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Editorial

## The Systems Biology Oriented, Holistic Vision of Personalized Medicine and The Emerging Concept of Proactive Herbal Medicine

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### Abstract

Application of -omics is rapidly growing in the clinic, providing a large number of clinically actionable information for clinical decisions. With new ability to analyze risk factors, a proactive, preventative and pre-emptive strategy may be used to sustain the individual's health balance and proactively "normalize" pathogenetic dysfunctions, before a disease condition develops. This shift from a disease-oriented, reactive medical approach, to one that includes wellness-oriented proactivity is a potential game changer in many aspects of clinical practice. Interestingly, traditional medicines possess a deep knowledge on preventative strategies and collectively represent today one of the largest experience based knowledge in prevention. This knowledge should be exploited using a patient centered Evidence Based Medicine approach so that herbal drugs and dietary interventions can have a central role in the emerging wellness oriented, proactive approach to health of Personalized and Precision Medicine. The advances of systems medicine, as well as -omic diagnostic techniques, or "diagnostic-omics", are now providing formidable new strategies and tools for a guided and assisted use of phytocomplexes, which could provide pro-active strategies for disease prevention.

Personalized medicine can be broadly described as a customization of healthcare, characterized by the diagnostic exploitation of high throughput -omic techniques and a holistic vision of the individual, seen as a unique biological super-system. The term P4 medicine has been also used to highlight four of the pillars of the new approach, that is "Predictive", as it uses molecular diagnostic tools to precisely predict individual health risks and treatment responses; "Preventive", aimed at acting to stop a disease before it occurs and maintain wellness; "Personalized", collecting and integrating each subject's unique clinical, genomic, molecular and environmental characteristics, in order to make informed decisions for the best individualized care; "Participatory", promoting patients' participation and empowerment [1,2]. Recently the term "precision medicine" [3] has been used to stress the ability of -omic techniques (diagnos-

tic-omics) to identify molecular patterns and guide targeted interventions with high specificity. Regardless of the label used, this innovative medical approach is fast spreading, and models for effective clinical application are being developed [4].

In the last 20 years, at least two main scientific advances have contributed to the current medical evolution: the simultaneous detection of entire molecular families in a given biological system, and the ability to collect, classify, network, and visualize an unexpectedly big number of analytical data through bio-informatics. Application of -omics, especially genomics, is extending rapidly in the clinical use, ranging from genome-wide approaches, to the analysis of pharmacogenomic relevant SNPs [2,5], providing a large number of clinically actionable information. Other -omic techniques,

such as proteomics and metabonomics, are being introduced in the clinic and in the next future should be available to the public. Especially metabonomics, by measuring the metabolic end points linked directly to the activity of the whole biological system, is considered by many a key technique to monitor closely any biological perturbation and evaluate the possible outcomes of a drug or dietary intervention [6]. To handle efficiently the large amounts of different types of data, new systems medicine databases and software are being developed. Integrating omics data with other biomarkers and clinical data is a challenging issue, given the complexity of the information, and transforming this multitude of data into actionable information for clinical decisions is one of the central issues in personalized/precision medicine. At the heart of this approach lies a holistic, systems biology driven vision of the individual, a unique and undivided body of mutually interrelated biological events, occurring simultaneously and causally intermingled, in a dynamic multi-dimensional network of molecules, functions and conditions. This systems approach to disease provides a comprehensive set of disease-relevant molecular information at the individual level, so that each patient can be managed according to her or his specificities and personalized strategies can be used [1, 7- 9].

The systems driven vision from a reductionist to a holistic one, in medical terms has also brought a paradigm shift from a reactive to a proactive approach, thanks to the ability to provide clinically relevant and actionable information on individual health risk factors, from the molecular to the environmental level. If identified early, when the molecular dysfunctions have not yet developed into frank disease conditions, a proactive, preventative and pre-emptive strategy may be used to avoid, retard or at least reduce the intensity of the pathologic conditions. To Sustain the individual's health balance and proactively "normalize" pathogenetic dysfunctions before a disease condition develops, should thus play a central role in personalized medicine, especially considering the increasing ability to identify health risk factors and the need to develop individually tailored programs aimed at precocious alert and early intervention. This shift from a disease-oriented, reactive medical approach, to one that includes wellness-oriented proactivity [10] is a potential game changer in many aspects of clinical practice. Western medicine has developed mostly along a line of reactive approach, targeting the disease once it develops, and is thus well-endowed with tools for therapeutic intervention. At the same time though, it has developed a rather limited range of proactive strategies to resort to, if a health risk factor is identified. While "passive" prevention, aimed at reducing health risk co-factors with the help of dietary adjustments, physical exercise and reduction of unhealthy habits, is well established, proactive prevention is still in its infancy and preventative tools are lacking, with some exceptions in specific fields, like oncology and cardiology, where there are some important examples of pharmacoprevention [11- 14]. Actually, not knowing what to do in case of identification of risk factors,

besides monitoring pathognomonic parameters, is often one major problem encountered by clinicians when approaching personalized medicine, raising the question of whether one should really know her/his disease susceptibility, without having an appropriate pre-emptive tool.

Interestingly in this perspective, well-structured traditional medicines like Chinese Herbal Medicine, Traditional Iranian Medicine and Ayurveda, highly personalized in their approach and with their deep knowledge on preventative strategies, are finding themselves at the forefront of a new impulse towards integrative strategies, aimed at bringing together deterministic and holistic medical traditions [15,16]. The special value of these ancient holistic medicines lies in their variety of formulae used for millennia for disease prevention [17,18] on an "evidence based experience" basis, which collectively represent today the largest experience based knowledge in prevention. Still, a full transition from experience-based medicine to evidence-based medicine (EBM) is indeed necessary and needs to be at the center of the whole process of integration of traditional medicines, with an evidence-based model of systematic evaluation of the clinical research evidence [19-21]. A result and patient centered EBM approach can indeed open the way to the reevaluation of herbal drugs, despite their often poor molecular characterization and the complexity of their molecular targets, potentially weighing in favor of their clinical use. At the same time -omic technologies, allowing the identification of simultaneous biological events and interactions, can give unprecedented insights into the complex simultaneous multi-target interactions of multi-component drugs [22], providing formidable tools to uncover the effects exerted by medicinal phytochemicals on biological systems. Indeed, at least some of the healing and health promoting properties of plants lie in the network of simultaneous actions elicited by the combination of multiple components of the phytochemical itself. The final balance of all the single interconnected activities is hard to predict and this has always been a limitation in the use of herbal drugs, which are also characterized by an extreme degree of intrinsic variability. The pleiotropic effects of herbal drugs are thus being investigated with the conscience of the multi-factorial nature of disease, causal or contextual, for which herbal medicine, whose therapeutic efficacy is based on the combined simultaneous action of a mixture of constituents, offers new treatment opportunities. Omic techniques, providing a comprehensive assessment of endogenous biofactors in a holistic context, are functional to this scope [23-25]. This is even more relevant when using multi-herbal mixtures, as in traditional medicines, where plants are often used as blended herbal preparations sometimes consisting of mixtures of mixtures, with each herbal component playing a specific role, either as an effector, an enhancer or a mitigator.

Herbal drugs and dietary interventions can have a central role in the emerging wellness oriented, proactive approach to health, and their effective and safe use should be carefully guid-

ed and closely monitored under appropriate medical supervision. The advances of systems medicine, as well as -omic diagnostic techniques, or “diagnostic-omics”, are now providing formidable new strategies and tools for a guided and assisted use of Phytocomplexes, which could provide those pro-active strategies that are necessary to tackle health risk factors identified with the personalized/precision medicine approach.

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