Perspectives

Tony Badrick*, Ashley Beasley-Green, Christa M. Cobbaert, Vincent Delatour, Liesbet Deprez, Graham R.D. Jones, Ralf D. Josephs, Anja Kessler, Qinde Liu, Stephanie Maniguet, W. Greg Miller, Glenda V. Roberts, Sverre Sandberg, Huub H. Van Rossum, Katleen Van Uytfanghe, Christian Vogl, Robert Wielgosz, Tianjiao Zhang and Mauro Panteghini

Result harmonization in medical laboratories: accomplishments and challenges

https://doi.org/10.1515/cclm-2026-0323
Received March 3, 2026; accepted March 4, 2026;
published online March 13, 2026

Abstract: The Joint Committee for Traceability in Laboratory Medicine (JCTLM) supports worldwide equivalence and comparability of measurement results in laboratory medicine to improve health care and facilitate national and international trade in *in vitro* diagnostic (IVD) medical devices. The 2025 biennial members and stakeholders' workshop focused on the expectations and benefits of harmonized results among medical laboratories, as well as the challenges associated with achieving this goal. Harmonization of results from end-user IVD measurement procedures (IVD-MPs) can be achieved by applying the principles of metrological traceability; however, there are several historical examples of standardization efforts that did not achieve the required level of harmonization. The reasons for these failures can be found in various elements of the calibration hierarchy including: a) an unclear definition of the measurand, b) differences in selectivity of the IVD-MPs, c) issues with the commutability characteristics of secondary certified reference materials (CRM), d) inconsistencies in handling of CRMs to prepare calibrators, and e) lack of adoption and implementation by the IVD manufacturers. The lack of harmonized results can lead to confusion, treatment delays, errors in medical decisions, and increased healthcare costs. There are still assays in common use that lack metrological traceability because they lack CRMs, reference method procedures (RMPs), and/or reference method services (RMSs). Producing and maintaining reference measurement system components is complex and expensive. There are multiple regulatory frameworks and requirements that IVD manufacturers must meet worldwide. There is a vital role for External Quality Assessment (EQA) providers to assess the

***Corresponding author: Tony Badrick**, Royal College of Pathologists of Australasia Quality Assurance Programs, Sydney, NSW, Australia, E-mail: tony.badrick@rcpaqap.com.au. https://orcid.org/0000-0003-4846-9134
Ashley Beasley-Green, Biomolecular Measurement Division, Material Measurement Laboratory, National Institute of Standards and Technology (NIST), Gaithersburg, MD, USA
Christa M. Cobbaert, Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Centre, Leiden, The Netherlands
Vincent Delatour, Laboratoire National de Métrologie et d'Essais, Paris, France
Liesbet Deprez, European Commission, Joint Research Centre, Geel, Belgium
Graham R.D. Jones, Department of Chemical Pathology, SydPath, St Vincent's Hospital, Sydney, Australia; and University of NSW, Sydney, Australia
Ralf D. Josephs, **Stephanie Maniguet and Robert Wielgosz,** Bureau International des Poids et Mesures (BIPM), Sèvres, France
Anja Kessler, Reference Institute for Bioanalytics, Bonn, Germany
Qinde Liu, Chemical Metrology Division, Applied Sciences Group, Health Sciences Authority, Singapore, Singapore. https://orcid.org/0000-0003-0769-4642
W. Greg Miller, Department of Pathology, Virginia Commonwealth University, Richmond, VA, USA
Glenda V. Roberts, Mount Sinai – Center for Kidney Disease Innovation, Dr. Barbara T. Murphy Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
Sverre Sandberg, Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), Haraldsplass Deaconess Hospital, Bergen, Norway; Department of Medical Biochemistry and Pharmacology, Norwegian Porphyria Centre, Haukeland University Hospital, Bergen, Norway; and Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
Huub H. Van Rossum, Department of Laboratory Medicine, Netherlands Cancer Institute, Amsterdam, The Netherlands
Katleen Van Uytfanghe, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ref4U-Laboratory of Toxicology, Ghent University, Ghent, Belgium
Christian Vogl, Roche Diagnostics GmbH, Penzberg, Germany
Tianjiao Zhang, National Center for Clinical Laboratories, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital/National Center of Gerontology, Beijing, China
Mauro Panteghini, Department of Laboratory Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Torun, Poland. https://orcid.org/0000-0002-7147-3433

agreement status of results across different IVD-MPs and identify any changes in their equivalence. However, EQA materials must be commutable with clinical samples for each of the examined IVD-MDs for results to reflect the status of harmonization of clinical sample results. The future will need leadership and cooperation between bodies such as JCTLM, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and IVD manufacturers.

Keywords: harmonization; reference materials; traceability; certified reference materials

Introduction

The Joint Committee for Traceability in Laboratory Medicine (JCTLM) was established in 2002 in response to the implementation of the European Community Directive 98.79/EC on *in vitro* medical devices. The Committee consisted of representatives from the International Bureau of Weights and Measures (BIPM), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Laboratory Accreditation Cooperation (ILAC). The International Committee on Standardization in Hematology (ICSH) further joined in 2019.

