From bench to diagnostic-therapeutic pathways

The 26th edition of the International Conference on Laboratory Medicine, held in Padova on October 23rd 2019, is entitled "From bench to diagnostic – therapeutic pathways". Laboratory (diagnostic) services are a key component of modern health care. It has been estimated that 70–80% of all medical decisions impacting diagnosis or treatment involve at least one pathology and laboratory medicine (PALM) investigation. Although laboratory medicine is apparently less visible than other health care domains, a body of evidence has been collected during the last decade to demonstrate that the place of clinical laboratories in many diagnostic-therapeutic (clinical) pathways has strong influences on quality of services across hospitals and in the community. In the process of recognizing the value of laboratory medicine for optimizing clinical pathways flow and patient care, laboratory professionals are asked to increasingly narrow their work within clinical teams, thus ensure a more effective communication and collaboration and improving clinical outcomes and patient safety. In addition, rethinking of diagnostic-therapeutic pathways ultimately fosters a large potential for savings than just focusing on reducing laboratory costs and chasing economies of scale (1). The translation of new laboratory tests and diagnostics from bench to clinical pathways represents a challenging issue, encompassing transition from accurate evaluation of analytical performances to diagnostic accuracy and, finally, to effective contribution for improving quality of diagnosis and treatment, as well as for achieving an optimal balance between benefits and costs.

In this issue of the Journal, we publish a series of papers emphasizing the debate regarding the future of laboratory medicine, translational health economics and some examples of translating new biomarkers into clinical practice. The first paper written by Mario Plebani provides some predictions on the future of laboratory professionals (2). This professional viewpoint highlights the need for better integration of laboratory tests in care pathways as the only possible means of guaranteeing that laboratory medicine and laboratory professionals will have the right value and visibility, and that quality and patient safety can be assured. This view is based on a re-evaluation of the key principles of the brain-to-brain-loop, as well as on the essential recognition of the need to assure close and effective interconnection and interrelation between different phases of the testing cycle, thus fostering a really effective and straightforward clinical laboratory stewardship. In this article, previously reported viewpoints that were part of ten-point "manifesto", are further discussed, with the main scope of assessing "what should be done now and in the future" for enhancing value in laboratory medicine (3,4). A central theme of the manifesto is cooperation and optimization in the workflow, the so-called "brain-to-brain loop", which has been first described by George D. Lundberg in 1981, and has then been broadly implemented by clinical care providers and laboratory medicine experts.

Another article written by Michael Wilson aims to discuss the essentiality of PALM in healthcare. Since this paper relates essentially to Universal Health Coverage (UHC), the known barriers that limit access to diagnostics in several parts of the world are reviewed, some potential solutions to overcome those obstacles are presented, highlighting some of the ongoing efforts for further developing and implement effective solutions (5). Several lines of evidence now confirm that laboratory testing is necessary for providing high quality healthcare and for supporting public health programs, whereby healthcare systems are less efficient without *in vitro* diagnostics, are more vulnerable to waste resources, whilst emerging problems such as antimicrobial resistance may even worsen. Despite the existence of important barriers for providing quality diagnostic testing around the world, there is growing recognition that laboratory tests are essential parts of clinical pathways, thus reinforcing local needs to developing strategic diagnostic plans, defining policies based on reliable regulatory and quality systems in support of those plans, developing sustainable financial systems, establishing the necessary infrastructure, and educating and training the workforce. It should also be emphasized that the vast heterogeneity characterizing the organization of many healthcare system worldwide, combined with a specific disease epidemiology, require that clinical pathways shall be locally developed for plenty fulfilling patients needs. These plans should involve multidisciplinary teams, where clinicians and laboratory experts will help disseminating a culture based on a more appropriate use of diagnostic services, thereby promoting further improvements in quality of care and patient safety.

The following article, written by Price and St John, is focused on translational health economics (6), intended as a translational tool which can be exploited in implementation of new laboratory medicine interventions, for informing the changes in resource utilisation needed for delivering value for money in service transformation. The introduction of a new test is predicted to modify one or more clinical pathways, resource allocation as well as the potential benefits that will

accrue to various stakeholders. The authors describe some key barriers for adopting new laboratory medicine investigations, emphasizing that laboratory organisation and funding are essentially based on its activities, namely production of test results, with limited or no consideration of their impact on care pathways. The strategy to overcome the current translational gap entails applying the concept of value proposition which, for a laboratory test, encompasses complete description of benefits, who these same benefits will target, and how they can be delivered. The value proposition, as recommended by the authors, provides a means of leveraging the real value of laboratory medicine tests by highlighting the clinical, practical and economic benefits that accrue across the whole stakeholder family.

