Opinion Paper

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Traceability in laboratory medicine: a global driver for accurate results for patient care

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Abstract: Laboratory medicine results influence a high percentage of all clinical decisions. Globalization requires that laboratory medicine results should be transferable between methods in the interests of patient safety. International collaboration is necessary to deliver this requirement. That collaboration should be based on traceability in laboratory medicine and the adoption of higher order international commutable reference materials and measurement procedures. Application of the metrological traceability chain facilitates a universal approach. The measurement of serum cholesterol and blood HbA_{1c} serve as examples of the process of method standardization where an impact on clinical outcomes is demonstrable. The measurement of plasma parathyroid hormone and blood HbA2 serve as examples where the current between-method variability is compromising patient management and method standardization and/or harmonization is required. Challenges to the widespread adoption of traceability in laboratory medicine include the availability of reference materials and methods, geographical differences, the use of variable units, complex analytes and limited global coordination. The global collaboration requires the involvement of several different stakeholder groups ranging from international experts to laboratory medicine specialists in routine clinical laboratories. A coordinated action plan is presented with actions attributable to each of these stakeholder groups.

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Introduction

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 and ethical responsibility to provide a high quality service that is optimized to the needs of the patient [1].

One increasingly important quality objective is to ensure that patient test results are traceable (equivalent) between different methods, laboratories and healthcare systems over time and location [2]. Harmonization of test results is being achieved by the process of good practice in traceability. 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 [3]. The many dimensions of harmonization require active involvement at local, national and international levels [4].

At a global level, traceability centers on reducing between-method variability, which is an important area of science that is often poorly understood by laboratory medicine specialists [5]. Achieving traceability is a global multi-stakeholder cooperative activity involving metrologists; international standards organizations; scientific and clinical experts from international professional bodies; healthcare regulators; and the in-vitro diagnostics (IVD) industry that is responsible for the manufacture and sale of diagnostic testing systems. The Joint Committee for Traceability in Laboratory Medicine

(JCTLM) was established to coordinate the activity of these stakeholders, to provide educational support for traceability, and to establish and maintain a database of reference materials, reference methods and reference laboratories [6].

This opinion paper seeks to explain traceability in laboratory medicine in practical terms and to illustrate why it is an important global contributor to accurate patient results.

The importance of reducing between-method and between-laboratory variability

There are several reasons why efforts should be made to reduce between-method and between-laboratory variability [3]. 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-centered. Patients expect results from laboratories and from self-testing to be identical and method independent. Increasing patient mobility reinforces the need to reduce variability at national and international level.
- Public confidence: The public will be reassured by the knowledge that patient results are accurate and transferable between laboratories.
- Consolidation and networking: Laboratory networks providing services to both primary and secondary care should be able to provide similar results from any laboratory site.
- Laboratory accreditation: The ISO 15189:2012 standard used for medical laboratory accreditation requires trueness of measurement and metrological traceability [7].
- Evidence-based 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.
- 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.

Reasons why methods may give different results on a patient sample

Patients, the public, physicians, and laboratory service users naturally assume that all methods for measurement of a single 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 summarized 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. Pre-analytical factors may have variable effects on these conditions.
- 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.

The science of measurement is called metrology, where it is known that the key to reducing measurement variability lies in adopting international reference systems to enable alignment from different methods. Everyday measurement such as weight (kilogram) and length (meter) demonstrate the importance of metrology. The introduction of reference systems in laboratory medicine, with traceability to those reference systems, is the global approach to reducing the variables that are responsible for methods giving different results [5].

Traceability in laboratory medicine

The basics of measurement involve:

- A measurable property, known as a quantity (e.g. concentration).
- Definition of the measurand – the quantity that is intended to be measured. The description of the measurand should include the matrix (e.g. plasma); the component (analyte) of interest, and the amount of substance concentration.
- The units in which the measurement will be made. Metrological traceability requires that the international system of units (SI) or units with well-established conversions (usually with the definition of the measurand for mass and molar units) should be used.
- The uncertainty with which the measurement can be made. Measurement uncertainty is a concept that is being clarified and gaining support [8].

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 ISO17511:2003 document [7] and in reviews arising from it [5, 9, 10]. The components of a reference measurement system comprise reference materials (calibrators) and measurement procedures (methods), both of which exist at different hierarchical levels.

