INTERVIEWS WITH PAST EFLM PRESIDENTS AND PAST EFLM OFFICERS

Reported by Ana-Maria Šimundić, EFLM President

We are happy to introduce a new section in the EFLM newsletter – Interviews with past EFLM Presidents and senior EFLM officers. It is a way to show our appreciation and gratitude to our predecessors and colleagues who have contributed significantly to developing and promoting the Clinical Chemistry and Laboratory Medicine profession and EFLM. We want to get to know the people who have been leaders, inspiration and role models for many years and even decades. Additionally, this section has been included in the EFLM Action plan for 2021, in order respond to the needs and expectations of all EFLM members and national societies, expressed in the survey conducted in 2020. We are very much looking forward to all the interviews, and we hope you enjoy them too.

In this edition, we publish an interview with Prof. **Mauro Panteghini**, the fifth EFLM President (2014-2016) and the Scientific Coordinator of the Research Center for Metrological Traceability in Laboratory Medicine (CIRME) of the University of Milan. This year, Prof. Panteghini is a recipient of the "EFLM Award for Achievements in Advancing Laboratory Medicine in Europe - sponsored by Roche". This is a major award of the EFLM, which honors individuals who have made substantial contributions to advancing the profession of Clinical Chemistry and Laboratory Medicine in Europe and enhancing the visibility of the discipline within diagnostic and therapeutic medicine. The Award has been granted to Prof. Panteghini as a recognition for his leadership and extensive expertise in metrological traceability, standardization, and the assessment of analytical uncertainty. It will be awarded to Prof. Panteghini during the Opening Ceremony of the 24th IFCC-EFLM EuroMedLab Congress in Munich on November 28, 2021.

You have recently been awarded by the "EFLM Award for Achievements in Advancing Laboratory Medicine in Europe - sponsored by Roche". This is a major award of our Federation which has been created to recognize an individual who has made important contributions to advance the profession of Clinical Chemistry and Laboratory Medicine in Europe and to enhance the visibility of the discipline within diagnostic and therapeutic medicine. The award was motivated by your leading role and extensive expertise in metrological traceability, standardization, and the assessment of analytical uncertainty. Could you name some major achievements and milestones in that area?

In 1990's, experts on both Atlantic sides started to debate the impact that poor comparability of laboratory results may have in clouding clinicians' interpretation of reported data, potentially creating a substantive problem for patient safety. They identified the lack of metrological traceability of assay calibration to suitable standards as one of the main causes. Establishing metrological traceability of IVD measuring systems depends on some basic requirements being fulfilled. First, it is essential to establish a calibration hierarchy starting from the unequivocal definition of the measurand as the quantity subject to measurement. The assay selectivity (formerly mentioned as 'specificity') for the measurand at each level of the traceability chain is a crucial aspect and in a standardization project correlation studies should preliminarily be performed to test the relationship among commercial methods and to demonstrate the harmonization potential. Elimination of measurement bias by the applied implementation strategy enables the reliable transfer of the measurement trueness from the highest level of the metrological hierarchy to commercial calibrator values, thereby leading to unbiased results on clinical samples. Finally, an adequate estimation of all sources of measurement uncertainty (MU) should be performed.

The **first milestone** starting the "traceability era" was the publication at end of **1998** of *The In Vitro Diagnostic (IVD) Medical Devices Directive 98/79/EC*, transposed into national laws within the European Union (EU) by the end of 1999. With the aim to improve equivalence of measurement results through more structured and understood approaches for standardization, the Directive, supported by two ISO standards (17511 and 18153) describing metrological principles, asked IVD manufacturers to ensure metrological traceability of their measuring systems to higher-order references. Only IVD devices providing the CE ("Communautés Européennes") marking, indicating the compliance with the EU Directive, may be distributed on the Community market. For the first time, a directive introduced a legal background for the use of metrologically correct measuring systems in Laboratory Medicine and gave to our profession a unique role in promoting and applying these concepts to the medical setting. We should therefore recognize the remarkable role of the European Parliament in providing the basis to obtain more comparability of laboratory results and ensuring that IVDs do not compromise the health and safety of patients.