The primary output of the JCTLM is a global database of higher-order certified reference materials (CRMs), reference measurement procedures (RMPs), and reference measurement services (RMSs). All references listed in the database are reviewed for conformance to applicable International Organization for Standardization (ISO) standards. The role of JCTLM is to support worldwide equivalence and comparability of measurement results in laboratory medicine for the purpose of improving health care, and facilitating national and international trade in *in vitro* diagnostic (IVD) medical devices, by [1]:

- Promoting the concept of metrological traceability of measurement results to the International System of Units (SI) or, where necessary, to other internationally agreed references.
- Evaluating CRMs, RMPs and RMSs for laboratory medicine for conformity with appropriate international standards.
- Producing educational materials and activities promoting the value of metrological traceability in laboratory medicine and raising awareness amongst stakeholders.
- Promoting close links between laboratories performing RMPs and national metrology institutes.
- Facilitating the identification and prioritization of measurands requiring international traceability and equivalence and thereby encouraging appropriate organizations to accept responsibility for the development of suitable RMPs and CRMs.
- Encouraging the IVD manufacturers to establish metrological traceability to the agreed reference measurement systems.
- Encouraging External Quality Assessment (EQA) organizers to apply RMP values to commutable EQA materials.

The JCTLM organizes a biennial workshop for its members and stakeholders. The 2025 workshop focused on the expectations and benefits of harmonized results among medical laboratories, as well as the challenges associated with achieving this goal. The workshop addressed necessary initiatives for CRMs, RMPs, and RMSs, along with the challenges of implementing them in compliance with relevant ISO standards. Sustaining these reference measurement systems, along with descriptions of how they should be implemented, was discussed. The workshop explored the implementation of metrological traceability by IVD manufacturers, its impact on regional and global regulatory requirements, and how new processes can harmonize measurement results.

Setting the scene

Patient expectations

Laboratory results shape life-altering decisions – yet for many patients, they remain confusing, inconsistent, or difficult to interpret. Patients consistently express four core needs:

- Clarity: results must be understandable across literacy levels. The average global reading level is between sixth and eighth grade, so explanations must be scientifically accurate yet accessible.
- Consistency: results should yield the same interpretation across laboratories, care settings, and time.
- Reliability: patients need confidence that results are accurate and actionable.
- Equity: result interpretation must reflect genetic, cultural, and socioeconomic diversity to avoid reinforcing disparities.

Current practices such as variable reference limits, inconsistent reporting units, and technical jargon undermine these expectations. Harmonization must extend beyond technical measurement to encompass the language, format, and context in which results are presented [2]. This includes co-designing result reports with patient partners, applying

community-based participatory research principles, and ensuring transparency about uncertainty and limitations [3, 4]. In a digital, data-driven healthcare landscape, harmonization must serve both machines and people. Patient expectations must inform both technical and communication standards, and meeting these expectations transforms harmonization from a technical achievement into a bridge of trust between science and lived experience.

Realizing the benefits of metrological traceability

Every day, we reap the benefits of metrological traceability in every aspect of our lives. Our food, our buildings, our computers, our communications, and our travel are all built using measurements traceable to SI. By contrast, the field of laboratory medicine is sadly far behind in both achieving widespread traceability of measurement results and in delivering the benefits of such traceability where it exists. Examples of failure to achieve such benefits is the widespread use of different reference intervals for the same test in laboratories, with the variation most commonly not reflecting differences in the assay results or the population served [5], and persistent variation in units of reporting [6].

All results are interpreted by comparison with a reference interval, a clinical decision limit, a previous result from the same patient, or the practitioner's prior experience. Each of these interpretive processes is at risk if the comparator is inconsistent relative to the result under consideration. Over the years, local solutions have been developed, for example, to validate reference intervals for local use or to indicate the methods used in reports, alerting users to possible differences. These approaches are no longer acceptable. Two key drivers of the need for metrologically traceable results are the growth in combining results into common databases or in other products that may cross international borders. The other driver is the need to use evidence-based medical decisions. If the results of a clinical study define a decision threshold, this cannot be effectively applied in practice unless the results are unbiased or the bias is known and managed. This approach provides the "clinical traceability" of laboratory results [7].

To realize the benefits of results that have verified metrological traceability, we should aim for common supporting information such as test names, reporting units, and reference intervals/decision thresholds. We also need the information and terminology (coding) to allow traceable results to be combined into clinical databases, as well as the same to keep non-traceable results separate. In the current digital and artificial intelligence world, it is clearly vital that information, whether for machines or people, does not carry unnecessary variation.

Why does harmonization theory not always work?

