New Biotechnology • Volume 29, Number 6 • September 2012

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

Leroy Hood[1] and Mauricio Flores[2]

[1] Institute for Systems Biology, 401N. Terry Ave, Seattle, WA 98121, USA
[2] P4 Medicine Institute, 401N. Terry Ave, Seattle, WA 98121, USA

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,

Corresponding author: Hood, L. (lhood@systemsbiology.org)

1871-6784/$ - see front matter doi:10.1016/j.nbt.2012.03.004

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

FIGURE 1

In 10 years a virtual cloud of billions of data points will surround each patient. These data will be of many different types and, accordingly, multistage. The challenge will be to convert these data into simple hypotheses about health and disease for the individual.

also crucial to integrate and model the many diverse data types arising in connection with each patient even although systems dynamics cannot be followed experimentally. The reasons for this are obvious – one cannot follow in humans the disease from initiation to the end, one cannot usually sample easily the diseased tissue at different time points, nor can one experimentally perturb the system with environmental signals. The need for systems dynamics, to deal with noise and create models, emphasizes the importance of experimental animal disease models where the starting point of the disease process can be known (e.g. by genetic activation of the disease process or the experimental initiation of disease such as an infection) and the dynamics followed until death. The key point is that animal models must closely mimic their human counterpart diseases. Scientists must clearly identify those aspects of the disease-perturbed systems that are orthologous to human disease and those that are unique to the animal – and use the former for gaining dynamical insights into human disease. Then animal studies will be powerfully informative about human disease.

2. My belief (LH) is that a special infrastructure is required for practicing systems medicine. This belief is driven by the conviction that leading edge biology must drive the development of new high throughput technologies to explore new dimensions of patient data space, and the data arising from these technologies in turn require the pioneering of new analytical tools for the integration and modeling of diverse data types. I (LH) have termed this the 'holy trinity' of biology – biology drives technology drives analytical tools – and integrated together these revolutionize our understanding of medicine (Fig. 3). This approach requires a cross-disciplinary environment where biologists, chemists, computer scientists, engineers, mathematicians, physicists and physicians all learn to speak the languages of the other disciplines and work together in biology-driven teams to achieve this holy trinity. A second point is the importance of the 'democratization' of data-generation and data analysis tools; that is, making these tools accessible to all individual scientists so that they may carry out either big science or small science projects. Thus the infrastructure of systems medicine consists of both the instrumentation to generate data for the diverse 'omic' technologies (genomics, proteomics, metabolomics, interactomics, cellomics, among others) and a culture that

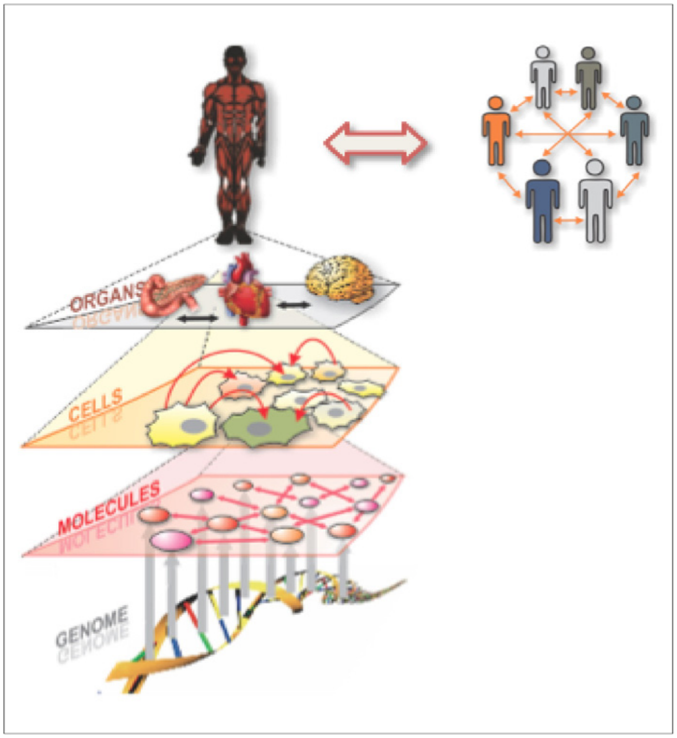

FIGURE 2

A figure depicting the 'network of networks' that specifies the nature of some of the integrated networks that specify normal biology and disease. The genetic, molecular, cellular, organ and individual networks are represented – and they represent a fully integrated network of networks. Networks are powerful tools for integrating and modeling biological data. Networks also provide a powerful means for dealing with signal to noise problems.

