What is the purpose of this website?

This website aims to explain:

- How it is possible for different methods to give different results for the same test on the same patient sample
- Why it is important to reduce between method variability
- Traceability in laboratory medicine as a tool to facilitate a global approach to reducing between method variability
- The challenges in introducing traceability in laboratory medicine
- The stakeholders responsible for implementing traceability in laboratory medicine

Additionally, the website:

- Tries to avoid too much technical language and jargon
- Gives regular updates on significant developments
- Provides an up-to-date list of publications, resources and meeting reports to illustrate the growing importance of traceability in laboratory medicine
- Invites communication and collaboration from interested parties

What is between method variability in laboratory medicine?

Laboratory medicine is an essential clinical specialty providing users with pivotal information for the prevention, diagnosis, treatment and management of health and disease. Laboratory medicine results provide information that impacts a high percentage of clinical decisions in healthcare. This central role means that laboratory medicine specialists have a professional responsibility to provide a high quality service that is optimized to the needs of the patient.

One increasingly important quality objective is to ensure that patient test results are traceable (equivalent) between different methods, laboratories and healthcare systems over time. Traceability of test results is being achieved through the process of harmonization in laboratory medicine. The ultimate aim of harmonization is to provide accurate, actionable and transferable patient results, which can facilitate improved clinical outcomes and patient safety. Harmonization in laboratory medicine has a wide scope. It can be applied across the total testing process of laboratory medicine, including requests, samples, measurements and reports. The many dimensions of harmonization require active involvement at local, national and international levels.

Patients and the public naturally assume that all methods for measurement of a single biomarker (analyte) will give the same result on a patient sample. For some simple analytes, such as plasma glucose, the results will be very similar. However, for more complex analytes the results may vary considerably. There are many potential reasons for these differences and these may be summarised under ‘the four Cs’:

- Companies: There are many IVD method manufacturers around the world. Their individual methods may have different specimen requirements; employ different method designs and use different signal detection systems. Variability may also be introduced by local modification to a company product.
- Components: Methods may use different calibrators; different enzymes and substrates; different antigens and antibodies; and a variety of other reagents
- Conditions: Different methods have variability in reaction time; temperature, pH and often use different software and curve fits to derive results
- Common target: Although methods will quote figures for imprecision and accuracy (trueness) these are of limited value unless they can be related to a common, international reference system

Why is it important to reduce between method variability?

There are several reasons why efforts should be made to reduce between-method variability. These include:

- Patient safety: Differences in practice and variability of results put patients at risk. Harmonization of patient results should contribute to improved clinical outcomes
- Patient empowerment: Healthcare is increasingly patient-centred. Patients expect results from laboratories and from self-testing to be identical and method independent
- Public confidence: The public will be reassured by the knowledge that patient results are accurate and transferable between laboratories
- Laboratory accreditation: The ISO 15189:2012 standard used for medical laboratory accreditation requires trueness of measurement and metrological traceability
- Clinical guidelines: The successful implementation of clinical practice guidelines often links patient management to specific values or changes in patient results
- Clinical governance: Differences between patient results leads to concerns about the quality and professionalism of the service that is provided
- Consolidation and networking: Laboratory networks providing services to both primary and secondary care should be able to provide similar results from any laboratory site
- Informatics: Laboratory information systems and hospital information systems will only be able to share and transfer results if they are harmonized
- Electronic patient record: National electronic patient records require that patient results may be inserted from any laboratory and so they should be transferable

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. The principles of a reference measurement system for establishing metrological traceability are described in the document ISO17511:2003 document and explained in the 'Resources' section of this website. The components of a reference measurement system comprise reference materials (calibrators) and measurement procedures (methods), both of which exist at different hierarchical levels.

The inter-relationship between the components of a reference measurement system constitute the metrological traceability chain, which is explained in the 'Resources' section. The traceability status of an individual measurement result depends on the existence of an unbroken chain to higher order materials and/or measurement procedures. For structurally simple molecules, like many of those measured routinely in clinical chemistry, it is possible to have a complete unbroken chain to primary reference measurement procedures and primary reference materials. Even for some protein molecules it is possible to achieve full metrological traceability by using a unique, signature peptide as the primary reference material.

For many biological materials, including complex proteins and viruses it is not possible to prepare secondary calibrators. In these circumstances international conventional calibrators are adopted as being the highest order materials available.

Commutability:

To be useful in clinical practice it is necessary for a reference material to perform in the same way as the analyte in a clinical specimen when used in measurement procedures. This is determined by analysis of a panel of samples together with the reference materials in two different measurement procedures, commonly a reference procedure and a routine

procedure. There will be a linear relationship between the results obtained for the clinical samples and the results from commutable reference materials will sit on the same line. Non-commutable reference materials will have a different relationship in the two measurement procedures invalidating the metrological traceability chain and, if used in clinical practice, could result in patient misclassification. Commutability is explained in the 'Resources' section.

