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Review

P4 Medicine: the Future Around the Corner

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ABSTRACT

Traditional medical practice has always been "reactive", meaning that the doctor intervenes when there is disease. Theoretical (scale-free networks and complex systems), technological (highly efficient "omic" technologies) and conceptual (systems biology) advances of the last decade prelude the transition towards "anticipatory" medicine centered on health and not disease. This review establishes the fundamental conceptual bases and discusses the principal aspects of this new medicine, known as "P4 Medicine" as it is personalized, predictive, preventive and participatory.

Isoenzimas de lactatodeshidrogenasa en el músculo esquelético de pacientes con EPOC

Palabras clave:
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RESUMEN

La práctica médica tradicional ha sido "reactiva" (el médico interviene cuando hay enfermedad). Los avances teóricos (redes libres de escala y sistemas complejos), tecnológicos (tecnologías "ómicas" de alta eficiencia) y conceptuales (biología de sistemas) habidos en la última década permiten anticipar la transición hacia una medicina "anticipatoria", centrada en la salud (no en la enfermedad). Esta revisión establece las bases conceptuales fundamentales y discute los principales aspectos de esta nueva medicina, denominada "Medicina P4" por ser personalizada, predictiva, preventiva y participatoria.

Introduction

Medical practice is on the verge of a transcendental change. In the years to come, it will progressively transition from reactive medicine, based on disease, to a **p**ersonalized, **p**redictive, **p**reventive and **p**articipatory medicine (P4 Medicine) centered on health. This change will be possible thanks to the advances made in the field of basic science (for example, complete sequencing of the human genome),[1] the development of computer tools (internet for example) and imaging techniques (CT, NMR, PET), and the use of concepts of engineering physics (such as scale-free networks and complex systems). This review discusses this new paradigm. In order to do so, it is structured into four sections that: 1) situate the evolution of biomedical research in a historic perspective; 2) present basic concepts about scale-free networks and complex systems necessary to 3) comprehend the implications of systems biology in human health and diseases; and, finally 4) discuss the requirements and potential risks and benefits of P4 Medicine.

Historical Perspective of Medical Research

Due to the enormous complexity of human biology, medical research has historically obeyed a reductionist strategy, which attempts to explain complex phenomena by defining the functional properties of the individual elements that make up the system. Thus, the research focus went progressively from the organism as a whole (anatomy), to the organs (physiology), cells (cellular biology) and, more recently, molecules (genes, proteins, lipids and metabolites;

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molecular biology). This reductionist strategy assumes that the world that surrounds us can be understood in terms of the properties of its constituting parts by decomposing Nature into its simplest parts and laws. This focus could be defined as "divide and conquer" and it is based on the assumption that complex problems can be resolved by dividing them into smaller, simpler problems that are therefore more manageable. Reductionism dominates Medicine and affects our methods for diagnosing, treating and preventing diseases. Our natural inclination is to isolate the individual factor responsible for the observed behavior. In fact, the birth of medical specialties themselves is a result of reductionist strategy.

One must admit that this strategy has been extraordinarily successful. Not only has it led to the discovery of the intimate nature of the cellular and molecular structure of human biology, but it also has resulted in spectacular advances in clinical practice in all its specialties. Reductionism, however, has its limit: it is not able to explain all phenomena, especially those that involve more than one origin and require the coordinated function of different structures (systems). It is becoming more and more evident that biological functions can only rarely be attributed to individual molecules. Contrarily, most biological systems, in health as well as in disease, arise from complex interactions among the numerous components of cells, such as protein, DNA, RNA and small molecules.[2] Biological research over the last 40 years has revealed the nature and profound complexity of biological systems. The biggest challenge of biology in the 21st century is to take on this complexity.[3] It is evident that this complexity cannot be understood by studying isolated genes and proteins individually. In fact, biological systems should be studied as an integrated whole.[4]

An alternative to the reductionist mindset is the perspective based on the "system", interpreted as a group of individual elements that possess emerging properties that cannot be attributed to any single element on its own. An example of a system is an airplane. The emerging property that characterizes the airplane is its capability to fly, but this capability does not depend on any single one of its elements separately (wings, motors, pilots, etc.). Instead, it depends on the integrated function of all of them as a whole. In another words, the new approach recognizes that one cannot understand forests by simply studying the trees individually.