encourages scientists to learn to speak the languages of multiple scientific disciplines and how to work together in biology-driven teams practicing the holy trinity in the context of specific big or small science problems. This systems-driven infrastructure is what the Institute for Systems Biology (ISB) has spent the first 10 years of its existence creating [11].

3. Experimental systems approaches to disease are holistic – generating global and comprehensive data sets, following the dynamics of disease-perturbed networks across disease initiation and progression and then integrating diverse data types together to create predictive and actionable models (Fig. 4) [10]. Thus systems medicine will give fundamental new insights into disease mechanisms – and hence will open new opportunities for diagnosis, therapy and prevention (see below).
4. The systems approach to disease mandates the need to develop new or emerging technologies that can explore new dimensions of ill or healthy individuals' data space as reflected in part by the dynamics of biological networks. These technologies include new approaches to genomics [12], proteomics, metabolomics, interactomics, cellomics, organomics, *in vitro* and *in vivo* imaging, and other high throughput phenotypic measurements. Microfluidic and nanotechnology approaches are moving towards miniaturization, parallelization, automation and integration of complex chemical procedures [13,14]. But these new technologies must be driven by the real needs of biology – in this case deciphering disease. The outcome is an exponentially increasing ability to generate enormous amounts of digitalized personal data, big data, which necessitates a translation of data into knowledge. Advances over the past five years in DNA sequencing represent a prime example of the 'data explosion' and the opportunity to explore new dimensions of patient data space.
5. The 'data explosion' requires that new analytic tools be created for capturing, validating, storing, mining, integrating and finally modeling all of these biological data sets – thus helping to convert them into knowledge. A crucial point is that these software solutions must be driven by the needs of leading-edge biology and medicine – and by biological domain expertise. One big revolution in medicine is that we will create massive amounts of digital data for the 'quantified self' of each individual that will transform our ability to monitor and optimize our own wellness.

These five pillars of systems medicine permit biological complexity to be deciphered by providing a path forward for both generating large amounts of data, integrating and modeling these data in ways that reduce noise and delineate biological mechanisms; thus they create the conceptual framework for converting data into knowledge. These pillars also create the medical opportunities embodied in P4 medicine – prediction, prevention, personalization and participation.

P4 medicine

Systems medicine is focused on developing biological, technical and computational tools to decipher the complexities of disease. P4 medicine employs the tools of systems medicine for quantifying wellness and demystifying disease for the well-being of the individual, as well as dealing with the societal opportunities and challenges created by this revolution in medicine.

The convergence of systems approaches to wellness and disease with newly activated and networked patients and consumers will result in a P4 medicine that integrates discovery science with clinical practice and health management by networked and activated consumers. This integration will generate the vast heterogeneous databases constituting the virtual cloud of billions of data points represented in Fig. 1. Analyses of this data cloud will yield the 'network of networks' for each patient and the discoveries and optimization of wellness and disease emerging from relevant patient (consumer) social networks. Systems (P4) medicine is now pioneering something that never existed before – actionable understandings of disease and wellness as a continuum of network states unique in time and space to each individual human being. These network states can be perturbed by various means, including but by no means limited to drugs, to restore and maintain health (Fig. 2).