Medical test standardization should ensure that various end-user IVD measurement procedures (IVD-MPs) targeting the same measurand provide harmonized results, i.e., equivalent results within a measurement uncertainty (MU) consistent with medical decision-making requirements, for any given clinical sample. Harmonization of results from IVD-MPs can be achieved by applying the principles of metrological traceability and establishing a suitable calibration hierarchy for the values assigned to the calibrators of the IVD-MPs, as specified in the ISO 17511:2020 standard [8, 9]. However, there are several historical examples of standardization efforts that did not achieve the required level of harmonization, and the bias in the measurement results of the various IVD-MPs remained excessive. The reasons for these failures can be found in various elements of the calibration hierarchy including: a) an unclear definition of the measurand, b) differences in selectivity of the IVD-MPs, c) issues with the commutability characteristics of secondary CRM, d) inconsistencies in handling of CRMs to prepare calibrators, and e) lack of adoption and implementation by the IVD manufacturers [10]. These past experiences teach us the importance of a good preparation phase for each standardization and harmonization project.[1] During this phase, the current disagreement among the IVD-MPs, including a candidate RMP if applicable, should be properly evaluated, including potential differences in non-selectivity. In addition, the commutability of various prototype reference materials should be assessed to find the most suitable production process for secondary CRMs.

Reference materials, reference measurement procedures, and reference measurement services

Metrological traceability of medical laboratory results is crucial to ensure global comparability, reliability, and meaningful interpretation in medical decision-making. Metrological traceability is established through structured

1 In the context of this paper, standardization describes an approach obtaining result equivalence by implementing metrological traceability to SI, while harmonization is related to an approach that permits to achieve equivalent results, even if non-SI traceable.

calibration hierarchies, in which CRMs, RMPs, and RMSs play crucial roles (Figure 1).

The development of CRMs, especially secondary commutable matrix materials targeting complex analytes such as proteins, is particularly demanding. Accurate determination of concentration in biologically complex matrices requires multiplexed approaches to achieve high precision and low MU. Commutability – defined as the agreement of analyte behaviour in both the CRM and clinical samples when tested with different IVD-MPs – is a critical criterion for JCTLM listing of secondary CRMs (m.3 in Figure 1) [11]. Demonstrating commutability necessitates complex interlaboratory studies, appropriate clinical sample panels, and rigorous statistical analysis (see section 'Commutability: Ten Years of IFCC Working Group Activity' below). Furthermore, when a CRM for a given measurand already exists in the JCTLM database, an extent-of-equivalence assessment is required to verify the interchangeability of the CRMs to avoid introducing bias [12].

RMPs are at a higher metrological order within calibration hierarchies and are used to assign values to CRMs and calibrators. According to ISO 15193:2009, RMPs must meet stringent criteria, including documented performance for metrological traceability of any calibrants, trueness, MU, interferences, selectivity for the defined measurand, sensitivity, measuring interval, and limits of detection [13]. Peer-reviewed publications describing RMPs are required [14]. Candidate RMPs must also be critically compared for the extent of equivalence with existing JCTLM-listed RMPs [15]. Establishing an RMP is time-consuming and methodologically complex, requiring both fundamental metrological expertise and robust implementation protocols.

RMSs – originating from national metrology institutes, qualified government/academic institutions, and IVD manufacturers – form the backbone for implementing and disseminating established metrological traceability structures. These services must be carried out under strict quality systems that conform to ISO 17025 and ISO 15195 [16, 17]. Challenges facing laboratories offering RMS include ongoing investment in infrastructure and personnel, and maintaining method performance after technical modifications (e.g., liquid chromatography-tandem mass spectrometry parameters or gradient conditions). Such modifications necessitate rigorous and continuous method validation and may represent causes of non-compliance identified during the JCTLM review process. Additionally, the growing demand for CRMs is accompanied by concerns over limited global availability, restrictive import/export regulations, and unequal resource allocation. A structural imbalance is evident: while many manufacturer-operated RMSs support only internal systems, academic laboratories are frequently overextended and unable to meet the growing global demand for services [18, 19]. At the same time, there is an increasing need for a broader portfolio of validated RMPs in the JCTLM database that can be implemented by additional laboratories to expand RMS capacity and improve global accessibility.

Ensuring equivalent results from IVD-MPs in laboratory medicine relies on continuous innovation and coordination in CRM and RMP development, as well as equitable and sustainable access to RMSs. Addressing technical challenges