Systems biology is a new interdisciplinary field of research in which the interactions of elements, both internal and external, that influence biological processes are formulated with mathematical expressions. Systems biology was conceived to manage the complexity observed in biological systems in a quantitative and modeled manner. This holistic or global approach allows us to comprehend the functions of biological systems (processes) and thoroughly research how their interactions, both internally as well as with other systems, result in the appearance of new emerging properties. Practically any biological process can be the object of study based on this systems biology strategy: for instance, the growth of a cell, the interaction between two bacteria or the blood circulation in an organism. To develop this strategy, it is necessary to incorporate knowledge provided by systems engineering, which was born from Norbert Wiener's *Cybernetics* in 1948 and Ludwig von Bertalanffy's *General System Theory* in 1969. The developing fields of chaos theory, nonlinear dynamics and complex systems science, together with computational science, mathematics and physics, have also contributed to the analytical tools used for systems analysis. The following is a brief description of the main characteristics of complex systems and scale-free networks.

Complex Systems and Scale-Free Networks

A complex system is a set of interconnected elements whose connections contain additional information that is hidden from the observer. From their interaction, new emerging properties arise that cannot be explained by the properties of each of the isolated elements. The cell is a typical example of a complex system, as it is composed of many individual elements (ribosomes, mitochondria, nucleus, membrane, endoplasmic reticulum, proteins, DNA, RNA, etc.), each of which is responsible for doing a specific function. These elements respond in a non-linear manner to external perturbations. For example, sometimes a DNA mutation has no effect on the survival of the cell, whereas other times one single mutation can be fatal.[2] In addition, the cell presents emerging properties that cannot be explained in terms of the properties of its individual elements.

The behavior of most complex systems, from a cell to the internet, emerges from the orchestrated activity of many components that interact through paired interactions. In this way, the components of a system (or network) can be represented as a series of nodes (or vertices) that are connected by links (or segments), each link representing an interaction between two components. Together, the nodes and links form a network or, in more formal mathematical terms, a graph.[5]

In nature, different types of networks can be found, depending on the number and type of nodes and links. In a social network, for example, the nodes are the people and the links could be the ties of friendship amongst them: two people are connected if they are friends. Other examples of networks include diseases (connected by shared proteins or genes), the economy (banks connected by shared investments), the internet, electrical grids, and many more. In fact, it is rare not to be able to find a network supporting most activities, be they biological or not.

Traditionally, to study the properties of networks, the graph theory has been used. This theory allows us: a) to recognize links and identify hubs (meaning nodes with many links); b) to illustrate the structure of the overall network and its possible subgroups; c) to thoroughly examine the nature of the relationships between the elements in the network; d) to clarify the rules that govern them; and e) to establish new global frameworks.

Perhaps the most important property that characterizes the structure of a complex network is the P(k) function of link distribution, which gives information about the probability of a randomly-chosen node to have k connections.[6] Two fundamental types of P(k) distribution have been described: Poisson (normal) and scale-free (fig. 1). The former are important mainly due to historical reasons, as said networks were the first to be mathematically analyzed. This analysis was carried out by the Hungarian mathematicians Paul Erdös (1913-1996) and Alfréd Rényi (1921-1970) in the 1950's. In Poisson networks, all the nodes have more or less the same number of connections, meaning that the connections in a Poisson network are homogeneously distributed amongst its nodes. On the contrary, the most important characteristic of scale-free networks is its high heterogeneity, as there are nodes with very few connections, moderately-connected nodes and extremely-connected nodes (fig. 1). The highly-connected nodes are called nuclei, network centers or hubs.[3] Apart from these characteristics, what is truly surprising is the ubiquity of scale-free networks, which appear in quite diverse settings, ranging from small metabolic networks within a cell to large computer networks like the internet, including banking networks, the distribution of gas and electricity or even terrorist networks.

