Int J Legal Med (2017) 131:897–899
DOI 10.1007/s00414-017-1624-4

EDITORIAL

P5 medicine and justice: the future is now

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Received: 2 June 2017 / Accepted: 6 June 2017 / Published online: 20 June 2017

The recent and rapid evolution of science, in its various connotations and in all its many forms, typical of the 'post-modern society of risk', at once globalized and glocalized, have not failed to influence legal medicine and the actions that characterize the professional scientific community, which fosters it with important, albeit undervalued, routine work. From reflections on this evolutionary stem, the considerations proposed for the attention of the readers, in the logical order set out, are as follows, from point 1 to point 9, with the hope of fostering a collegial exchange of ideas and actions.

1. It is universally acknowledged and widely shared in the scientific community that the bio-medicolegal sciences are characterized by *identity* of 'methodology for ascertainment', 'criteria for evaluation' and for the solution of the historical problem and issues of 'causality' occurring in daily routine work.
2. The identity is confirmed in the 'historical background', from which are derived: the early writings on 'pharmacology and poisons' of the third millennium before Christ, in China; the 'Code of Hammurabi', in Mesopotamia; the healthcare-related documents inherent to the medical profession in Greek civilization; the lex Aquileia and Justinian of Roman civilization and the ancient world of Charlemagne and the middle ages; the first documents concerning 'medico-legal autopsies'; the fundamental treaties of Zacchia in the seventeenth century, as well as the first chairs of legal medicine established between the end of the eighteenth (′700) and the beginning of the nineteenth century (′800), in which the 'birth of modern legal medicine' can be placed and the 'unitarian knowledge' underwent a process of consolidation, remaining unchanged until about the middle of the last century, with the beginning of the fragmentation into specialized knowledge.
3. It is generally agreed that the same knowledges are distinguished by a significant number of *different* 'techniques and methods', elaborated, applied and used, as well as by 'theories and criteria' of critical interpretation, which imply a dignity and value of disciplines, namely, forensic pathology, genetics, toxicology, anthropology, psychiatry and criminology.
4. It is equally foreseeable that the historical unitarian knowledge of the disciplines, which sustained a process of fragmentation during the last decades, will most likely restore the *original unitariness* by means of interdisciplinary research and transdisciplinary innovations, in a dynamic and cyclic process of Hegelian and Vichian evolution of history, in general, and of science, in particular.
5. As an outcome of the process, the 'present' finds general and transversal connotation in the respective definitions of Antonio Cazzaniga and the European Council of Legal Medicine, as 'the goal of legal and forensic medicine is to discover the truth so that justice be done' and *legal medicine* finds its basis and raison d'être as 'the application of medical knowledge and methodology to the resolution of legal questions and problems for individuals and society'.
6. In this context, the result of the historical process and the cogent themes of greatest importance that affect the bio-medicolegal sciences are the 'lack of knowledge', the 'evidence' of the knowledge acquired and its value in the

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various disciplines and the development of 'education and training' of the young community who are coming into contact with such sciences.

7. The lack, or *black holes*, of the most important and general knowledge will govern the direction of future research, specifically within the fields of dating, markers of disease and damage, to be understood as disease in evolution and stabilized disease, as well as in personal identification, in dating estimation and in cause of death and criminogenesis.

The development of bio-medicolegal scientific research and the reduction of the "black holes" will benefit from the biomedical sciences and, in particular, from the platforms of the future constituted by imaging, omics and bio-analytical sciences. *Imaging* will evolve at the same pace both in the field of the living and that of the dead and the *omics* and *bio-analytical sciences* as well as in the clinical and forensic fields.

In the current state of omic maturity, recent innovations in the development of mass spectrometry, cutting-edge technology and computational tools have considerably increased the power and the potential application of the multi-omic approach, and despite the still ongoing progress in the methodologies, their application can already provide informative results leading to more accurate interpretations and evidence. The integration of omic strategies in the bio-analytical research pipeline has created new opportunities to better understand the molecular mechanism involved in physiological and pathophysiological states. The methodology has been successfully applied in numerous areas (cancer, cardiovascular disease, obesity, etc.), creating the *integrative personal omics profile*. Because of its capability to detect slight changes in large datasets, *metabolomics* is also impacting the field of medico-legal disciplines, particularly toxicology, to determine signatures of exposition, susceptibility or toxicity and to identify new direct or indirect biomarkers of drug abuse.

Quantitative *imaging techniques* such as functional MRI, molecular imaging, photoacoustic tomography/endoscopy or the integration of the two, as well as X-ray CT fluorescence molecular tomography will be the second key platforms of bio-medical research in the future. Ptychographic-CT, optical frequency domain, spectral optical tomography and fluorescence molecular tomography will enable the development of algorithms, for the time being based on population data which, if adopted uniformly and methodically applied by the international scientific community, will be able to increase the accuracy of each of the aforementioned disciplines.

An example is an algorithm regarding 'forensic pathology' and 'imaging', in the search for a gold standard that can be achieved only with a uniform and systematic application, commencing from the quotidian and leading to new research topics and scientific works that will foster scientific research and increase the accuracy of the algorithm.

Ante-mortem imaging remains anchored to some cornerstones of medical imaging, which mirror those commonly applied in clinical practice with regard to the topic of clinical forensic medicine and age estimation. On the contrary, non-violent crimes, in the field of transports, drug trafficking and international terrorism involve the use of other methods, marked by the screening of large population flows.

