Traceability in laboratory medicine: a driver of accurate results for patients

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Joint Committee for Traceability in Laboratory Medicine

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Outline

• Laboratory medicine in healthcare
• Traceability in laboratory medicine
• Joint Committee for Traceability in Laboratory Medicine
• Facing the challenge
Some big numbers

- Global cost of healthcare $\sim$8.2 trillion pa
- Global cost of laboratory medicine $\sim$200 billion pa
- Global cost of reagents & equipment $\sim$62 billion pa
- Global cost of staff and overheads $\sim$138 billion
- Global IVD tests $\sim$35 billion pa
- Number of different IVD tests $\sim$4000

Annual growth of $\sim$5% for all of above
Pathology and laboratory medicine (PLM)

- Anatomic pathology
  - Cytopathology
  - Embryology
  - Histopathology

- Molecular pathology
  - Bioinformatics

- Common to all PLM

- Laboratory medicine
  - Clinical chemistry
  - Genetics
  - Haematology
  - Immunology
  - Microbiology
  - Transfusion
  - Transplantation
  - Virology
Central role of pathology & laboratory medicine

A high percentage of all clinical decisions are informed by data from pathology & laboratory medicine.

<3% spend
Central role of pathology & laboratory medicine

Pathology & laboratory medicine is part of the multi-disciplinary team at the centre of healthcare.

With this influence comes responsibility to deliver a high quality service.

LAB

Identify risk factors & symptoms
Diagnose disease
Determine appropriate treatment
Evaluate response
Laboratory medicine methods

- Some measurands are structurally simple and available in pure form (e.g. glucose)
- Most measurands are complex, often heterogeneous (e.g. viruses)
- Method calibration is a challenge
- >100 diagnostic companies producing IVDs – using ‘own’ calibrators
- Result is often variability between methods for the same measurand
- The same patient specimen can give different results in different methods!
Current HbA2 EQA performance

Figure from UK NEQAS with permission
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Traceable measurement results are compatible.
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
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

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

Metrological traceability

2. International CC (non-SI)
3. International conventional RMP
4. 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.”
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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
BIPM leads on metrology and provides the Secretariat
What does JCTLM do?

Maintains a global database of:
- Reference materials
- Reference methods
- Reference services
  www.bipm.org/jctlm

Co-ordinates the nomination and review process for database entries
  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

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

Reset Search
289 Certified Reference Materials
194 RMPs that represent 80 different analytes in 9 categories
176 reference measurement services delivered by 17 reference labs
Higher order reference materials

- NMIs provide higher order reference materials (both pure and matrix materials) to support the IVD industry
- Currently 95% of Certified Reference Materials in the JCTLM database come from NMIs

- BIPM functions as an external quality assessment provider for NMIs:
  - Coordinates Key Comparisons
  - Send samples of pure materials for NMIs to value assign and compare
  - Use own labs to value assign the materials independently.
### CCQM-K115: Peptide Primary Reference Material Comparison Series

**Pure peptide comparisons coordinated by BIPM for the NMIs**

<table>
<thead>
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<th>Relative molecular mass</th>
<th>1 kDa</th>
<th>no cross-links</th>
<th>low cross-links</th>
<th>high cross-links</th>
<th>modifications</th>
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</thead>
<tbody>
<tr>
<td>10 kDa</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Active large proteins</td>
<td></td>
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</tbody>
</table>

**Diabetes monitoring biomarker**

- **C-peptide** (2016)
  - Diabetes diagnostic biomarker
  - **HbA1c Hexapeptide** (2019)
    - Diabetes monitoring biomarker
  - **PTH** (2021)
    - Chronic kidney disease monitoring
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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.
Stakeholder coordination to address the challenge

Select methods based on quality performance

Use commutable materials to monitor method performance

Produce methods that are traceable to a reference system, when available

Raise analytical and clinical quality targets

Lists available materials and methods. Promotes traceability

Provide reference materials and higher-order reference methods

Define clinical decision values and analytical requirements

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