Another fundamental characteristic of complex systems is their robustness, a term which refers to the capacity of the system to respond to changes in external conditions or in internal organization without affecting its normal behavior. In this sense, it is important to point out that scale-free networks are amazingly resistant to accidental failures. This is because a random error mainly affects the small-sized nodes, whose absence does not disturb the integrity if the network. However, their dependence on the hubs causes an effect known as "vulnerability to attack", which implies that the elimination of a few key hubs exscind the system into isolated clusters of small

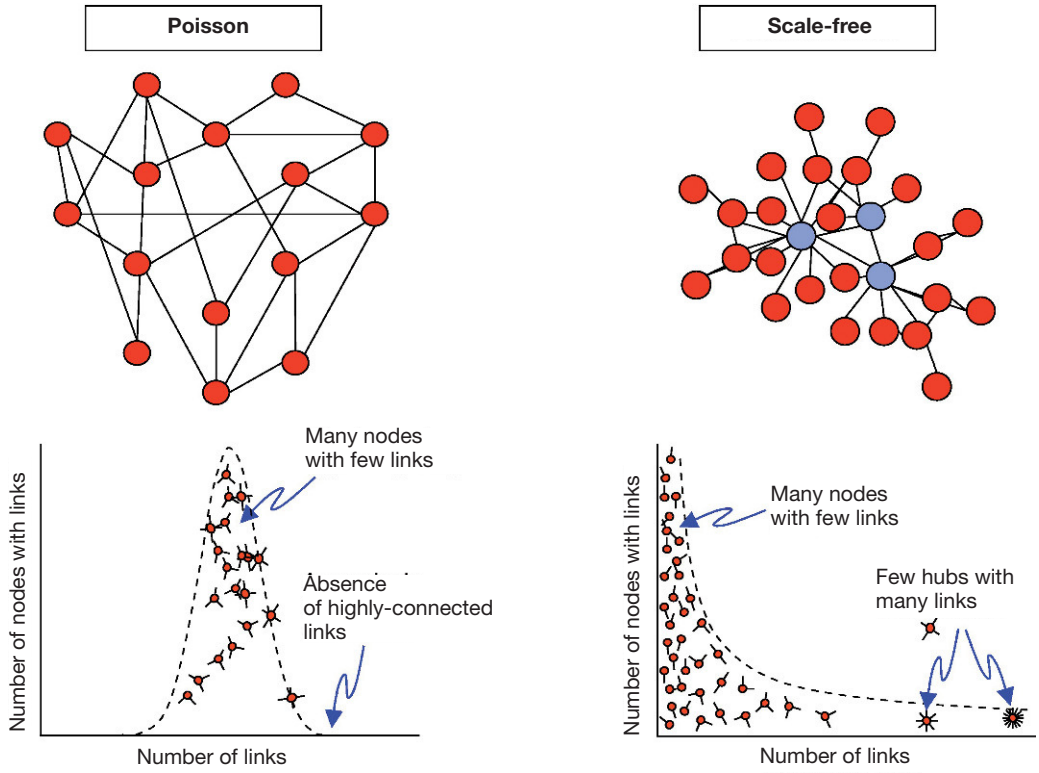

Figure 1. Poisson or normal distribution and scale-free distribution, courtesy of Dr. M. Perpiñá.

nodes.[6,7] A clear example of this characteristic of scale-free networks is the network of airports: there are many small airports, with few connections, and few large airports that are very connected (Heathrow Airport, for example). The recent air traffic crisis in Europe, due to the cloud of ash from an Icelandic volcano that forced Heathrow to close, caused the collapse of the entire European airport network. If the volcanic cloud had affected a non-hub airport, Europe would have still kept flying. This concept can easily be applied to the underlying molecular and cellular networks implicated in human health and disease.

