68 (Services)
- **Coagulation Factors**: 1 (Materials), 1 (Methods), 1 (Services)
- **Blood Groupings**: 2 (Materials), 2 (Methods), 2 (Services)
- **Blood cell counting**: 2 (Materials), 2 (Methods), 2 (Services)
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Case study: haemoglobin A\textsubscript{1c} (HbA\textsubscript{1c})

Established from major clinical trials as key analyte for long-term monitoring of diabetes

Method improvement following IFCC standardisation [Ref 1]

IFCC reference laboratory network established [Ref 2]

Many laboratory and POCT methods available

2. IFCC network laboratories for HbA1c [www.ifcchba1c.net](http://www.ifcchba1c.net)
Why is HbA\textsubscript{1c} so important?

DCCT* showed that HbA\textsubscript{1c} is the best long-term marker of diabetes control.

Better control of HbA\textsubscript{1c} leads to better outcomes in people with diabetes.

- Deaths related to diabetes: 21%
- Microvascular complications: 37%
- Myocardial infarction: 14%

* DCCT = Diabetes Control and Complications Trial

HbA1c: typical current EQA

Specimen: 370B

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Between-laboratory agreement by concentration for HbA1c [IFCC]

CV %

Concentration (mmol/mol)
HbA1c as a diagnostic test for diabetes

- Many clinical practice guidelines exist that link monitoring of diabetic control to target HbA1c levels.
- WHO guidelines for HbA1c in diagnosis of diabetes

WHO Guideline 2011

“HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to international values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 48mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes. A value of <48mmol/mol does not exclude diabetes diagnosed using glucose tests.”
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Facing the challenge

The world population of 7.7 billion people is entitled to believe that all methods will give the same result on their specimen.
What can EQA achieve?

- EQA is an essential and effective tool to reduce between method variability.
- In addition to its proficiency testing role, EQA has an important educational role with users and IVD method manufacturers.
- Wherever possible, EQA specimens should perform like fresh patient specimens (commutable EQA).
- However, EQA alone may not be sufficient to harmonise patient results from different methods:
  - Different measurands
  - Different reference materials
  - Different measurement procedures (e.g. antibodies)
- EQA organisers have a vital role in highlighting analytes with high between method variability that may benefit from an international standardisation / harmonisation initiative.
Possible roles for EQALM

Possible Projects

Project 1
Review clinically important analytes where EQA performance is poor and identify candidates for method harmonisation (www.harmonization.net)

Project 2
• Lead / support a project to explore relationship of EQA performance to method traceability
• Outcome
  • Review article
  • Presentation at international meeting
  • Freely available webinar

Publicity and Promotion

Working with JCTLM
• Encourage EQA organisers to include a session on TLM in their user group meetings
• Distribute news and educational material on traceability in laboratory medicine (TLM) to participants and manufacturers
• Highlight methods where performance is improving as a result of EQA leadership
• Promote www.jctlm.org to participants and manufacturers