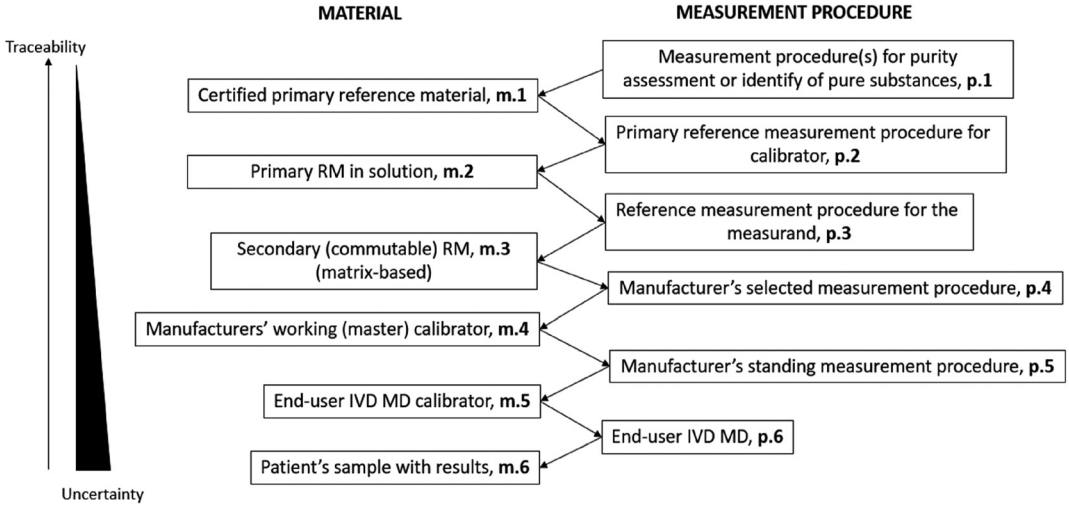

Figure 1: Metrological traceability/calibration hierarchy as described in ISO 17511:2020 standard (8). RM, reference material; IVD-MD, *in vitro* diagnostic medical device.

such as commutability assessment, full method validation, regulatory alignment, and effective knowledge dissemination is essential for broader inclusion in the JCTLM database and for advancing the harmonization of clinical measurements worldwide.

The role of professional bodies: IFCC projects with an immediate effect on clinical practice

The mission of the IFCC Scientific Division is to advance the science and application of clinical chemistry and laboratory medicine. Prioritization is given to diagnostic test-care pathways with clinical gaps. As global data exchange of medical test results is now required in some current legislation (such as the European Health Data Space), a primary focus remains on implementing the metrological traceability concept by establishing CRMs, RMPs, and RMSs in task-oriented working groups or theme-oriented committees. Activities are conducted in cooperation with other IFCC divisions/parties, clinical societies, relevant national and international organizations, and interested stakeholders of the test-treatment pathways. Recently, the added value of advanced technologies, artificial intelligence, and machine learning-based algorithms and predictive models, as well as integrated diagnostics, has also been included.

Recent publications for prioritized clinically relevant peptide- and protein-based tests, such as parathyroid hormone, cardiac troponin I, and hemoglobin A_2 [20–22], and small molecules, including immunosuppressive drugs [23], underscore the need to enhance the comparability of clinical sample results for caregivers and patients. However, funding is limited, and establishing endorsed CRMs, RMPs, and RMSs is a lengthy process. Significant challenges include the heterogeneity of peptide/protein measurands, leading to varying selectivity and cross-reactivity; non-comparability in immunoassay test results; and associated costs. The current state of play of immunoassay-based IVD-MDs remains confusing for caregivers, especially given the lack of adequate CRMs, RMPs, and a functioning network of RMSs.

What is the role of EQA in assessing metrological traceability?

Two critical presuppositions must be fulfilled to assess metrological traceability through EQA programs: 1) the EQA material must be commutable [24], and 2) the target value should be set by an RMP or be traceable to a commutable CRM [25]. Running a “commutable EQA scheme” can be more expensive and more difficult than running ordinary schemes with non-commutable control materials. Therefore, providing a few “high-quality surveys” each year that are fit for assessing metrological traceability is preferred to offering many surveys that are often of poor quality. Such “high-quality” EQA schemes can, for example, be run once a year. The national EQA providers must educate participants and the accreditation body on how to evaluate reports from different types of EQA schemes.

EQA programs that monitor daily patient medians can serve as a supplement to sample-based EQA programs and even replace some if they lack suitable EQA materials [26]. EQA programs with patient medians can monitor equivalence between IVD-MPs. However, assessing which IVD-MP best aligns with metrological traceability requires EQA schemes that use commutable materials and target values assigned by RMPs.

Challenges for IVD manufacturers in meeting different regulatory requirements for traceability in the international market

Many quantitative IVD-MPs currently in use were developed decades ago, when only a limited number of CRMs and RMPs were available. Consequently, IVD manufacturers established calibration hierarchies based on in-house reference standards, leading to variability in results among IVD-MPs from different manufacturers when measuring the same measurand. Recent efforts to expand the availability of CRMs and RMPs have supported greater harmonization of patient sample results. However, implementation is complicated by regional-specific adaptations, such as national standards (e.g., China GB/T 21415, based on ISO 17511) and regulatory pathways based on predicate devices (e.g., in the United States). Such regional variations influence IVD manufacturers’ calibration strategies and contribute to persistent variability in inter-IVD-MP results. Despite the global progress in developing reference measurement systems, the lack of uniform regulatory expectations continues to impede the establishment of a universally applicable calibration hierarchy. Achieving consistent clinical interpretation across IVD-MPs will require greater international alignment on traceability requirements and the adoption of standardized metrological frameworks.