Someway unexpectedly, this new European legislation, given the globality of IVD market, had immediately a worldwide impact and an international consensus and agreement on how to implement metrological traceability was urged by all players in the field. This was the reason for the creation in **2002** of the Joint Committee on Traceability in Laboratory Medicine (JCTLM), representing the **second milestone** in the history of metrological traceability in Laboratory Medicine. In the last twenty years, the main objective of JCTLM has been to identify, through a transparent review process, reference materials and reference measurement procedures that fulfil the definition of "higher order", and laboratories offering a reference service, and made this information publicly available on a database (https://www.bipm.org/jctlm/).

In the meantime, other concepts such as commutability of calibration materials, estimate of MU, and definition of analytical performance specifications (APS) that permit to provide test results that are clinically suitable, have emerged, all contributing to correctly implementing metrological traceability. EFLM made a landmark contribution by organizing in **2014** its first Strategic Conference in which a consensus was reached in defining models for establishing APS. We can consider the Conference as the **third milestone** as it originated several important outcomes contributing to the improvement of traceability implementation.
The concept of MU in medical laboratories has also achieved a central role, moving from being considered just as a 'foe', because its calculation is requested to comply laboratory accreditation requirements, to become a 'friend', because it can be used to describe both the performance of an IVD measuring system and the laboratory itself, assuming the role of a key quality indicator. The ISO Technical Specification 20914, released in **2019**, providing a practical guidance to be applied in medical laboratory settings for the purpose of estimating MU of values produced by measuring systems, can be therefore considered the **fourth milestone** in the standardization activity.

What is the role of IVD industry in method standardization?
The EU Directive (and now the EU Regulation 2017/746) has asked IVD manufacturers to ensure metrological traceability of their measuring systems to higher-order references. Thus, the primary onus is on the manufacturers to drive traceability. Manufacturers are responsible for implementing suitable commercial systems that fulfil this requirement and individual medical laboratories should therefore rely on the manufacturers who must ensure metrological traceability of their measuring systems to the highest available hierarchical level. Better said, IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process uncertainty limits, which represent a proportion of the uncertainty budget allowed for medical laboratory results. IVD manufacturers are asked to provide end-users with technical documentation, instructions for use, and a QC material suitable for post-market surveillance of the measuring system performance, when working according to the manufacturer's indications. End-users must strictly observe these indications, as only operating in conformity with them the intended purpose of the CE marketed measurement system can be warranted, including the performance declared in terms of metrological traceability. This requires a paradigm shift in the thinking that many stakeholders, including laboratory professionals and many manufacturers, have still not perceived. If, according to the EU legislation, the manufacturer should assume total responsibility for supplying products of acceptable quality in terms of metrological traceability and MU of the measuring systems, it is no longer possible to consider separately the components of each measuring system (i.e., platform, reagents, calibrators, and control materials), which in terms of performance can only be guaranteed and certified by the manufacturer as a whole set. Any change introduced by users or third parties (for instance, the use of reagents, calibrators, or control materials from other suppliers) may significantly alter the quality of the measuring system performance, removing any responsibility from the manufacturer and depriving the system (and, consequently, the produced results) of the certification originally provided through CE marking. Particularly, IVD manufacturers are requested to provide QC materials as a qualified part of the measuring system; these materials, representing what I call the internal QC component I, should be designed by the manufacturer for daily monitoring of the measuring system alignment, with appropriate target values and acceptability range, which defines the tolerance of value deviation from the target, permitting the suitable application of test results in clinical setting. This relies on the concept that, if the metrological traceability of the measuring system to higher-order references must be granted by the manufacturer, QC materials, which are part of the whole system, should be a suitable surrogate of the employed (and declared) reference to permit routine checking of the correctness of system alignment to such reference. In practice, however, manufacturers of measuring systems commonly derive mean values of their QC materials just from replicates performed by independent laboratories using the same measuring system, with no explicitly certified quality, and frequently provide them as approximate targets, only for convenience, with no trueness claims regarding assigned values. On the other hand, information reported on QC data sheets shows that the acceptability range provided by manufacturers is usually based on the statistical dispersion of data obtained by *n* laboratories (e.g., ±2SD or ±20% of the mean value), with no relationship with clinically suitable APS.
Sometimes data from interlaboratory programs are used in the determination of validation range, with the risk to include results from laboratories working under biased analytical conditions, and quite often both mean QC values and ranges are provided only "as guide", with the recommendation that each laboratory should establish its own acceptability limits [sic]. You may easily understand the high vulnerability of this approach, adopted by manufacturers to assign QC values and define acceptability ranges, in terms of metrological traceability. Unfortunately, taking care of the metrological quality of the assigned values to offered QC materials is still not an issue for manufacturers, with very few exceptions.

