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A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory

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Systems biology and the digital revolution are together transforming healthcare to a proactive P4 medicine that is predictive, preventive, personalized and participatory. Systems biology – holistic, global and integrative in approach – has given rise to systems medicine, a systems approach to health and disease. Systems medicine promises to (1) provide deep insights into disease mechanisms, (2) make blood a diagnostic window for viewing health and disease for the individual, (3) stratify complex diseases into their distinct subtypes for a impedance match against proper drugs, (4) provide new approaches to drug target discovery and (5) generate metrics for assessing wellness. P4 medicine, the clinical face of systems medicine, has two major objectives: to quantify wellness and to demystify disease. Patients and consumers will be a major driver in the realization of P4 medicine through their participation in medically oriented social networks directed at improving their own healthcare. P4 medicine has striking implications for society – including the ability to turn around the ever-escalating costs of healthcare. The challenge in bringing P4 medicine to patients and consumers is twofold: first, inventing the strategies and technologies that will enable P4 medicine and second, dealing with the impact of P4 medicine on society – including key ethical, social, legal, regulatory, and economic issues. Managing the societal problems will pose the most significant challenges. Strategic partnerships of a variety of types will be necessary to bring P4 medicine to patients.

Introduction

Medicine is undergoing a revolution that will transform the practice of healthcare in virtually every way. This revolution is emerging from the convergence of systems biology – a holistic approach to biology (and medicine) – and the digital revolution with its ability to generate and analyze 'big data' sets, deploy this information in business and social networks and create digital consumer devices measuring personal information.

Systems biology focuses on analyzing the incredible complexity of biological systems (normal and diseased) by (1) defining the components of the system, (2) determining how these components interact with one another and (3) delineating the dynamics of these components in space and time which are necessary for carrying out their biological functions. This means that the analyses must be global, integrative and dynamical. Systems medicine, the child of systems biology, is beginning to alter the face of healthcare through (1) a systems approach to disease, (2) driving the emergence of technologies that permit the exploration of new dimensions of patient data space (e.g. sequencing the individual human genome) and the analyses of the quantized units of biological information – single genes, single molecules, single cells, single organs – to provide disease-relevant information on health or disease for the individual and (3) the resulting explosion of patient data that are transforming traditional biology and medicine into an information science [1–3].

The digital revolution is harnessing big data sets through computational analyses and by creating powerful new business and social networks that have already transformed communications,

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finance, retail and information technology. The digital revolution is contributing to healthcare for the individual in several important ways: (1) providing tools and strategies for managing and analyzing large biological and environmental data sets; (2) catalyzing the invention of personal monitoring devices that can digitalize biological and social information to access, thus enabling an assessment of wellness and disease for the individual (e.g. the 'quantified self'); and (3) providing models for the creation of consumer (patient) driven social networks that focused on optimizing wellness and/or dealing with disease.

The convergence of the digital revolution and systems approaches to wellness and disease is beginning to lead a proactive P4 medicine that is predictive, preventive, personalized and participatory [4–6]. Thus P4 medicine is the clinical application of the tools and strategies of systems medicine to quantify wellness and demystify disease for the well-being of the individual. The digital revolution has given scientists the ability to generate and analyze previously inconceivably large quantities of digital data. Using these new capabilities and employing the domain expertise of biology to direct the development of software, systems biologists have developed powerful suites of new tools for mining, integrating and modeling 'big data' sets of heterogeneous biological data to generate predictive and actionable models of health and disease for each patient. 'Actionable' means that the data provide information that is useful for improving the health of the individual patient. Thus, systems biologists have transitioned from the reductive studies of traditional biology that focus on a few genes or proteins to the new holistic and comprehensive analyses of systems biology, analyzing how all of the components of biological system interact.

Unlike the reactive, pauci-data, population-based, hierarchical approach of our contemporary evidence-based medicine, P4 medicine will not be confined to clinics and hospitals. It will be practiced in the home, as activated and networked consumers use new information, tools and resources, such as wellness and navigation coaches and digital health information devices and systems to better manage their health. In what follows, we will provide a brief picture of systems medicine and its role in the emergence of this proactive P4 medicine.

Systems medicine

In 10 years we see every consumer of healthcare surrounded by a virtual cloud of billions of data points (Fig. 1). These data will range from molecular and cellular data, to conventional medical data, to enormous amounts of imaging, demographic and environmental data. Big data sets are required to deal with the complexities of disease and wellness. This complexity arises naturally from Darwinian evolution – a random and chaotic process that builds current solutions to environmental challenges based upon past chaotic successes. The results are biological systems, both normal and diseased, that resemble Rube-Goldberg-like devices with many components connected in complex ways operating dynamically to achieve a function [7]. In this regard, systems medicine is all about identifying all the components of a system, establishing their interactions and assessing their dynamics – both temporal and spatial – as related to their functions. The innate complexity of human biology is compounded by a myriad of social and environmental factors that are crucial determinates of health. A systems approach to medicine and health requires that enormous amounts of data be deciphered and integrated into a 'network of networks' model that includes network interactions and integrations at many levels, relating the individual's relevant biological, social and environmental information (Fig. 2). Big data sets pose two significant problems – how to deal with the enormous signal-to-noise challenges intrinsic to all large data sets and how to convert data into knowledge. Solving these problems is the role of systems medicine.

One of the grand challenges of systems medicine is how to integrate multiscale biological information into predictive and actionable models. Descriptions of the emergence of the four paradigm changes that led to systems medicine and P4 medicine – high throughput biology, the human genome project, the creation of cross-disciplinary biology and systems biology – are discussed in Refs [8,9].

Systems medicine underlies P4 medicine and provides key strategies and technologies for deciphering the complexities of disease. Ironically many people use the term 'genomic medicine' to denote the medicine of the future – yet in principle genomic medicine is one-dimensional in nature – only encompassing nucleic acid information. Systems medicine, by contrast, is holistic and utilizes all types of biological information – DNA, RNA, protein, metabolites, small molecules, interactions, cells, organs, individuals, social networks and external environmental signals – integrating them so as to lead to predictive and actionable models for health and disease. We believe that many who use the term genomic medicine actually take this much broader systems view – but then why not call it systems (or P4) medicine?

Systems medicine employs five strategies for dealing with biological complexity:

1. It views medicine as an informational science – and this provides an intellectual framework for dealing with complexity. For example, there are two types of biological information – the digital information of the genome and the environmental signals that come from outside the genome. Together these two types of information are integrated in the individual organism (e.g. a human) to produce its phenotype – normal or diseased. These two types of information and the phenotypes they produce are connected through biological networks that capture, integrate and then transmit the information to molecular machines that execute the functions of life. It is the dynamics of networks and molecular machines that constitute a major focus of systems studies. The 'network of networks' provides yet another multi-scale approach to organizing and integrating information (Fig. 2). Indeed, a fundamental postulate in systems medicine is the idea that disease arises from disease-perturbed networks (perturbed by genetic changes and/or environmental signals) and the resulting altered molecular machinery encoded by the disease-perturbed networks leads to the pathophysiology of the disease. Thus following the dynamics of the disease-perturbed networks gives deep insights into disease mechanisms and provides a powerful tool for dealing with the signal-to-noise challenges of big data sets as we have shown in two mouse models – neurodegeneration (prion infection) [10] and glioblastoma (from mice genetically engineered in a combinatorial manner with oncogenes and tumor suppressors). It is