Reference materials

- Primary reference material: This is a preparation of the analyte to be measured of defined purity, which has been characterized by physicochemical methods. Primary reference materials are prepared by national metrology institutes and accredited reference measurement laboratories recognized for the purpose [11]. They are available with certificates that include traceability to an SI unit, purity, stability and homogeneity [12].
- Primary calibrator: This is a measurement standard with a value assigned using a primary reference measurement procedure. It is usually in aqueous solution with a defined SI unit concentration and a small measurement uncertainty.
- Secondary calibrator: This is a matrix-matched material (e.g. serum) with an assigned quantity value and measurement uncertainty. It is value assigned using a secondary reference measurement procedure. Secondary calibrators may be used by IVD method manufacturers to calibrate their selected measurement procedures.
- International conventional calibrator: This is used as a calibrator when a secondary calibrator is unavailable. It is not SI-traceable and has the status of an internationally recognized measurement standard prepared and assigned arbitrary or other units according to protocols developed by expert groups.
- Manufacturer's calibrator: This is an in-house calibrator assigned a quantity value using a manufacturer's measurement procedure. It may be a master calibrator or a product calibrator.

Measurement procedures

- Primary reference measurement procedure: This defines the highest metrological order. It produces quantity values that have low measurement uncertainty and are metrologically traceable to an SI unit without using a material lower in the calibration hierarchy. In laboratory medicine, it is common to employ isotope dilution mass spectrometry in the primary reference measurement procedure.
- Secondary reference measurement procedure: This is used to assign a quantity value to a matrix matched secondary calibrator. Secondary reference measurement procedures usually employ a different measurement principle to the primary reference measurement procedure.
- International conventional measurement procedure: This is used when secondary calibrators are not available to promote international acceptance of a single reference measurement system for a measurand. It may also define the non-SI units for some measurands, such as enzyme activity.
- Manufacturer's measurement procedure: An IVD method manufacturer may have two of these for a particular measurand. The selected measurement procedure is used to assign quantity values to master calibrators, whereas the standing measurement procedure is used to assign quantity values to the commercial product calibrators.

Metrological traceability chain

The inter-relationship between the components of a reference measurement system describes the metrological traceability chain [13]. Figure 1 depicts this traceability

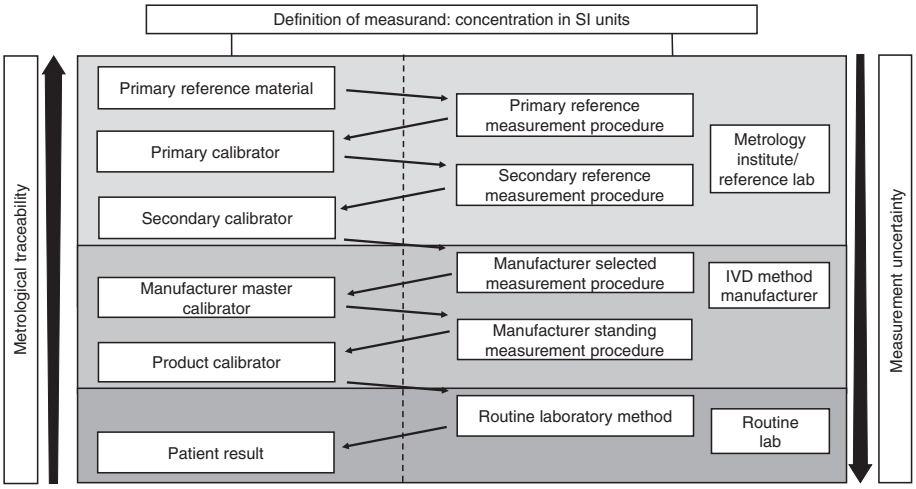

Figure 1: Metrological traceability chain. Adapted from EN ISO 17511:2003 [13].

chain with higher order reference materials and measurement procedures at the top and lower order toward the bottom. This hierarchy is depicted by the rising 'metrological traceability' arrow. Descent through the traceability chain is accompanied by increasing measurement uncertainty as depicted by the downward arrow.

The traceability status of an individual measurement result depends on the existence of an unbroken chain to higher order materials and/or measurement procedures. To be effective the unbroken chain requires commutable materials and sufficiently low imprecision at each step. In the case of 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. The measurement of serum cholesterol and blood HbA_{1c} will be presented below as examples of full metrological traceability.

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.

Method standardization and harmonization

The terms standardization and harmonization, when applied to methods, are often used interchangeably. This leads to confusion among laboratory medicine specialists and users of the services that they provide. The ISO 17511:2003 standard recognizes five categories of reference measurement system depending on the highest order of possible materials and procedures [13]. The simple interpretation of this categorization is that metrological traceability that includes a reference measurement procedure will result in method standardization whereas traceability to an international conventional calibrator or to a manufacturer's materials will result in method harmonization. It should be noted that ISO 17511:2003 is under revision and the updated standard may adopt a different categorization.