You are the Scientific Coordinator of the Research Center for Metrological Traceability in Laboratory Medicine (CIRME) of the University of Milan. What are the activities of the Center?
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), well summarizes the main points that are object of attention by CIRME.
CIRME offers activities related to reference measurement services (including six enzymes, glucose, and HbA1c) contributing 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. CIRME also organizes international conferences on the topic of metrological traceability and standardization in Laboratory Medicine and works actively for promoting the related concepts to the laboratory professional and IVD manufacturer audience.
I like to remember here that some of the proposals elaborated by CIRME scientists in the last 15 years have become points of reference in the following scientific discussions. I refer to: the image of the 'Temple of laboratory standardization' (2014), describing the pillars of the metrological traceability; the concepts behind the 'Rethinking of QC (internal and external) in the traceability era' (2010), more recently consolidated in a whole theoretical approach; the recommendation of limits for combined uncertainty budget (expressed as percentage of total MU budget goal) in metrological traceability implementation (2015); the update of the approaches to be used for generation of data on biological variation (2016); the utility of MU measurement in medical laboratories (2017); and, quite recently, the definition of APS for MU of common biochemical measurands (2021). 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/).
Finally, I would like to mention that, in collaboration with the Clinical Pathology Unit of the 'Luigi Sacco' academic hospital, one of the two Italian reference centers for infectious diseases, CIRME has supervised studies on hospitalized COVID-19 patients to evaluate the role of laboratory tests as clinical

predictors of disease severity. Optimum biomarker cut-offs were specifically selected to have a high ability in detecting patients at risk of in-hospital death and in identifying patients at very low risk of ICU admission. One of the major strengths of the published results is represented by the use of methodologies for which standardization and metrological traceability had been verified and validated, enabling the universal application of results obtained in our clinical studies and permitting their unambiguous interpretation, providing institutions implementing them also use standardized assays. This work provides an excellent example showing that the implementation of assay standardization is an absolute priority for optimizing healthcare. Only the use of assays providing standardized results allows the application of common decision limits, as those defined in our COVID-19 studies, worldwide and the comparability of clinical studies performed in different institutions. Related papers are available on the 'CIRME COVID-19 page' (https://sites.unimi.it/cirme/the-cirme-covid-19-page/).

You have served in many leading roles both nationally and internationally *(among others: EFLM President, IFCC Scientific Division Chair, JCTLM Executive Board Member, 20th EuroMedLab President).* What is your greatest motivation? Was it difficult for you to allocate time for these tasks?
Driving motivations have been always the same: providing medical dignity to our profession and promoting the visibility of the role of laboratory professionals to guarantee optimal care for patients. If you want to play a significant role in medical science, you should dedicate all your time and efforts to justify the existence of Laboratory Medicine as a medical discipline and as a vocation. In my working life, I have been prepared to accept only tasks that in principle permitted me to promote Laboratory Medicine as the science that underpins Medicine. Using activities just to promote myself (as often happens, not only in our world) have never interested me. If you believe on the need to do something, you should find time for it: usually, a good working organization and a proper selection of coworkers permit to obtain the expected results.