These databases and networks will provide physicians and other healthcare providers with the information they need to deliver care tailored to the circumstances of each individual. We are beginning to see this in the case of certain cancers, where the DNA sequencing of the tumors provides insights into the mutations in signal transduction pathways that inform the choice of therapy for the individual patient. In addition, data from clinical encounters, and from networked patients and consumers actively involved in managing their health and that of their families, will provide millions of data points that will facilitate enabling systems

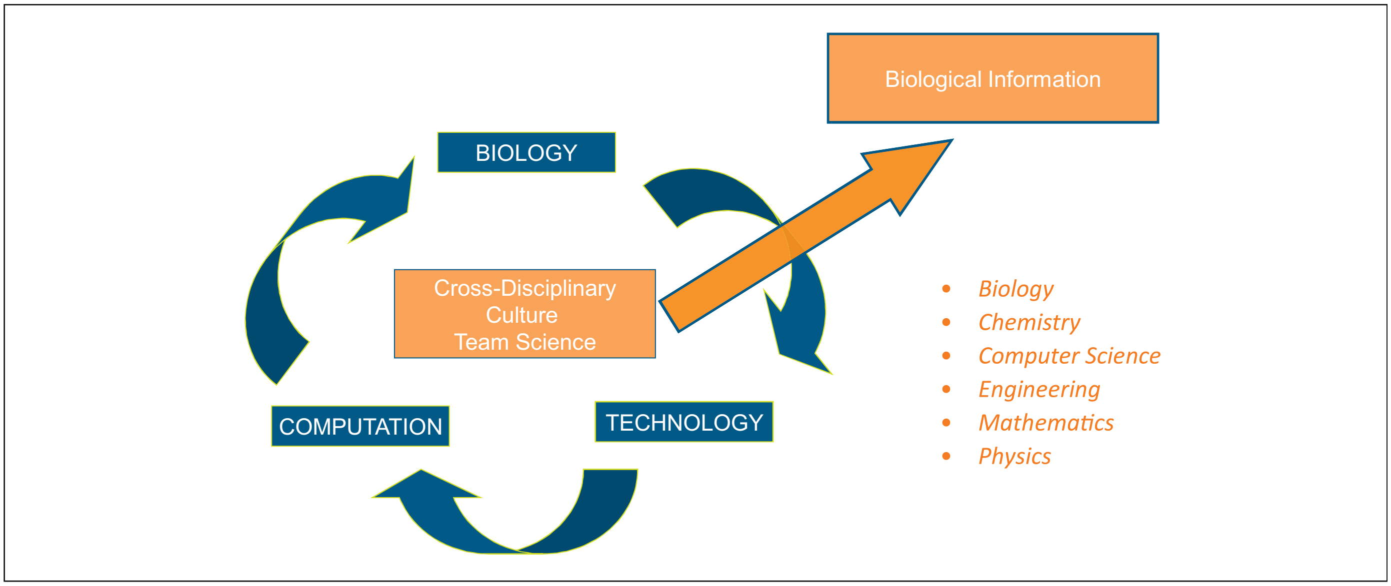

FIGURE 3

The 'holy trinity of biology' where biology drives technology drives computational/mathematical tools. Practicing this ideally requires a cross-disciplinary environment where scientists of many different disciplines (see lower right hand side of figure) learn to speak the languages of the other scientists and learn to work together in teams. When the holy trinity is practiced effectively enormous amounts of biological information can be generated rapidly.

biologists to decipher signal from noise in complex biological networks. These data will be funneled to scientific research centers and emerging health information companies to fuel large-scale studies, eventually on hundreds of thousands or even millions of patients, that will increasingly demystify disease and quantify wellness based on finely stratifying disease and health based on physiological, cellular and molecular markers.

An exciting new cycle of accelerating biomedical innovation will emerge as systems-medicine discoveries are routed back to patients and consumers, thereby generating more data to fuel further advances in actionable insights into individual biological systems. P4 medicine will include novel techniques and paradigms for facilitating new relationships between scientists, care providers, patients and consumers, as well as for dealing with the social opportunities and challenges that inevitably will arise from these new relationships.

Let us provide a 10-year glimpse into the future of the four Ps

Predictive

In 10 years, everyone will have his or her genome sequenced. 'Actionable genetic variants' – those whose identification opens the door to a course of action that will improve physical health or relieve anxiety – will drive forward the acceptance of the complete genome sequence as a part of the individual's medical record. While most of the medically relevant variation catalogued to date occurs in the coding regions of genes, it is becoming clear that copy number, structural variations, and other features of chromosomal architecture might also play a significant role in disease etiology. We believe that complete genome sequencing should be done in families. Family sequencing enables the correction of a significant fraction of the DNA sequencing errors – thus generating very accurate sequence. It also provides a deep understanding of the one-dimensional organization of the many genetic variants in the chromosomes of each individual (this is denoted haplotype determination) (Fig. 5) – thus enormously facilitating the discovery of disease genes or loci. We have identified more than 300 of these actionable variants and many more are being identified with every passing year. Indeed, every person's genome will be reviewed yearly for new actionable variants – and these will provide powerful insights to optimize the wellness of the individual. The genomes of individuals will provide an investment in individual information that yield increasing value for the rest of the person's life.