Describing an assay as 'traceable' is not enough to ensure the quality of laboratory measurements

Implementing traceability of IVD-MP calibration to metrologically higher-order references does not automatically ensure equivalence of results from different IVD-MPs, but if conducted correctly, it should work. Many stumbling blocks still hinder the practical implementation of metrological traceability concepts, making them slow, variable, and sometimes inadequate or oversimplified [10]. Traceability is often declared but not consistently adhered to and/or correctly implemented.

Unsatisfactory harmonization can be attributed to several reasons. Non-commutability of CRMs is a significant issue that frequently prevents achieving IVD-MP harmonization. In addition to the need for suitable CRMs as common calibrators, it is essential to establish an unequivocal definition of the measurand as the quantity intended to be measured for the clinical application of the test. The concept of a reference measurement system is valid only if the higher-order measurement procedures and corresponding IVD-MPs have similar selectivity for the measurand [27]. If (some) IVD-MPs exhibit poor selectivity for the measurand as defined by consensus, a harmonizing recalibration is impossible. The IVD-MP(s) in question should be either re-engineered by the manufacturer to improve the selectivity demonstrated due to their non-selectivity in the analytical principle, or the consequent impossibility of standardization.

The metrology approach theoretically allows multiple traceability schemes when available and leaves it to each IVD manufacturer to develop and validate the calibration hierarchy. However, unless the available higher-order references are appropriately compared and shown to be unbiased with respect to each other, two or more "metrologically legitimate" traceability hierarchies can be constructed for some measurands, and each is believed to produce "unbiased values" that may not be equivalent but are nevertheless metrologically acceptable. The JCTLM requires demonstration of the extent of equivalence to an existing higher-order reference when a new candidate reference (CRM or RMP) is characterized, to verify the suitability of the old and newly proposed references and avoid introducing bias in the calibration hierarchies of commercially available IVD-MPs [28].

Commutability: 10 years of IFCC working group activity

Commutability of secondary CRMs with clinical samples is a crucial property when these materials are used as higher-order calibrators for end-user medical laboratory IVD-MPs. Similarly, commutability is a crucial property for EQA samples when evaluating the trueness or equivalence of results. The IFCC working group (WG) began addressing commutability in metrological traceability in 2013. At that time, the Clinical and Laboratory Standards Institute (CLSI) had published EP14, 2nd edition: Evaluation of Matrix Effects, while in 2014, it published EP14, 3rd edition: Evaluation of Commutability of Processed Samples. These guidelines had limitations as the commutability criterion was based on the standard deviation of the measurement procedures being evaluated; the commutability assessment did not account for the selectivity of the measurement procedures; and it did not consider MU in the measured values of the materials being evaluated.

The IFCC WG has developed a series of peer-reviewed publications with recommendations for assessing the commutability of CRMs, new experimental designs to evaluate commutability [29, 30], and a criterion for commutability of a CRM based on the maximum allowable MU of medical laboratory test results [31]. In addition, clarification of which calibrators in a calibration hierarchy need to be commutable with clinical samples, correction for the non-commutability of a matrix-based CRM used in a calibration hierarchy, assessing commutability of a replacement batch of a CRM, assessing commutability of a CRM for use with an IVD-MP not included in the original commutability assessment, and an approach for determining commutability of EQA samples that considers non-selectivity were developed. All the IFCC recommendations are listed on the website: https://ifcc.org/ifcc-scientific-division/sd-working-groups/wg-cmt/.

The COMET (manufacturing of COMmutable calibrators and quality control materials for standardisation and post-markET surveillance of IVD tests) project

The paucity of CRMs and RMPs (spanning small molecules to proteins and nucleic acids) often prevents IVD manufacturers from complying with regulations requiring the implementation of metrological traceability to higher-order references. To help the IVD manufacturers meet the requirements of the European Union IVD Regulation 2017/746, the COMET project was developed. Metrological traceability will be achieved by establishing the necessary metrological infrastructure to provide cost-effective calibration services to IVD manufacturers. This will allow us to properly

calibrate IVD-MPs and monitor their performance more effectively. New CRMs and quality control materials will be produced for IVD-MPs to implement standardization and post-market surveillance activities. It is expected that the COMET project will identify common causes of poor commutability in CRMs and enhance their manufacturing processes by developing more efficient procedures for conducting commutability studies.

Challenges in adopting and maintaining new standards

By continuously innovating, proactively adapting workflows, and leveraging their collective strengths, laboratories can strengthen quality and efficiency even as demands and complexity rise. When all pillars operate cohesively, the reference measurement system not only withstands future challenges but also advances diagnostic excellence. Examples of how the system is adapting and the challenges it faces are provided in the following section, where cases involving measurements of thyroid hormones and tumour markers are discussed.