You were the fifth EFLM President. Your term of office was during 2014-2016. What were the greatest challenges during your Presidency? Did you achieve your goals?
When I started my involvement in this apical position in the Federation, I noted there were some basic issues still unsolved, probably because, at that time, EFLM was a quite recent entity with just a brief history. There were no financial and administrative autonomy, poor international (and even regional) recognition, and an organization fully based on voluntary dedication. My previous experience in the IFCC, where I covered for a decade management positions in the Scientific Division, working with outstanding persons like Profs Mathias Mueller and Jean-Claude Forest, helped me to find alternatives and propose solutions. For example, for the first time, an EFLM Procedure Manual was released (and you may remember well this because you covered the EFLM Secretary position at that time), the numbering system for classifying different items to be discussed introduced, and a policy for EFLM publications finalized. Thanks to a good relationship with the IFCC top officers, I was able to obtain a full-time person dedicated to the EFLM office and to negotiate a new memorandum of understanding with the International Federation, also including a more remunerative agreement for the EuroMedLab organization. I am not in the position to say if I have achieved or not important goals, but, just recently, a valued person (I cannot disclose the name for privacy reasons) has confirmed to me that I remain her favorite EFLM President and, after years, it is surely a positive signal.

How do you see the future of our profession? What are the biggest challenges and how to overcome them?
Advances in science and technology will continue to result in the introduction of more complex, expensive, and difficult-to-interpret tests. Furthermore, new diseases (COVID-19 represents the last test case) will probably appear where laboratory contribution may undoubtedly provide better care. So that, laboratory tests have for sure a brilliant future. The question is however what will happen of Laboratory Medicine? Its raison d'être can be summarized as 'to help clinicians understand diseases by making lab voices heard'. I am always convinced that Laboratory Medicine will have (or not) a future only by combining the unique talent of performing high-quality laboratory assays with knowledge of the pathophysiological rationale behind the tests. The biggest challenges are always the same. To play a central role in healthcare delivery, we need to change our own attitude, become more outward looking and innovative, and create opportunities to demonstrate the value of our profession. This needs for an excellent cultural and scientific background of laboratory professionals, starting from the postgraduate schools training new colleagues.
SARS-Cov-2 diagnostics recently offered a good example of the two sides of the coin, i.e., laboratory tests vs. Laboratory Medicine (note the use of uppercase just for the latter). From the beginning of the pandemic, plenty of papers were published, the great majority including laboratory test results. It is however embarrassing to note the extremely low number of papers that at the same time dealt with the real-life performance of employed tests. And we know that when not properly evaluated in the quality of provided results, they have indeed the potential to misdiagnose and misinform. Laboratory Medicine professionals have therefore a unique role in evaluating the preanalytical, analytical, and post-analytical quality of employed assays, fighting the battle against the poor quality that may be the bane of medical use of laboratory tests. The very good news is that in the last few years, at least in our academic center, there has been an increasing number of promising young scientists and physicians who see their future in Laboratory Medicine. Thus, the future of Laboratory Medicine may be less critical than we imagined just few years ago.

Which skills and competencies, besides professional competencies, are most important for a young individual to become a successful specialist in laboratory medicine? What advice would you give to young colleagues who have just started their professional career in the medical laboratory?
From the first moment when the young colleagues decide to pursue the Laboratory Medicine career, they should be stimulated in increasing their knowledge and improving their skills by acquiring a working methodology that is sufficiently critical and enables them to correctly evaluate the collected information. Laboratory daily tasks and applied research should be kept both active, constantly supported and improved by the study. By the way, the electronic era markedly helps, and we carry now whole libraries in our pockets with electronic librarians at our beck and call. Those newly entering the field should also be stimulated to publicly presenting their experiences and publish their observations in scientific journals, showing the ability to correctly apply methodologies to manage and solve laboratory issues as well as to promote studies for test evaluation and their appropriate utilization in clinical practice. For this, it is very important to find a mentor who can guide the individual through this still neglected task. As Director of the Post-Graduate School in Clinical Pathology and Clinical Biochemistry of the University of Milan, my final advice at the end of the first meeting with new registered graduates is always: 'love Science, never give up on studying, and don't take anything for granted'.

Is there something, outside work, that you are passionate about? What kind of music do you like?
Literature, old movies, and music (all types except rap) take up all my free time, except when I ski (in winter) or ride a bike (in good weather). But my free time is not so much because it takes a long time to get results that deserve an award and then an interview by the current EFLM President.