

## Biennial activity report from Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Italy

**Organization:** Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

**JCTLM Member status:** JCTLM Stakeholder Member

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**Period covered:** 2022 – 2023

### Major achievements in supporting standardization in laboratory medicine

CIRME was created in 2006 with the scope to promote standardization in the field of the Laboratory Medicine through the application of the metrological traceability concepts, with the main objective of improving the clinical value of laboratory information and permitting a common global approach to diseases. The 'CIRME traceability revolution manifesto', launched in 2014 (available in <https://sites.unimi.it/cirme/public/UploadAttach/Pubblications%202018/Foreword.pdf>), summarizes the main points that are object of attention by CIRME. One can find the most important contributions displayed as '**CIRME cardinal points for implementing traceability in Laboratory Medicine**' in the CIRME website homepage (<https://sites.unimi.it/cirme/>).

CIRME has a reference laboratory for the following measurands: ALT, ALP, AST, CK, GGT, LDH, Glucose, HbA1c, by using the reference procedures listed in the JCTLM database, working to the characterization and certification of reference materials and assessment of their commutability, validation of metrological traceability of commercial IVD measuring systems, and value targeting of EQAS materials.

**Recent activities related to the validation and verification of IVD measuring systems** are described in the following papers published in peer-reviewed journals:

1. Pasqualetti S, Carnevale A, Dolci A, Panteghini M. A step towards optimal efficiency of HbA1c measurement as a first-line laboratory test: the TOP-HOLE (Towards OPTimal glycoHemOgLobin tEsting) project. *Clin Chem Lab Med.* 2022 Jan 18;60(3):441-450.
2. Capoferri A, Aloisio E, Pasqualetti S, Panteghini M. More about the random uncertainty of photometric determination of hemolysis index on the Abbott Alinity c platform. *Clin Biochem.* 2022 Jul-Aug;105-106:94-95.
3. Braga F, Pasqualetti S, Frusciante E, Borrillo F, Chibireva M, Panteghini M. Harmonization Status of Serum Ferritin Measurements and Implications for Use as Marker of Iron-Related Disorders. *Clin Chem.* 2022 Sep 1;68(9):1202-1210.
4. Bianchi G, Colombo G, Pasqualetti S, Panteghini M. Alignment of the new generation of Abbott Alinity  $\gamma$ -glutamyltransferase assay to the IFCC reference measurement system should be improved. *Clin Chem Lab Med.* 2022 Aug 9;60(10):e228-e231.
5. Braga F, Pasqualetti S, Borrillo F, Capoferri A, Chibireva M, Rovegno L, Panteghini M. Definition and application of performance specifications for measurement uncertainty of 23 common laboratory tests: linking theory to daily practice. *Clin Chem Lab Med.* 2022 Oct 26;61(2):213-223.

6. Borrillo F, Pasqualetti S, Panteghini M. Measurement Uncertainty of Thyroid Function Tests on a Chemiluminescent Microparticle Immunoassay System Needs to Be Improved. *J Appl Lab Med*. 2023 Mar 6;8(2):420-422.
7. Rovegno L, Civera E, Infusino I, Panteghini M. State of the art of measurement uncertainty of serum ferritin. *Clin Chem Lab Med*. 2023 Jul 20. doi: 10.1515/cclm-2023-0711. Epub ahead of print.
8. Bianchi G, Frusciante E, Colombo G, Infusino I, Aloisio E, Panteghini M. Validation of metrological traceability of the new generation of Abbott Alinity alkaline phosphatase assay. *Clin Chem Lab Med*. 2023 Aug 25. doi: 10.1515/cclm-2023-0553. Epub ahead of print.
9. Borrillo F, Capoferri A, Rovegno L, Panteghini M. Closed analyser lids do not reduce the measurement uncertainty of serum total carbon dioxide. *Ann Clin Biochem*. 2023 Nov 18:45632231216598. doi: 10.1177/00045632231216598. Epub ahead of print.