The ensuing three papers deal with translational journey of some biomarkers. It is well known that glycated albumin (GA) is the result of non-enzymatic glycation of albumin occurring in the circulation. The albumin glycation rate mostly depends on the levels of circulating glucose and the time of albumin persistence within the bloodstream. Therefore, GA has been proposed as a reliable indicator of glycaemic status and many studies have investigated its clinical usefulness in diabetes, concluding that this test has a good diagnostic accuracy and may also be proposed as a clinically useful screening test. As underlined in the article of Marcello Ciaccio (7), due to the shorter lifespan of albumin compared to traditional biomarkers of glycaemic control such as glycated hemoglobin (HbA1c), GA can be considered an index of early response to hypoglycaemic treatment. This test has also been proposed as index of glycaemic control in patients with diabetic nephropathy, anemia, pregnancy, haemoglobin variants, blood transfusions, all conditions where the diagnostic accuracy of HbA1c is reportedly lower. Recent evidence has also been provided that GA values are significant predictors of diabetes progression and complications (e.g., microangiopathy, retinopathy, nephropathy and cardiovascular diseases). However, only recently an accurate and easy automated assay for GA has been developed, validated and applied in clinical practice, thus leading the way to broaden its routine use in diabetes care. The introduction of GA in clinical practice is then eased by accurate knowledge of its concentration in healthy subjects and in the general population which, along with comprehensive data on its biological variation (8), would allow an appropriate interpretation of test results.

Procalcitonin (PCT), the 116-aminoacid precursor of the active hormone calcitonin, is encoded by the *CALC-1* (calcitonin gene-related peptide 1) gene on chromosome 11. Under normal conditions PCT is synthesized by thyroid C cells and its plasma concentrations is generally lower than 0.05 µg/L, displaying a typical plasma half-life comprised between 20 and 24 h. In patients with severe infections of bacterial origin, production of PCT suddenly initiates in a number of extra-thyroidal tissues, thus paving the way to its clinical use for diagnosing these forms of infection. Several lines of evidence now attest that measuring PCT has become virtually unavoidable in patients with suspected infectious diseases, for both making an early diagnosis and for antibiotic stewardship (9). The article of Sivapalan and Ulrik Jensen (10) support the definite role of PCT in clinical practice, as evidence-based and safe approach or reducing unnecessary use of antibiotics in hospitalized patients with acute respiratory tract infections. A large body of evidence now supports the assessment of PCT in patients with community-acquired pneumonia and Chronic Obstructive Pulmonary Disease (COPD) exacerbations, as well as in septic and critically ill patients. This strategy seems especially effective when PCT is measured at admission, and then every ~24–48 hours, provided that PCT-based algorithms are followed.

The final article in this issue is published by Cosma and coworkers, who describe a comprehensive evaluation of an automated immunochemiluminescent assay for glutamate decarboxylase 65-kDa isoform (GAD65) (11). In this report, repeatability and intermediate precision measured at different clinical levels appeared satisfactory. A good agreement was also observed with another reference method, despite a significant bias could be identified. This evidence reinforces the need of further harmonization and standardization initiatives to provide improved interchangeability among commercially available immunoassays for GAD65.

In conclusion, we are willing to thank all the authors of the manuscripts included in this third special issue of *Journal of Laboratory and Precision Medicine* containing the Acta of the last edition of the International Conference on Laboratory Medicine, which follows the earlier two special issues (12,13), and we sincerely hope that these contributions may be of interest for the readership of the journal.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Mario Plebani

Giuseppe Lippi

Mario Plebani
Department of Laboratory Medicine, University Hospital of Padova, Padova, Italy
(Email: mario.plebani@unipd.it)
Giuseppe Lippi
Section of Clinical Biochemistry, University of Verona, Verona, Italy
(Email: giuseppe.lippi@univr.it)
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