Commutability applies not only to reference materials. External quality assessment (EQA) specimens also should behave in routine measurement procedures as if they are clinical patient specimens in order to compare the performance of different routine measurement procedures for the same analyte.

What are the challenges in implementing traceability in laboratory medicine?

Geographical differences:
The ready availability of rapid electronic communication offers the possibility of global harmonization across laboratory medicine. However, there are a number of barriers to be overcome if this is to be achieved, including:

- Language difficulties
- Lack of understanding of traceability in laboratory medicine
- Local and regional manufacturers of methods who may not subscribe to international standards
- Differing regulatory requirements for laboratory medicine methods
- Lack of adoption of clinical practice guidelines
- Financial pressures that may compromise quality in laboratory medicine

The variable use of international (SI) units:
In many parts of the world laboratory medicine results are expressed in conventional rather than SI units, even for analytes where it is possible to define the substance intended to be measured in SI units, and develop primary reference materials and primary reference measurement procedures. For such analytes another level of measurement uncertainty is introduced, namely the conversion factor used between SI and conventional units. As traceability in laboratory medicine gathers momentum the case for reporting results in SI units, when possible, becomes stronger. Medical doctors should be encouraged to use SI units as they are the final users of laboratories´ results.

Complex analytes:
It is conceptually straightforward to think of traceability in laboratory medicine when measuring a pure substance such as glucose in blood plasma. The earliest and most numerous applications of traceability are from the discipline of clinical chemistry where chemically pure substance and definitive chemical and physical methodology are available. However, many clinically important biomarkers are more complex in structure and some may not exist as a single entity. These include:

- Complex proteins, including glycoproteins
- Viruses and bacteria that may be found in different and changing strains
- Nucleic acids that may involve different sequences and primers

Methods for measuring these complex analytes often rely on biological methodology, including antibody: antigen and nucleic acid binding technology where the measurement uncertainty may be relatively high.

There is a perception that traceability is not possible for such challenging analytes. However, it is possible to reduce between method variability by adopting international conventional

calibrators and/or international conventional measurement procedures. The key to introducing traceability in such circumstances relies on global leadership.

Global coordination:
There is no definitive list of biomarkers used across laboratory medicine. A national database in Finland suggests that there could be as many as 4000 analytes. In January 2017 the JCTLM database (www.bipm.org/jctlm/) contained entries for:

- 293 certified reference materials
- 180 reference measurement methods covering 80 analytes
- 146 reference measurement services covering 39 analytes

In the same month the WHO-ECBS catalogue of international conventional calibrators for blood products and biological standards (http://www.who.int/bloodproducts/catalogue/en) contained ~300 entries, with little overlap with the JCTLM database. Taken together these two sources of reference materials and methods account for ~15% of the total number of methods used in laboratory medicine, although it is the case that methods for many of the most commonly performed analytes are included. What this demonstrates is that a coordinated global initiative is required to address the many methods for which there is currently no traceability. The methodology for such a coordinated global initiative has been described.

Who are the stakeholders in implementing traceability in laboratory medicine?

There are seven groups of stakeholders involved in implementing traceability in laboratory medicine. They have complementary roles and should co-ordinate their efforts as follows:

1. Internationally recognized expert clinical / laboratory committees:
   - Develop an international consortium for communication and sharing information on the need for traceability
   - Prioritise and agree methods that are in need of harmonization and issue invitations to expert groups to undertake method harmonization projects

2. National metrology institutes /international professional bodies / societies:
   - Develop commutable reference materials and measurement procedures for individual analytes to the highest available order of metrological traceability
   - Publish the outcome of harmonization projects in peer-review scientific literature

3. Global database of reference materials and methods:
   - Using freely available lists and catalogues publicise available reference materials and methods that meet agreed standards, including information on commutability and measurement uncertainty
   - Provide educational support materials to promote the importance of traceability in laboratory medicine

4. Standards / accreditation /professional bodies:
   - Include traceability in laboratory medicine in the training of laboratory medicine specialists and in the standards required for laboratory accreditation
   - Provide educational support materials to promote the importance of traceability in laboratory medicine

5. IVD method manufacturers:
   - Produce diagnostic methods that conform with the highest available order of metrological traceability
   - Provide details of the traceability status of methods in the information for use documentation

6. External quality assessment (EQA) providers:
    - Promote the use of commutable, value-assigned EQA materials
    - Provide educational support about traceability for EQA scheme participants

7. Routine laboratory medicine specialists:
    - Know the traceability status of the methods used and understand the measurement uncertainty involved
    - Educate staff and users about traceability in laboratory medicine and its importance to healthcare

Further information:

A more detailed explanation of the above text, together with illustrations, is available from the 'Publications', 'Resources' and 'Meetings' sections of this website. Any queries or comments should be directed to: jctlm@bipm.org