Establishing metrological traceability for the two most frequently performed thyroid hormone tests required the development of dedicated reference measurement systems, the strategy for these being based on ISO 17511 [32]. For free thyroxine (FT4), the development of a conventional secondary RMP, endorsed by the IFCC, led to its listing in the JCTLM database. For thyroid-stimulating hormone (TSH), due to its complex molecular nature, a harmonisation process was validated, always in accordance with ISO 17511:2020. A proof-of-concept for the implementation of both reference systems was published in 2016–17. Through the activities of the IFCC Committee for Standardisation of Thyroid Function Tests, a system is in place to ensure the sustainability of TSH harmonization. For FT4, a network of reference laboratories is operational. Although the agreement between TSH and FT4 assays has improved, formal implementation has, however, not yet been achieved [33]. The slow progress is associated with several factors: limited mechanisms to enforce implementation (despite the inclusion in legislation); lack of clinical demand as well as financial considerations by the IVD manufacturers; variations in global regulatory frameworks that increase both the logistic and administrative burden of implementation; coordination of activities by volunteers (inherent to the coordination via an IFCC committee); and the growing administrative demands related to the collection, processing, and distribution of dedicated clinical specimens. The anticipated change in FT4 values following standardization is considered less of a challenge, as IVD manufacturers and medical laboratories have established standardized communication protocols.

Tumor marker testing constitutes an essential part of the medical laboratory portfolio. Most tumor markers were discovered and developed decades ago and have been available for clinical use ever since. However, results from many tumor marker assays are not harmonized, and results obtained with different assays can vary significantly. Established in 2024, the IFCC WG on Tumor Marker Harmonization (WG-TMH) became a joint WG with the International Society of Oncology and Biomarkers in 2025. The WG-TMH first activity was to investigate the current status of harmonization for six commonly used tumor markers [34]. The results from international EQA programs indicated that results for carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 15-3, CA19-9, and CA125 were not sufficiently harmonized. The feasibility of harmonization through recalibration was investigated and it was indicated that improvement of CEA and CA15-3 harmonization was feasible [35]. A verification study in one laboratory confirmed that the average difference between assays for these four biomarkers could be reduced by recalibration with a bias correction derived from individual patient sample results. However, relevant differences in results specific to individual samples remained. Currently, new CRMs for CEA and CA15-3 are being developed. Furthermore, to address the differences when various assays are used for tumor markers, a questionnaire was designed to gather information about how tumor marker results are reported. We envision that the results of the questionnaire and the method comparison studies will inform the clinical reporting of tumor markers, highlighting the more relevant differences between IVD-MPs.

Conclusions

The key discussions from the JCTLM workshop centered on the importance of metrological traceability to ensure the concept of “accurate results for patient care” (Figure 2). Figure 2 also shows that accrediting bodies audit EQA-organisers on compliance with specific ISO standards. EQA organisers verify trueness when they use adequate (commutable and value-assigned) EQA tools; they check end results for fitness for purpose, but do not have a role in test standardisation. Laboratory professionals (not clinicians) are responsible for creating test menus, designing medical labs, and equipping them with equipment from selected vendors. Laboratorians may consult clinicians, but they are the diagnostic leads and decision makers.

