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Editorial

From a drop to the ocean: an immersion in individualized medicine

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"*When it comes to the future, there are three kinds of people: those who let it happen, those who make it happen, and those who wonder what happened.*"
John M. Richardson

Keywords

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In an increasingly complex and intriguing scientific context the need to bridge the gap between research and patient care is felt today more than ever. There are currently approximately one hundred biomarkers used in clinical practice, very few (a drop in the ocean) in comparison with the large numbers acclaimed in more than 150,000 scientific papers; intriguingly, most of these promising biomarkers will never become part of routine clinical practice [1].

Despite the fact that biomarkers, currently used in clinical practice, have contributed substantially to improve the care of many diseases (e.g., glucose and glycosylated hemoglobin for diabetes, serum creatinine values for kidney impairment, etc.), a new evolutionary scenario for the use of biomarkers to assess and monitor health and disease status has been created. Biomarkers are the linchpins of personalized medicine, and as such they should be able to facilitate the incorporation of basic and translational research findings into preventive, diagnostic and therapeutic aspects of modern healthcare.

The ability of high throughput proteomics, metabolomics and other 'omics' platforms to profile a large number of analytes in a single array is increasing the complexity of biomarker validation. This innovation calls for global re-thinking of the role of clinical pathologists in transforming experimental data into clinically available tests [2, 3]. The same can be said, for example, for congenital errors of metabolism [4]. The dismal patchwork of fragmented research on disease-associated biomarkers should be replaced by an integrated 'big science' approach. Researchers should definitively prove that their new diagnostic tests will change clinical practice both by generating value in healthcare, namely by improving patient outcome and reducing costs [1].

It has become more and more clear that health and disease can only be studied in an outstanding way by using complex systems such as integrative systems biology, systems medicine, and network medicine [4] organized in a modular way such as a topological module, a functional module and a disease module. The description of these complex concepts is beyond the scope of this editorial but can be found in excellent contributions on the subject [5]. The new concepts of health and disease emphasize the capacity of a person to resist (resilience) a change (allostasis), avoiding the progression of a disease. We would highlight that an overwhelming majority of diseases have multi-etiological causes: the phenotype is quite complex (a large number of genetic and environmental factors are involved) and highly dynamic, being optimally addressed using a holistic in stead of a reductionist approach. The disease phenotype is the reflection of different pathobiological processes interacting within a complex network capable of comprehending the complexity of the human organism, both in health and disease. It must also be emphasized that today's map of the human interactome is far from complete. In any case, only an integrated knowledge on the interactions between genome, proteome, environment, pathophenomenon, organized by an underlying cell network, will lead to effective advances in medicine of the third millennium. This perspective has led to the paradigm "think globally – act locally", which means: if we act on the metabolic pathways involved in the therapeutic treatment of a disease, we cannot overlook the global biochemical network of cells and their hierarchical way of communicating. Otherwise, drugs will not cure patients but simply modify the symptoms and sign of diseases [5].

Several years ago, limits and pitfalls of the reductionist approach of medicine came to the front: the question was if systems biology and systems medicine might become adequate to solve problems in healthcare [6]. In recent years, there has been an exponential increase in the number of publications in PubMed concerning the -omics disciplines and in particular metabolomics. In the literature, the following definitions have been advanced: genomics = to be able to; transcriptomics = to start; proteomics = to do; metabolomics = to be [4]. Metabolomics will contribute to guiding the medicine of the past, the medicine of the present and the medicine of the future [7, 8] and perhaps will actually contribute to unveil many mysteries of medicine [9]. From a financial point of view, the global market for metabolomics, expressed as revenue, was estimated to be worth $343 million in 2012 and is expected to reach $1.5 billion by 2017, growing at a compound annual growth rate of 35% from 2012 to 2017 [10].

Metabolomics, also called the "new clinical biochemistry" is an approach based on the systematic study of the complete set of metabolites in a biological sample. It is a "functional" technology for identifying, quantifying and characterizing simultaneously hundreds/thousands of low-molecular-weight metabolites. It is capable of producing a snapshot of the metabolome, the entire set of low-molecular-weight metabolites

produced by an organism, a mirror that reflects the physiological, evolutionary and pathological state of a biological system. The metabolome is so close to the phenotype that it can be considered the phenotype itself. The metabolic profile is a unique characteristic of everybody, capable of identifying a subject or a sub-set population with a nearly 100% specificity [11-13].