Systems Biology, Health and Disease

The analysis of complex networks has recently been applied satisfactorily in human health and disease in such diverse settings as the characterization of epidemics[8,9] and how to control them[10,11] or the identification of the mechanisms that influence the metastatic propensity and lethality of cancer.[12] An example applicable to respiratory medicine was the study of allergic response in an experimental asthma model by Lu et al.,[13] based on the fact that asthma is a polygenic disease in which there are many genes interacting.[14] The authors created a network of molecular interactions using the database of the Biomolecular Object Network Databank and they superimposed the changes observed in gene expression that changed with experimental intervention (exposure to ovalbumin). A topologic analysis of the genes expressed under these experimental conditions determined an inverse relationship between the change of expression and the connectivity of the gene. In other words, genes with high changes in expression levels were more frequently situated in the periphery of the network (nodes with low connectivity), while the hubs (nodes with high connectivity) and superhubs (nodes that link hubs) tended to be less reactive to experimental intervention. These observations have methodological and biological implications. First of all, they suggest that genes with important biological functions could not be detected without using this type of research strategy. Secondly, they indicate that at least some biological responses, such as the allergic immune response, are mediated by changes in nodes with low connectivity.

The methodology derived from the scale-free networks and complex systems formerly described has also been used to evaluate the role of environmental or social factors in diseases. For example, Christakis and Fowler, in an article published in the New England Journal of Medicine,[15] studied the effects of social networks on the prevalence of obesity. In doing so, they constructed a network with the participants of the Framingham study, establishing connections among friends, neighbors, spouses and family members. They observed that the risk for developing obesity increased 40% if the individual had an obese sibling, but it increased 171% if the individual had an obese friend, suggesting that this social network was a stronger factor in the risk for obesity than the individual genetic load. In the same cohort, the same authors also studied the dynamics of smoking cessation over a 29-year period (from 1971 to 2000).[16] They observed that entire groups of connected people stopped smoking at the same time and that the smokers progressively appeared in the periphery of the network.

These and other studies have manifested a fact that is frequently ignored: networks dominate all aspects of human health and disease. To understand the mechanisms of disease, merely having a list of "disease genes" is not sufficient. One needs the graph or map of connections of the cellular components that are influenced by these genes and by the products of said genes. Given the dynamic situation of human health and disease, it is not enough to simply have a photo of the system; what is needed is a video that captures the evolution of the biological complexity in normal conditions (health) and abnormal conditions (disease), before as well as after therapeutic intervention.

The existence of specific alterations in molecular and genetic networks brings into play the possibility that diseases are not as