P4 medicine will make blood a window for assessing health and disease. Organ-specific proteins found in the blood will be analyzed in a longitudinal manner across the individual's life (Fig. 6). Changes in baseline measurements will give early disease warning [15]. Organ-specific blood proteins will also be used to assess drug toxicities. Within 10 years, we also envision a hand-held device that can prick your finger, take a fraction of a droplet of blood and quantify several thousand organ-specific proteins in five minutes. This device will permit one to follow the health or impairment status for each of your major 50 organ systems in a longitudinal manner over time [14]. Moreover, these 'microfluidic protein assays' will permit hundreds of millions of patients to be analyzed routinely, for example, bi-annually. Thus transitions from health to disease may immediately be identified and acted upon. Moreover, the organ-specific blood fingerprints will allow us to stratify diseases into their distinct subtypes (for impedance match against proper therapies) and to follow the progression of a disease. In the future, different drugs will be effective against different progression stages of a disease. In addition, P4 medicine will enable one to analyze the responses of multiple organs to a given disease – and thus extend the analyses of the 'networks of networks' from DNA, molecules and cells to organs (Fig. 2).

Preventive

Systems analyses provide insights into the dynamics of disease-perturbed networks. A new 'network-centric' rather than 'gene-centric' approach to choosing drug targets will employ multiple drugs to 're-engineer' a disease-perturbed network to make it