Commutability of reference materials

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 [14, 15]. 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 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 measurand.

Sources of reference materials and reference measurement procedures

The JCTLM maintains a database of reference materials, reference measurement procedures and reference laboratories [16]. Strict criteria are required for inclusion in the JCTLM database, including evidence of commutability of reference materials and measurement uncertainty. The World Health Organization Expert Committee for Biological Standardization (WHO-ECBS) maintains a catalog of international conventional calibrators for blood products and biological standards [17].

Case studies to demonstrate the value of traceability in laboratory medicine

Serum cholesterol

Raised serum cholesterol is well established as a risk factor for cardiovascular disease. There are many clinical practice guidelines linking patient management to specific serum cholesterol results. Such guidelines will only be valid if the methods used to measure cholesterol give the same results. The standardization of serum cholesterol methods with full metrological traceability was established >20 years ago [18] and an international reference laboratory network was established [19]. Consequently, the between-method variability of serum cholesterol methods is <5% and global standardization is a reality. The ability to measure serum cholesterol accurately has facilitated the optimal use of statins, which have contributed to a dramatic reduction in deaths from coronary disease [20]. Furthermore, the cholesterol standardization program has been shown to be cost-effective [21].

Blood hemoglobin A_{1c} (HbA_{1c})

HbA_{1c} is a glycated form of hemoglobin that is always present in blood. The concentration of HbA_{1c} is well established as the key analyte for long-term monitoring of diabetes mellitus. Lowering HbA_{1c} toward target concentrations improves clinical outcomes. Therefore, huge numbers of HbA_{1c} measurements are made across the world using many different methods. These methods used to show great variability but as a result of IFCC Scientific Division leadership the IFCC reference measurement procedure was introduced in 2004 [22] followed by an international reference laboratory network [23]. An international consensus statement recommending the use of IFCC-aligned methods for HbA_{1c} measurement was issued [24] and adopted. Consequently, the between-method variability for HbA_{1c} measurement in hospital laboratories is now ~5% in EQA schemes. This improved performance contributed to a recommendation from WHO that HbA_{1c} measurement using IFCC aligned methods may be used to diagnose as well as to monitor diabetes [25]. Realizing the need for even higher quality in HbA_{1c} measurement an expert group has developed quality targets for HbA_{1c} methods to assess if they are fit for purpose [26].

In both examples above, millions of patients from around the world have benefitted from improved clinical care as a result of laboratory medicine methods that have been standardized using metrological traceability at a global level.

Case studies to demonstrate the need for traceability in laboratory medicine

Plasma parathyroid hormone

Intact parathyroid hormone (PTH) is an 84-amino acid peptide, with the biological activity residing in the N-terminal 34 amino acids. Both PTH 1-84 and PTH 1-34 have short half-lives (2–4 min) in human plasma. Conversely, the C-terminal fragments of PTH that are created by cleavage of PTH 1-84 have much longer half-lives in plasma, especially in patients with chronic renal failure. PTH is used to diagnose hyperparathyroidism

and hypoparathyroidism but the most frequent use of PTH is in assessing the risk of and monitoring the treatment of renal osteodystrophy in patients with impaired kidney function. In this latter application the challenge is to measure the concentration of the bioactive, intact PTH in the presence of much higher concentrations of biologically inert C-terminal fragments [27].

Plasma PTH is normally measured using two-site immunometric assays. The specificity of the assays is influenced by the antibody combinations used. Data from EQA schemes demonstrate a threefold difference in the PTH results obtained from commonly available PTH assays [28]. These differences may be attributed to a range of factors, including pre-analytical variability and calibration as well as molecular heterogeneity, Consequently, PTH results are not transferable between assays and there is a risk to patient safety from misinterpretation of PTH results [29].

Having identified a risk to patients, the short-term recommendation is to ensure that assay-specific action limits are used. In the longer term a global partnership, led by IFCC, is working to produce reference materials and a reference measurement procedure for the standardization of PTH methods.

Blood hemoglobin A2

Hemoglobin A2 (HbA2) is a normal variant of hemoglobin A that consists of two α and two δ chains (α2δ2). It exists in small amounts in the blood of all adult humans. Its biological importance is uncertain. HbA2 concentration may be increased in β-thalassemia or in people who are heterozygous to the β-thalassemia gene.

Consequently, clinical practice guidelines exist for thalassemia that link diagnosis to target HbA2 levels. One typical example from the UK recommends a cut-off for HbA2 of 3.5% has as the action point in the diagnosis of carriers of β-thalassemia [30].