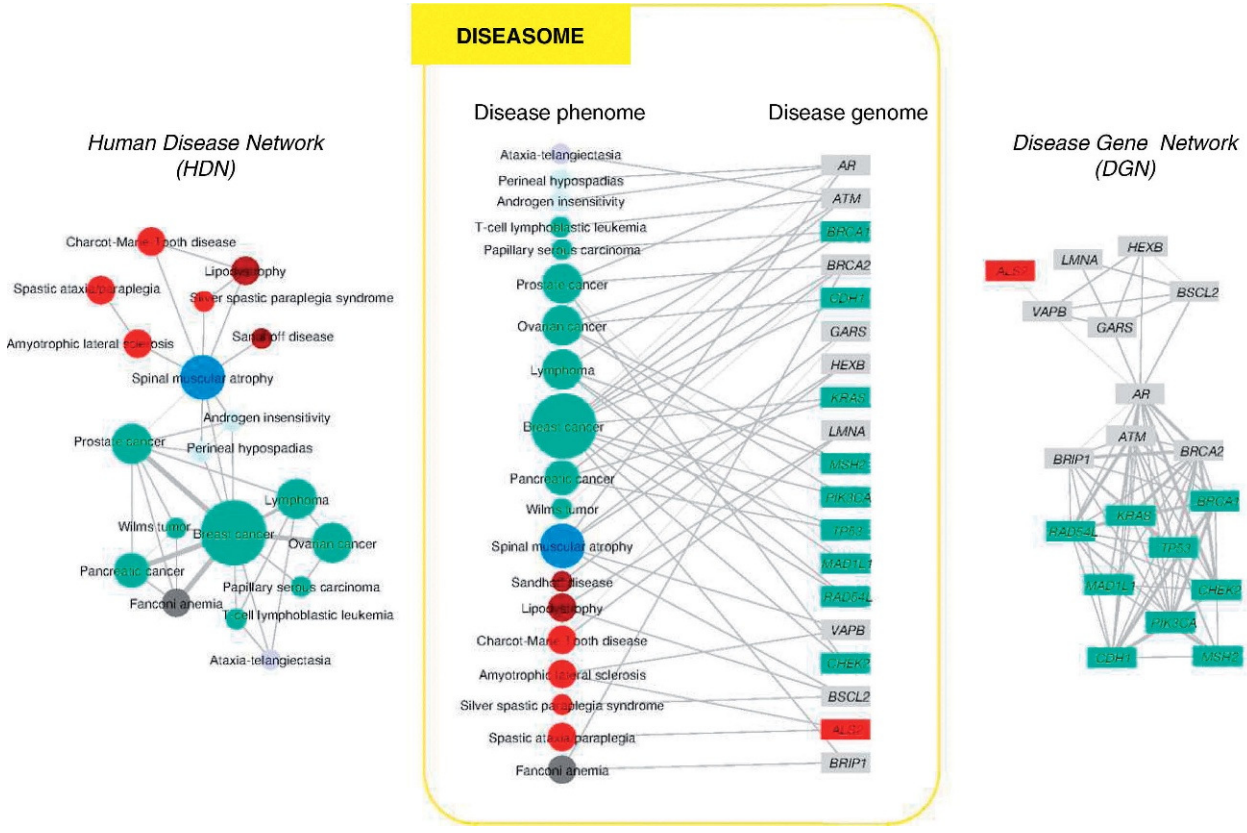

Figure 2. Construction of the "Diseasome". The circles represent diseases and the rectangles genes. A disease and a gene are linked if mutations in said gene provoke said disease. The size of the circle is proportional to the number of genes that participate in said disease. Disease Gene Network, DGN: two genes are connected if they are involved in the same disease; Human Disease Network, HDN: two diseases are connected if the same gene is involved in both. Source: Goh K et al.[19] ©2007 by National Academy of Sciences.

independent from each other as they are generally considered. There is a great number of diseases that, despite having different forms of clinical expression, form part of a same network.[17,18] In fact, with this approach the "diseasome" (fig. 2) has been described as the network of human diseases that share common genetic and molecular elementos.[19] This approach has revealed that there are many connections between individual disorders or groups of disorders, suggesting that the genetic origin of most diseases is, in a certain way, shared with other diseases. Cancer and neurological diseases are diseases with more connections; whereas metabolic and skeletal diseases, for instance, present low genetic heterogeneity and are less connected (fig. 2). Of the 1,777 genes studied, 1,377 are connected with other genes. Although the number of genes shared by various diseases declines as the number of diseases increases, some other genes, such as TP53 or PAX6, are associated with up to 10 diseases, representing the largest hubs in the network. These observations suggest that the majority of genes associated with disease are not essential. On the other hand, essential genes whose effects are frequently lethal in the womb or in early extra-uterine life tend to codify hubs and occupy a central position in the network. Finally, the authors observed that the proteins that are associated with the same disease show a ten-times-greater tendency to interact amongst themselves than those that are not associated with the same disease. As a whole, all these observations support the existence of specific "modules" for specific diseases.

The contemporary classification of diseases is fundamentally based on clinical presentation (phenotypes). Loscalzo et al.[20] propose a new approach in the classification of diseases based on four different networks that interact: 1) principal molecular abnormality (primary genome or proteome) associated with the principal phenotype; 2) modifier genes or proteins of the main phenotype principal (secondary genome or proteome); 3) polymorphisms or haplotypes (intermediate phenotype) that influence each genetic response to stress (inflammation, apoptosis, proliferation, reparation); and 4) environmental determinants. Based on the confirmation of the pathophysiological relevance of these four networks, new alternatives can be considered for optimizing therapeutic approaches to disease[21]: to identify new therapeutic targets (for example, the androgenic receptor in prostate cancer[12]), to determine the appropriate dosage of a medication, based on its metabolic profile,[22] and to establish the causes of resistance to treatments or to improve the toxicity of drugs.[23]

