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

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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
Anatomic pathology
Cytopathology
Embryology
Histopathology

Common to all PLM
Molecular pathology
Bioinformatics

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.

1. Identify risk factors & symptoms
2. Diagnose disease
3. Determine appropriate treatment
4. Evaluate response
Laboratory medicine sectors

- Point of care
- Immunoassay
- Clinical chemistry
- Other
- Haemostasis
- Haematology
- Flow cytometry
- Molecular diagnosis

Morgan Stanley Research Estimates
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!

Variability between methods
- Incorrect patient results
- Mis-diagnosis / mis-management
- Poor clinical outcomes
- Impact on patient safety
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

Routine lab

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

1. Primary reference material → Primary RMP
2. Primary RMP → Primary calibrator (SI traceable) → International CC (non-SI) → International conventional RMP
3. International conventional RMP → Calibration materials
4. International CC (non-SI) → 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](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

Analyte keyword search for reference materials, measurement methods/procedures and services

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

Refine search by analyte category

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

Refine search by matrix category

Search
JCTLM Database: Entries in 2018

- 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.
Pure peptide comparisons coordinated by BIPM for the NMIs

CCQM-K115: Peptide Primary Reference Material Comparison Series
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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

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

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