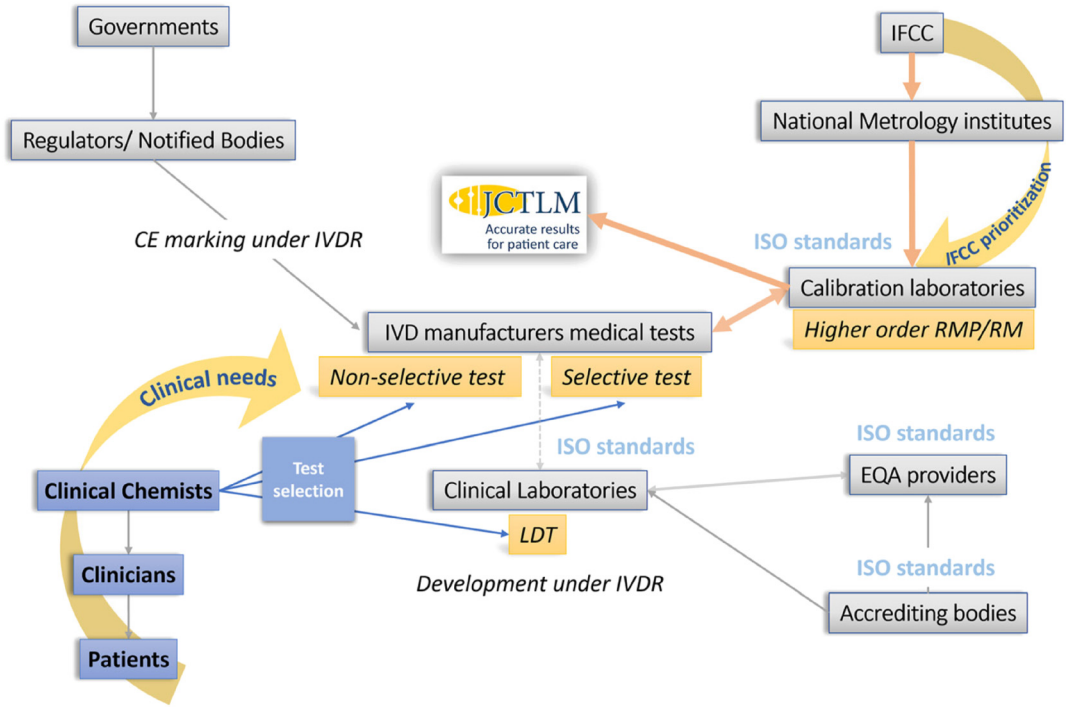

Figure 2: Collaboration among stakeholders to ensure metrologically traceable and thus accurate results from IVD-MPs used by medical laboratories (specified for the European Union under the IVDR 2017/746). Adapted from van der Helm M. P., et al. [36]. CE, Conformité Européenne; LDT, laboratory developed test; IVDR, in vitro diagnostic regulation 2017/746; RMP, reference measurement procedure; EQA, External Quality Assessment; RM, reference material. Blue arrows demonstrate the inputs for clinical needs and test selection by lab professionals, caregivers (clinicians), and patients. Orange arrows demonstrate the relationships among IFCC, NMIs, and calibration labs, and that deliverables/output must be endorsed by JCTLM and/or adopted by the IVD industry. Grey arrows indicate that IVD manufacturers should meet regulatory requirements before market entry; in the right-hand quadrant, independent supervisors (EQA, accreditation bodies) of medical laboratories are mentioned.

The lack of harmonized results can lead to confusion, treatment delays, errors in medical decisions, and increased healthcare costs. There are still assays in common use that lack metrological traceability because they lack CRMs, RMPs, and/or RMSs. In some cases, measurands have multiple calibration hierarchies, potentially producing different results for the same patient sample. Producing and maintaining reference measurement system components is complex and expensive. Non-selectivity of some IVD-MPs limits the ability to establish equivalence between IVD-MPs. There are multiple regulatory frameworks and requirements that IVD manufacturers must meet worldwide. There is a vital role for EQA providers to assess the agreement status of results across different IVD-MPs and identify any changes in their equivalence. However, EQA materials must be commutable with clinical samples for each of the examined IVD-MDs for results to reflect the status of harmonization of clinical sample results [37]. The future will need leadership and cooperation between bodies such as JCTLM, IFCC, and IVD manufacturers.

Research ethics: Not applicable.
Informed consent: Not applicable.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission. CRediT Statement: Conceptualisation, Methodology: MP, TB. Writing (Original draft, review and editing): All. Supervision, Project Admin: RJ, MP, TB.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

References

1. The Joint Committee for Traceability in Laboratory Medicine (JCTLM). https://jctlm.org/about-us/ [Accessed February 2026].
2. Plebani M. Harmonization in laboratory medicine: the complete picture. Clin Chem Lab Med 2013;51:741–51.
3. Tuttle KR, Bebiak J, Brown K, Campbell C, Dighe A, Hyashi L, et al. Patient perspectives and involvement in precision medicine research. Kidney Int 2021;99:511–4.
4. Horowitz CR, Robinson M, Seifer S. Community-based participatory research from the margin to the mainstream are researchers prepared? Circulation 2009;119:2633–42.