Computer tomography and magnetic resonance micro-CT will contribute to the development of the post-mortem *cross-sectional imaging* and to the solution of diagnostic problems concerning the presence of the bone and vascular lesions, of soft tissue and organs, toolmarks and GSR deposits.

The current fragmentation of 'post-mortem imaging' will be surpassed in the future with the adoption of a shared *algorithm*, based on a 'quantitative model', such as evolution, reflected by the bio-medical imaging of the current 'qualitative model'.

Imaging mass spectrometry, with proteomic and metabolomic imaging, will be a *link* between forensic pathology, toxicology and radiology. The simultaneous mapping of the untargeted profiles of hundreds of molecules including proteins, peptides, lipids, drugs and metabolites will enable a high correlation between the resulting molecular images and the histology of the sections, and the implementation of IMS will lead to new research opportunities in forensic pathology. Despite numerous technical challenges still to overcome, *3D IMS*, developed to provide spatial molecular information of tissue or organisms, is highly promising and has already been successfully applied. Also integrated with MRI, 3D IMS enables the correlation of post-mortem proteomic imaging with the corresponding in vivo anatomical data provided by radiological imaging.

Hence, the hypothesis of *radiomics* is far more realistic than might be imagined—the high-throughput extraction of image features from radiographic images could capture additional information not currently used—or rather, genomic and proteomics patterns can be expressed in terms of macroscopic image-based features, inferring phenotypes or gene-protein signatures, possibly containing prognostic information, from the quantitative analysis of medical image data. Following further validation in a multi-centric laboratory setting, imaging features could be related to gene signatures. In light of the contributions of omics and 'imaging sciences and techniques', a number of different series and systems of innovation are prefigured.

The *systems clinic* with markers will derive from the 'molecular systematic approach'. Thus, applying omics sciences in forensic medicine could lead to a new concept of *damage* ascertainment. The metabolic snapshot could indeed become the indicator of the degree of psychological and physical well-being of a subject. The 'systems biology' studies of large populations, beginning from metabolomic could identify new markers of disease/disability, identifiable not only in metabolites, but also in enzymes, RNA or DNA. The integration of

these markers could not only provide indicators of the state of psycho-physical well-being of an individual (metabolomics), but also his/her full potential state of mental and physical well-being based on the genome, allowing an evaluation of the damage effectively attributable to a specific event. The integration of the various markers of damage would lead to the formation of 'barèmes' based on the 'omic sciences', with potential accurate assessments not only of the degree of injury to the psychophysical integrity of a person, but also of future damage.

Equally, by utilizing the conquests of the omic and imaging sciences, a *systems pathology*, where *causes and mechanisms of death are clarified*, is prefigured, where the age, vitality, order and correlation of *internal and external wounds* are identified.

The same strategic integrations of radiomic scientific research will clarify the 'complex interplay' between *nature, nurture, epistasis* and *epigenesis* of human behaviour.

8. As for the second important issue affecting the bio-medicolegal sciences, namely, that of *evidence*, one sees above all in the current post-modern society, where holistic—personalized and humanistic biomedicine is axiomatic, that its value can be revealed and understood in full as *accuracy*, namely, *truth* equivalent to *reality*. Moreover, the growing need for certainty in the realm of justice is reflected in the demand for bio-medical molecular as opposed to opinion-based evidence.

Evidence, in this period of history, finds its sources, in small part, in the bio-medicolegal sciences due to the lesser publicized contribution of these in relation to the bio-medical sciences as a whole, mainly driven by the omics and imaging sciences.

To be effective and entirely suited to the needs and requirements of the judicial system, *the future should therefore* be oriented towards the elaboration of a *mathematical algorithm* of evidence founded on the increased accuracy of the various disciplines. In the meantime, it will be the task of the scientific community and, markedly, of the international scientific societies to sustain an effort of collaboration in the realization of a *master plan* on *evidence* and *accuracy*, so as to be able to definitively declare to the *justice system* the real capacity of the bio-medicolegal sciences to furnish truth and proof.

To realize such a long-standing process, it is necessary to create an *interdisciplinary working group*, and the International Academy of Legal Medicine has already moved in such a direction with the recent Venice Symposium dedicated to, 'P5 medicine and justice', a natural development of P4 medicine, enriched by the fifth '*P*', indicative of the *protection* of the values and dignity of the person. An example of innovative interdisciplinarity and affirmation of values protective of the dignity of the person is provided by the new development and aims of *'humanitarian forensic action'* that some distinguished colleagues are currently promulgating.

9. Humanitarian protection is achievable, moreover, through the 'P5 network of networks' as the expression of the *virtual link* between the *genome, systems biology, hand-held devices* and *big data*, driven by patient and social networks. A 'P5 network of networks' aimed at achieving the 3rd millennium medical mission and the *educational training* of young students, always founded on the principle of *learning to doubt and to hunt for error*.

The *monograph* 'P5 Medicine and Justice', currently undergoing publication by Springer, will deal with these and many other issues. With contributions from 61 authors, experts operating in all of the bio-medicolegal disciplines from every continent, it will complete the trilogy of IALM monographs, begun with 'malpractice and medical liability' [1] and continued with 'personal injury and damage' [2], published by Springer in 2013 and 2016, respectively.

An important prospective contribution to the development of innovations, evidence and educational training will certainly still be offered by the 'International Journal of Legal Medicine', its editors and publisher, to whom the international scientific community addresses its thanks for the valuable informative role carried out for decades in constant observance of the strict pursuit of excellent editorial quality.

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