In this two-year period CIRME published the results of the **APERTURE**, a project for establishing Analytical Performance Specifications for Measurement Uncertainty of 44 common laboratory measurands using models recommended during the Milan Strategic Conference held in 2014 under the auspices of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), JRC Institute of Reference Materials and Methods (IRMM), and CIRME. Both minimum and desirable quality levels of analytical performance specifications (APS) for standard measurement uncertainty (MU) of clinical samples were defined by using information obtained from available literature preliminarily checked in terms of robustness. The following publications have summarized the model allocation together with APS for standard MU on clinical samples for the selected measurands to be used in laboratory practice to validate MU of employed IVD-MDs and to ascertain if estimated MU for a given laboratory result may significantly affect its interpretation:

1. Braga F, Panteghini M. Performance specifications for measurement uncertainty of common biochemical measurands according to Milan models. *Clin Chem Lab Med* 2021;59:1362–8.
2. Braga F, Pasqualetti S, Borrillo F, Capoferri A, Chibireva M, Rovegno L, et al. Definition and application of performance specifications for measurement uncertainty of 23 common laboratory tests: linking theory to daily practice. *Clin Chem Lab Med* 2023;61:213–23.
3. Borrillo F, Pasqualetti S, Panteghini M. Measurement uncertainty of thyroid function tests on a chemiluminescent microparticle immunoassay system needs to be improved. *J Appl Lab Med* 2023;8:420–2.
4. Cattaneo D, Panteghini M. Analytical performance specifications for measurement uncertainty in therapeutic monitoring of immunosuppressive drugs. *Clin Chem Lab Med*. 2023 Oct 20. doi: 10.1515/cclm-2023-1063. Epub ahead of print.
5. Panteghini M. A Comment About Analytical Performance Specifications for the Combined Measurement Uncertainty Budget in the Implementation of Metrological Traceability of Parathyroid Hormone. *Clin Chem* 2023; in press.

APERTURE outcomes have been summarized in: Panteghini M. Redesigning the surveillance of in vitro diagnostic medical devices and of medical laboratory performance by quality control in the traceability era. *Clin Chem Lab Med*. 2022 Dec 22;61(5):759-768.

### Promoting traceability in laboratory medicine

CIRME has promoted traceability in laboratory medicine by publishing/contributing to the following **papers on peer-reviewed journals**:

1. Badrick T, Miller WG, Panteghini M, Delatour V, Berghall H, MacKenzie F, Jones G. Interpreting EQA-Understanding Why Commutability of Materials Matters. *Clin Chem*. 2022 Mar 31;68(4):494-500.
2. Panteghini M. The simple reproducibility of a measurement result does not equal its overall measurement uncertainty. *Clin Chem Lab Med*. 2022 Jul 11;60(10):e221-e222.
3. Badrick T, Jones G, Miller WG, Panteghini M, Quintenz A, Sandberg S, Spannagl M. Differences between Educational and Regulatory External Quality Assurance/Proficiency Testing Schemes. *Clin Chem*. 2022 Oct 6;68(10):1238-1244.
4. Miller WG, Greenberg N, Panteghini M, Budd JR, Johansen JV. Guidance on Which Calibrators in a Metrologically Traceable Calibration Hierarchy Must Be Commutable with Clinical Samples. *Clin Chem*. 2023 Mar 1;69(3):228-238.
5. Krintus M, Panteghini M. Judging the clinical suitability of analytical performance of cardiac troponin assays. *Clin Chem Lab Med*. 2023 Feb 20;61(5):801-810.
6. Panteghini M. Evaluating and monitoring analytical quality by internal quality control. *Clin Biochem*. 2023 Aug;118:110594.
7. Miller WG, Keller T, Budd J, Johansen JV, Panteghini M, Greenberg N, Delatour V, Ceriotti F, Deprez L, Rej R, Camara JE, MacKenzie F, Lyle AN, van der Hagen E, Burns C, Fauskanger P, Sandberg S; IFCC Working Group on Commutability in Metrological Traceability. Recommendations for Setting a Criterion for Assessing Commutability of Secondary Calibrator Certified Reference Materials. *Clin Chem*. 2023 Sep 1;69(9):966-975.
8. Panteghini M. Documenting and validating metrological traceability of serum alanine aminotransferase measurements: a priority for medical laboratory community for providing high quality service in hepatology. *Clin Chem Lab Med*. 2023 Sep 13. doi: 10.1515/cclm-2023-0900. Epub ahead of print.
9. Sandberg S, Fauskanger P, Johansen JV, Keller T, Budd J, Greenberg N, Rej R, Panteghini M, Delatour V, Ceriotti F, Deprez L, Camara JE, MacKenzie F, Lyle AN, van der Hagen E, Burns C, Greg Miller W; IFCC Working Group on Commutability in Metrological Traceability. Recommendations for Setting a Criterion and Assessing Commutability of Sample Materials Used in External Quality Assessment/Proficiency Testing Schemes. *Clin Chem*. 2023 Nov 2;69(11):1227-1237.
10. Çubukçu HC, Vanstapel F, Thelen M, van Schrojenstein Lantman M, Bernabeu-Andreu FA, Meško Brguljan P, Milinkovic N, Linko S, Panteghini M, Boursier G. APS calculator: a data-driven tool for setting outcome-based analytical performance specifications for measurement uncertainty using specific clinical requirements and population data. *Clin Chem Lab Med*. 2023 Nov 17. doi: 10.1515/cclm-2023-0740. Epub ahead of print.

CIRME has organized three **international meetings**:

**14th International CIRME Meeting** on 'Implementation of metrological traceability in laboratory medicine: where we are and what is missing (November 30, 2022 – Milano, Italy).

In cooperation with **JCTLM Workshop** on Developments in reference measurement systems for C-reactive protein and the importance of maintaining currently used clinical decision-making criteria (December 1, 2022 – Milano, Italy). As outcomes of the meeting the following papers were published:

1. Panteghini M. Developments in reference measurement systems for C-reactive protein and the importance of maintaining currently used clinical decision-making criteria. *Clin Chem Lab Med*. 2023 Jun 5;61(9):1537-1539.

2. 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 May 30;61(9):1558-1560.
3. Borrillo F, Panteghini M. Current performance of C-reactive protein determination and derivation of quality specifications for its measurement uncertainty. Clin Chem Lab Med. 2023 Feb 13;61(9):1552-1557.
4. Aloisio E, Colombo G, Dolci A, Panteghini M. C-reactive protein and clinical outcome in COVID-19 patients: the importance of harmonized measurements. Clin Chem Lab Med. 2023 Apr 11;61(9):1546-1551.

**5th CELME (Cutting Edge of Laboratory Medicine in Europe) Symposium** “Analytical performance specifications: moving from models to practical recommendations” (Prague, Czech Republic, October 13-14, 2023).

The following **lecturers on traceability at international conferences** were done by CIRME officers:

1. Judging the clinical suitability of analytical performance of cardiac troponin assays. “Medical test performance should keep pace with evolution in science and clinical guidelines: state of play and challenges for cardiovascular disease tests in this era of Precision Medicine.” The IFCC-SD and the Greek Society of Clinical Chemistry symposium (Herakleion – Creta Greece, October 2, 2022) – M. Panteghini
2. Judging the clinical suitability of analytical performance of cardiac troponin assays. 20th National Congress of Polish Society of Laboratory Diagnostics (Kielce, Poland, October 19-22, 2022) – M. Panteghini
3. Implementing traceability in laboratory medicine: a not easy task. 14th International Scientific Meeting “Implementation of metrological traceability in laboratory medicine: where we are and what is missing” (Milan, Italy, November 30, 2022) – M. Panteghini
4. The JCTLM Task Force on Reference Measurement Systems Implementation: mission and first results. 14th International Scientific Meeting “Implementation of metrological traceability in laboratory medicine: where we are and what is missing” (Milan, Italy, November 30, 2022) – M. Panteghini
5. The irreplaceable contribution of measurement uncertainty to the standardization process. 14th International Scientific Meeting “Implementation of metrological traceability in laboratory medicine: where we are and what is missing” (Milan, Italy, November 30, 2022) – S. Pasqualetti
6. How to correctly validate the traceability of an IVD measuring system: practical examples. 14th International Scientific Meeting “Implementation of metrological traceability in laboratory medicine: where we are and what is missing” (Milan, Italy, November 30, 2022) – E. Aloisio
7. Current performance of CRP determination and derivation of quality specifications for its measurement uncertainty. JCTLM Workshop on Developments in reference measurement systems for C-reactive protein and the importance of maintaining currently used clinical decision-making criteria (December 1, 2022 – Milano, Italy) – F. Borrillo
8. Evaluation and monitoring of analytical quality. 25th International Congress of Clinical Chemistry and Laboratory Medicine (Rome, Italy, May 23, 2023) – M. Panteghini
9. Harmonization in the analytical phase. 25th International Congress of Clinical Chemistry and Laboratory Medicine (Rome, Italy, May 23, 2023) – M. Panteghini
10. Analytical quality. The International Conference of Laboratory Medicine: 30 years later (Padova, Italy, September 20, 2023) – M. Panteghini

11. What the Milan conference has taught us about APS model definition and measurand allocation. 5th CELME Symposium “Analytical performance specifications (APS): moving from models to practical recommendations” (Prague, Czech Republic, October 12, 2023) – M. Panteghini
12. State-of-the-art model: How to define the highest level of analytical performance technically achievable. Examples of APS. 5th CELME Symposium “Analytical performance specifications (APS): moving from models to practical recommendations” (Prague, Czech Republic, October 13, 2023) – F. Borrillo
13. APS for combined uncertainty budget in the implementation of metrological traceability. 5th CELME Symposium “Analytical performance specifications (APS): moving from models to practical recommendations” (Prague, Czech Republic, October 13, 2023) – M. Panteghini

Prof Panteghini did a **Visiting Lecturer Travel on behalf of IFCC in Argentina** in November 2022, where the following three presentations were given during the National Congress on Quality in Clinical Laboratory:

1. Conferencia: Por qué es importante conocer la incertidumbre de las mediciones en los laboratorios clínicos?
2. Estandarización de las mediciones de enzimas en el Laboratorio clínico: Navegando entre las expectativas y las barreras
3. Conferencia Prof. Dr. Daniel Mazziotta: El rol de los laboratorios que realizan procedimientos de referencia en la aplicación y validación de la trazabilidad metrológica: el caso de las enzimas.

#### **Collaborations focusing on developing/implementing reference measurement systems**

Participation of CIRME officers as member in:

1. ISO/TC 212 WG2 ‘Reference systems’
2. JCTLM WG-DB and related RTs (Enzymes and Proteins)
3. JCTLM Task Force on Reference Measurement System Implementation (Chair)
4. European Commission Expert panels in the field of medical devices
5. IFCC Committee on Traceability in Laboratory Medicine
6. IFCC WG on Commutability in Metrological Traceability
7. IFCC WG on Standardization of Troponin I
8. IFCC WG on Standardization of HbA2
9. IFCC WG on Standardization of Albumin Assay in Urine
10. IFCC WG on Pancreatic Enzymes
11. EFLM WG on Biological Variability and Task Group on Biological Variability Database
12. CLSI EP30ed2 – DDC on Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine
13. CLSI EP32 – DDC on Implementation of Metrological Traceability in Laboratory Medicine