5. Van Schrojenstein Lantman M, Van Berkel M, Kuijper P, Langelaan M, Brouwer N, Thelen M. Clinical decision-making suffers from inequivalent measurement results and inadequate reference intervals. Clin Chem 2024;70:1383–92.
6. Farrell CJ, Jones G, Shepherd S, Tran D, Badrick T. Mass or molar units? Australia's drug problem persists. Pathology 2023;55:865–7.
7. Jones GRD, Delatour V, Badrick T. Metrological traceability and clinical traceability of laboratory results – the role of commutability in external quality assurance. Clin Chem Lab Med 2022;60:669–74.
8. ISO 17511:2020. In vitro diagnostic medical devices – requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples. Geneva: International Organization for Standardization; 2020.
9. Schimmel H, Zegers I. Performance criteria for reference measurement procedures and reference materials. Clin Chem Lab Med 2015;53: 899–904.
10. Panteghini M. An improved implementation of metrological traceability concepts is needed to benefit from standardization of laboratory results. Clin Chem Lab Med 2025;63:270–8.
11. ISO. ISO 15194:2009 – in vitro diagnostic medical devices – measurement of quantities in samples of biological origin – requirements for certified reference materials and the content of supporting documentation. ISO. Geneva: International Organization for Standardization; 2009.
12. Beasley-Green A, Camara J, Wood E, Heckert N. Extent-of-equivalence assessment of certified reference materials for albumin and creatinine in human urine. Gaithersburg: NIST; 2025. Available from: https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.260-262.pdf.
13. ISO 15193:2009 – in vitro diagnostic medical devices – requirements for the content and presentation of reference measurement procedures. ISO. Geneva: International Organization for Standardization; 2009.
14. Panteghini M, Wielgosz R. Keeping pace with patient safety by developing and qualifying higher-order reference measurement procedures for laboratory measurement standardization. Clin Chem Lab Med 2026;64:1–3.
15. Joint Committee for Traceability in Laboratory Medicine. Demonstrating the extent-of-equivalence between multiple reference measurement methods/procedures (RMM/Ps) for the same measurand. JCTLM DBWG P-04B 2023/02/01. https://www.bipm.org/en/committees/jc/jctlm/wg/jctlm-dbwg/publications [Accessed February 2026].
16. ISO/IEC 17025:2017 – general requirements for the competence of testing and calibration laboratories. ISO. Geneva: International Organization for Standardization; 2017.
17. ISO 15195:2018. Laboratory medicine – requirements for the competence of calibration laboratories using reference measurement procedures. ISO. Geneva: International Organization for Standardization; 2018.
18. Greaves RF, Mackay LG. The development of reference measurement procedures to establish metrological traceability. Clin Chem Lab Med 2023;61:1887–9.
19. Seger C, Kessler A, Taibon J. Establishing metrological traceability for small molecule measurands in laboratory medicine. Clin Chem Lab Med 2023;61:1890–901.
20. Cavalier E. Determination of parathyroid hormone: from radioimmunoassay to LCMS/MS. Clin Chem Lab Med 2023;61:946–53.
21. Asicioglu M, Swart C, Saban E, Yurek E, Karaguler NG, Oztug M. Comparative evaluation of peptide vs. protein-based calibration for quantification of cardiac troponin I using ID-LC-MS/MS. Clin Chem Lab Med 2025;63:1016–30.
22. Mosca A, Paleari R, Harteveld CL. A roadmap for the standardization of hemoglobin A2. Clin Chim Acta 2021;512:185–90.
23. Taibon J, van Rooij M, Schmid R, Singh N, Albrecht E, Anne Wright J, et al. An isotope dilution LC-MS/MS based candidate reference method for the quantification of cyclosporine A, tacrolimus, sirolimus and everolimus in human whole blood. Clin Biochem 2020; 82:73–84.
24. Sandberg S, Fauskanger P, Johansen JV, Keller T, Budd J, Greenberg N, et al. Recommendations for setting a criterion and assessing commutability of sample materials used in external quality assessment/proficiency testing schemes. Clin Chem 2023; 69:1227–37.
25. Braga F, Pasqualetti S, Panteghini M. The role of external quality assessment in the verification of in vitro medical diagnostics in the traceability era. Clin Biochem 2018;57:23–8.
26. Solsvik AE, Fauskanger P, Stavelin A, Rønneseth E, Sandberg S. A new international patient-based external quality assessment program to monitor harmonization and standardization efforts. Clin Chem 2025;71: 1257–68.
27. Panteghini M, Krintus M. Establishing, evaluating and monitoring analytical quality in the traceability era. Crit Rev Clin Lab Sci 2025;62: 148–81.
28. Miller WG, Panteghini M, Wielgosz R. Implementing metrological traceability of C-reactive protein measurements: consensus summary from the joint committee for traceability in laboratory medicine workshop. Clin Chem Lab Med 2023;61:1558–60.
29. Nilsson G, Budd JR, Greenberg N, Delatour V, Rej R, Panteghini M, et al. IFCC working group recommendations for assessing commutability part 2: using the difference in bias between a reference material and clinical samples. Clin Chem 2018;64:455–64.
30. Budd JR, Weykamp C, Rej R, MacKenzie F, Ceriotti F, Greenberg N, et al. IFCC working group recommendations for assessing commutability part 3: using the calibration effectiveness of a reference material. Clin Chem 2018;64:465–74.
31. Miller WG, Keller T, Budd J, Johansen JV, Panteghini M, Greenberg N, et al. Recommendations for setting a criterion for assessing commutability of secondary calibrator certified reference materials. Clin Chem 2023;69:966–75.
32. Cowper B, Lyle AN, Vesper HW, Van Uytfanghe K, Burns C. Standardisation and harmonisation of thyroid-stimulating hormone measurements: historical, current, and future perspectives. Clin Chem Lab Med 2024;62:824–9.
33. Ribera A, Sugahara O, Buchannan T, Vazquez N, Lyle AN, Zhang L, et al. Evaluation of the current state of thyroid hormone testing in human serum – results of the free thyroxine and thyrotropin interlaboratory comparison study. Thyroid 2025;35:471–84.
34. Van Rossum HH, Holdenrieder S, Ballieux BEPB, Badrick TC, Yun YM, Zhang C, et al. Investigating the current harmonization status of tumor markers using global external quality assessment programs: a feasibility study. Clin Chem 2024;70:669–79.
35. Van Rossum HH, Holdenrieder S, Yun YM, Patel D, Thelen M, Song J, et al. External quality assessment-based tumor marker harmonization simulation; insights in achievable harmonization for CA 15-3 and CEA. Clin Chem Lab Med 2025;63:410–21.
36. Van der Helm MP, Ruhaak LR, Cobbaert CM. Mass spectrometry based precision diagnostics: on the cusp of selective testing. Clin Chem Lab Med 2026;64:539–54.
37. Miller WG, Jones GRD, Horowitz GL, Weykamp C. Proficiency testing/external quality assessment: current challenges and future directions. Clin Chem 2011;57:1670–80.