The between-method variability of methods for measuring HbA2 is poor owing to the lack of standardization [31]. Therefore, HbA2 results are not transferable between methods and there is a risk of patient misclassification using a single cut-off concentration. To address the problem a project has commenced to reduce the between-method variability of HbA2 methods [32].

In both examples above, large numbers of patients from around the world are at risk of misdiagnosis as a consequence of between-method variability arising from the absence of reference materials and/or reference measurement procedures.

Challenges in implementing traceability in laboratory medicine at a global level

Geographical differences

The ready availability of rapid electronic communication offers the possibility of global harmonization across laboratory medicine [3]. 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 lack of uniformity of 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 measurand in SI units and develop primary reference materials and primary reference measurement procedures. In some countries SI units and conventional units are both in use by different laboratories. In both circumstances, another source of variability is introduced. As traceability in laboratory medicine gathers momentum, the case for the uniform use of units for reporting results at national and international level becomes stronger and this reinforces the relevance of SI units. Medical doctors should be encouraged to demand uniform units for reporting 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 hierarchy of reference materials and measurement procedures is a logical sequence. It is not surprising, therefore, that the earliest and most numerous measurands to benefit from 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, as described earlier, 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 (P Laitinen, personal communication). In January 2017, the JCTLM database [16] 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 catalog of international conventional calibrators for blood products and biological standards [17] 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 [33, 34].

Stakeholders in implementing traceability in laboratory medicine

The stakeholders involved in delivering traceability in laboratory medicine into routine practice are summarized in Figure 2.

The initiative begins at the bottom of the triangle with international recognition of the need for traceability for a specific analyte. Thereafter, international and national

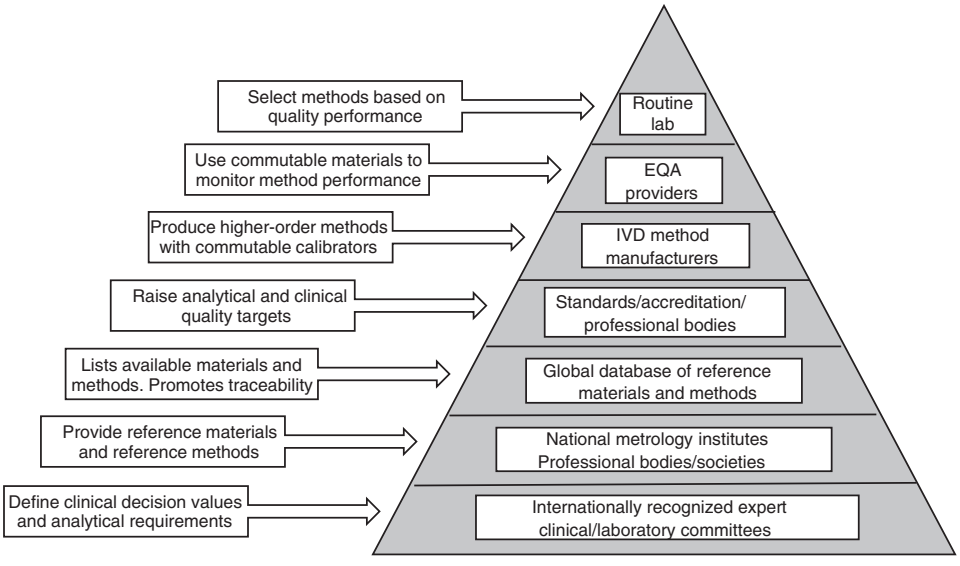

Figure 2: Stakeholders involved in achieving traceability in laboratory medicine. Adapted from White GH Ann Clin Biochem 2011; 48: 393–409.

standards organizations and metrology institutes are responsible for producing and listing the available reference materials and measurement procedures. These are used by the IVD method manufacturers to produce the methods made available for routine use with their performance evaluated through EQA schemes.

Action plan to implement traceability in laboratory medicine at a global level

In order to implement traceability in laboratory medicine at a global level it is necessary to have a coordinated action plan. This can be derived from Figure 2 by assigning actions to each of the stakeholder groups:

1. Internationally recognized expert clinical/laboratory committees:
   - Develop international consortium for communication and sharing information on the need for traceability [33, 34]
   - Prioritize 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 catalogs publicize available reference materials and methods that meet agreed standards, including information on commutability and measurement uncertainty [16, 17]
   - 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 IVD 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. 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

Resources for educational support are available from JCTLM [6]. Readers of this review are invited to discuss with their peers how they can contribute to the coordinated action plan.

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