One of the main objectives of metabolomics is the discovery of reliable biomarkers that play an important role in estimating the risk inherent in different pathologies, in early diagnosis, in prognosis, monitoring and assessment of the therapeutic response, in the prescription and follow-up of a nutritional approach. It represents a detailed molecular phenotype that is rich enough to reveal biological complexity [7, 13]. Wang-Sattler R., using metabolite-protein network analysis in adult patients, demonstrated that it is not necessary to study all the "omics", but it is sufficient to execute metabolomics which summarizes gene-environment interactions in a simpler and easier way. Moreover, if an individual presents an alteration in three metabolites he/she will probably not develop type 2 diabetes (epidemiologic medicine), but he/she will surely develop type 2 diabetes [14]. These results may help in developing novel strategies to prevent type 2 diabetes. If not, they may delay the development of the pathology or its complications. Moreover, the application of more than one "omic" platform will make it possible to speed up the discovery of biomarkers not only for diabetes and its complications [3], but also in the other quite different medical and paediatric fields. All this may be considered the platform of a new medicine, the so-called three Ps: prospective, predictive, personalized (or customized). We are faced with a shift paradigm that will gradually transform medicine from reactive to preventive, from reductionist to holistic, from genetics-oriented to epigenetics-oriented [7]. The prerequisites for this are the convergence of complex systems approaches to disease, new measurement, modelling and visualization technologies and new computational and mathematical tools.

Indeed, in the next few years we will witness a profound change in medicine and healthcare as a result of progresses in technology and the ability to analyze large amounts of data from single patients (Big Data). In the future of medicine, parents (and patients in general) will not be interested in trivial data on percentages and statistics, but in what will happen to their children. It is no longer of interest to know, for example, that two out of five children may have a problem and/or a disease, but to know if they will be affected or not and what complications may originate from the disease and when (thus knowing when to intervene as soon as possible) [7]. We cannot change our past, but we should try to ameliorate our future, for example by changing our eating habits and limiting or personalizing the use of drugs, avoiding pollution and modulating our life styles. Genetics is printed in ink and cannot be deleted, while epigenetics is written in pencil and can be modified. Genetics proposes while epigenetics provides [7]. Actually, this is not a futuristic vision of medicine, considering that an article published by Time Magazine stated that "almost all parents interviewed wanted to know the future health of their children, even if this was negative and short-term and even when the disease predicted was incurable at that time" [14].

Metabolomics has experienced extraordinary development in paediatrics and neonatology in the last few years, with the involvement of many fields of research [11-13, 16]. It is correct to say that the "omic" disciplines, and specifically metabolomics, will contribute to the solution of some of the mysteries affecting newborns [9]. The newborn has always represented an ideal "laboratory" for the observation of brusque short-term physiological changes and the understanding in depth of the physiopathological modifications useful in gaining an understanding of all the stages in the lives of human beings. Furthermore, it is being demonstrated more and more frequently that events occurring in the prenatal and perinatal periods influence, in a strategically decisive way with epigenetic modalities, an individual's entire life cycle (perinatal programming). All this assumes an extraordinary value in the light of the integrated approach of the -omics disciplines [17].

The vast majority of our genes (99.99%) are of ancient origin so that in practice our physiology and biochemistry are tuned to the conditions of life that existed more than ten thousand years ago and have developed in the course of a hundred thousand generations. We cannot refrain from investigating the sudden exposure of a very large number of critically preterm or ELBW neonates to a mass of environmental factors, since in the past preterm and critically preterm neonates did not survive. The biological truth is that individual humans differ in their health in many aspects as a result of genetics, life state, life history and all the external influences that make up an individual's environment [18, 19]. In any case, the lesson that appears to emerge from

both experimental studies and those on humans, including children and neonates, is the basal presence of a noteworthy interindividual variability. The dynamic range of the metabolome is revealed by subjecting the organism to physiological and pathological changes in the state of health: this means that we are quite different from each other and these differences are accentuated when faced with changes, especially if very significant and/or extreme, for example, in cases of fasting [19] or asphyxia [20].

On the subject of individual variability, we can conclude with a sentence by Montaigne "there is a greater difference between one man and another than there is between a man and an animal". Only by being aware of complexity and biological variability, by improving our knowledge, by feeding and treating different individuals in different ways, and most of all by better defining the state of health of each individual and his/her resilience, will medicine be in a position to respond in a personalized and customized way (and not approximately and epidemiologically) to the problems of human health.

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