Hidalgo et al.[24] have demonstrated that the progression of disease (the "video" discussed previously) can also be represented and studied with a strategy based on networks. These authors have generated the Phenotypic Disease Network (PDN) (fig. 3) by reviewing the electronic clinical data of more than 30 million patients (Medicare). The PDN study shows that: 1) patients develop diseases that are closer to each other in the network; 2) progression of the disease along the links of the network is different between patients of different sexes and different ethnicities; 3) patients diagnosed with diseases that have many connections in the PDN tend to die before those affected by less-connected diseases; and 4) diseases that tend to be preceded by others in the PDN tend to be more connected than diseases that precede others, and they are associated with higher mortality rates.[24]

P4 Medicine

The phrase "P4 Medicine" (personalized, predictive, preventive and participatory) was coined by David Galas and Leroy Hood from the Institute for Systems Biology (ISB) in Seattle.[4,25] The ISB studies

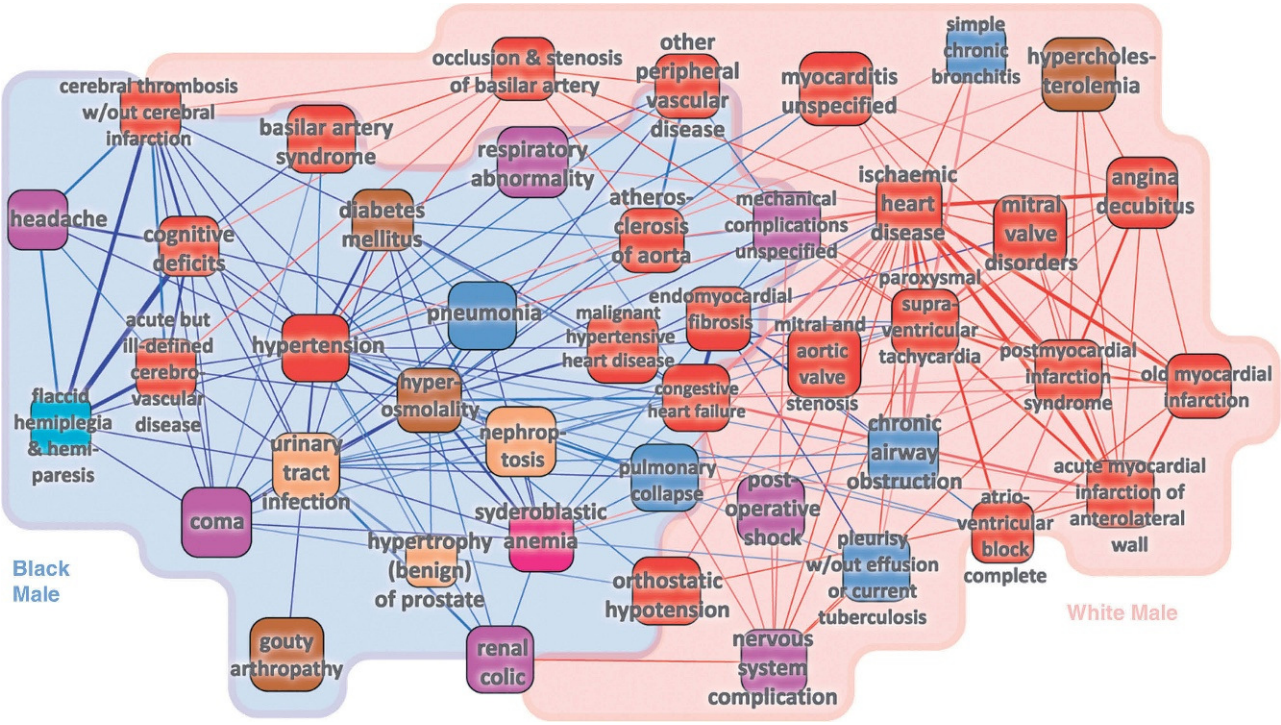

Figure 3. Phenotypic Disease Network. Differences between race and sex. The nodes identify diseases. The color of the node represents an ICD9 category; blue links indicate comorbidities that are stronger among black men, while the red links indicate comorbidities that are stronger among white men. For more information, consult the text. Source: Hidalgo CA et al.[24]

biological complexity based on three fundamental premises: 1) there are two types of biological information: digital genome information and environmental information, outside the genome, that modifies said digital information; 2) biological information is captured, processed, integrated and transferred by means of biological networks (RNA, proteins, controlling regions of the genes and small molecules) to the molecular systems that execute vital functions; and 3) biological information is codified in a multi-scale hierarchy: DNA, RNA, proteins, interactions, biological networks, tissues and organs, individuals and, finally, ecologies. It is important to highlight that the environment affects each level of this hierarchy and modulates the reception of the digital information from the genome.

Galas and Hood predict that in the next 5 to 20 years, technological and computational advances will allow us to compile, analyze and put this complexity into clinical use and public health care applications (P4 Medicine). It is said that P4 Medicine will be "personalized" because it will be based on the genetic information of each individual; it will be "predictive" because this personalized information will be able to determine the risk for certain diseases in each individual; it will be "preventive" because, given the prediction of risk, prophylactic measures will be able to be taken (lifestyle or therapeutic) to decrease risk; and, last of all, it will be "participative" because many of these prophylactic interventions will undeniably require the participation of the patient. Due to such participation, one of the most traditional aspects (and possibly the least positive) of clinical practice will therefore disappear: doctor-patient paternalism.

Theoretically, P4 medicine should provide an important number of benefits for the patient as well as for the health-care system. Galas and Hood highlight[25]: 1) the possibility to acquire and process billons of data for each particular individual; 2) the compilation and analysis of longitudinal information for each individual, enabling early disease detection and monitoring the therapeutic effectiveness of established treatments; 3) the stratification of patients into disease groups, where the specific pathological processes involved are better defined (clinical phenotypes),[26] leading to the development of alternative therapies specifically directed at these phenotypes, thus achieving greater success rates; and 4) the facilitation of the entire drug development process by identifying new therapeutic target hubs, reducing adverse reactions to medication (human genome) and reducing time, cost and failure rate of therapeutic assays (*in silico* clinical assays).

Although science and technology have advanced enormously in the last decade, new advances are still necessary for P4 Medicine to become a reality, including[25]: 1) the development of methods for determining the structures of individualized genomes (sequencing of personalized genomes); 2) microfluidic techniques, analysis of individual cells and molecular imaging; 3) identification and validation of organ-specific protein, micro RNA and other molecular biomarkers; and 4) new mathematical and computational methods like dynamic networks enabling the study of the perturbations caused by treatments in biological networks.

Moreover, significant changes will be equally necessary in the education of patients and health-care professionals about P4 Medicine. The former should be well-informed about the significance of the information available and their personal options; the latter should understand not only the most complex biological aspects derived from this new approach of systems biomedicine, but also its legal and ethical implications. Finally, the entire healthcare industry (from pharmaceutical companies to healthcare providers, insurance companies and medical diagnostic laboratories, etc.) will also have to transform in the years to come, possibly favoring the creation of global strategic alliances between academics, industry and administrations in order to facilitate and catalyze the arrival and development of P4 Medicine.

Conclusions

The scientific advances (genomic and proteomic, fundamentally) and technological breakthroughs (bioinformatics and imaging techniques, especially) of recent decades, together with the birth of

the new science of complex systems and networks, prepare the ground for the birth and development of a new way to practice medicine: P4 Medicine. Our text justifies this possibility, while discussing its main advantages and current limitations. For those skeptical readers who consider that what we have reported is still far off and is confined, or nearly so, to the realm of science fiction, the authors would like to remind these skeptics that just 15 years ago none of us had a mobile phone or access to the internet. Hardly but a few years have passed and it is difficult to imagine how we could have done many of the activities that are part of our daily work regime without either of them. We only need to look forward to at least accept the possibility that the future, P4 Medicine, is just around the corner!

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Conflict of interest

The authors declare having no conflict of interest.

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