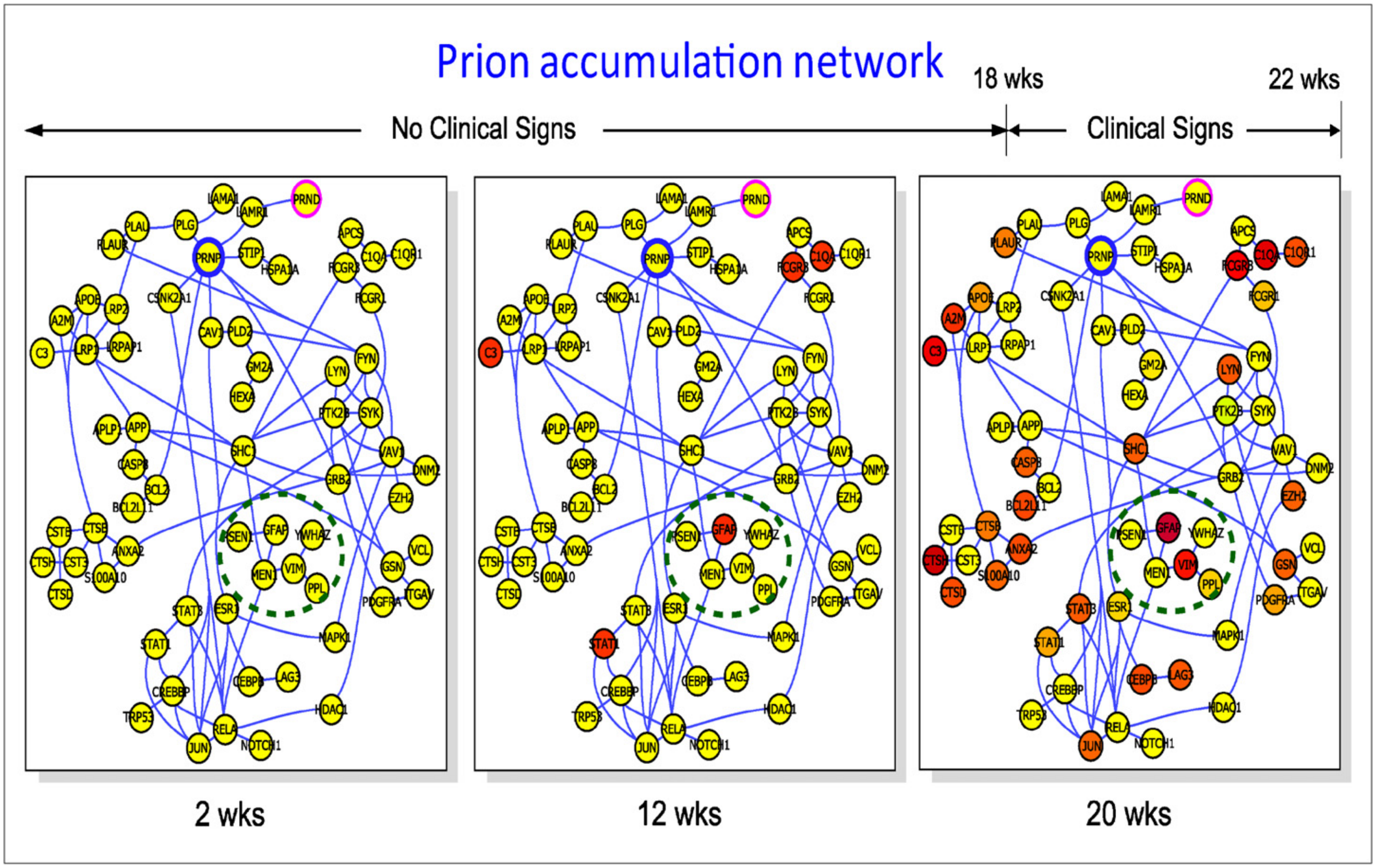

FIGURE 4

A schematic of the prion accumulation and replication network in the prion-induced mouse neurodegenerative disease. The red indicates transcript levels that have been increased in the brains from prion-infected animals as compared with normal control brains. The yellow indicated transcripts that are the same in control and diseased animals. The three panels represent the network at 2, 12 and 20 weeks in animals that live about 22 weeks with this disease. The disease-perturbed networks appear about eight weeks before the clinical signs appear in these animals.

behave in a more normal manner. We are now exploring this possibility in microorganisms [16]. This could make drugs more effective – and far less expensive – because there is a rationale for the choice of drug targets and their perturbations by drugs. Moreover, P4 medicine will in the future be able to predict the potential future emergence of disease-perturbed networks in patients and then design 'preventive drugs' that will block the emergence of these disease-perturbed networks and their cognate diseases. A systems approach to the immune response will, in time, give us the deep understanding of how to create effective cellular as well as humoral immune responses – and thus permit us to create effective vaccines for scourges such as AIDS. Clearly stem cells will provide powerful possibilities in the future for replacing damaged cellular and even organ components (as well as being powerful tools for understanding disease mechanism and stratifying disease). Finally, the digitalized data defining the quantified self will provide powerful new insights into optimizing wellness for the individual. Indeed, increasingly the focus of P4 medicine will move from disease to wellness.

Personalized

On average, humans differ from one another by about six million nucleotides in their genomes – and hence we, individually, are genetically unique. Even identical twins each may Exhibit 35 different 'intergenerational mutational nucleotide differences' from each parent and one another [12]. Each person must be treated as a unique individual and not as a statistical average. We must take account of the fact that individuals vary in ways that significantly impact effective treatment. Individuals should each serve as their own controls to determine when their own data reflect transitions from health to disease. Moreover, there is a growing sentiment that observations on single individuals may collectively provide fundamental new insights into the disease (or wellness) process – the so-called experiments where patient number *N* equals 1 may open up powerful new approaches to more effectively dealing with the individual patient and aggregating the useful data they generate, Imagine, in 10 years, 340 million Americans each with billions of data points – this will potentially create a powerful aggregated data source from which to infer the predictive medicine of the future. In this regard, we believe that it will be crucial to champion the idea that it is essential that all patients' data be made available, through an appropriately constituted entity, for qualified researchers and physicians to mine for the predictive medicine of the future. After all, this contribution will enable us to revolutionize the healthcare for our children and grandchildren – a point to which most patients are responsive. The data obviously should be anonymised. Moreover, laws must be enacted to protect the individual against the exploitation of their

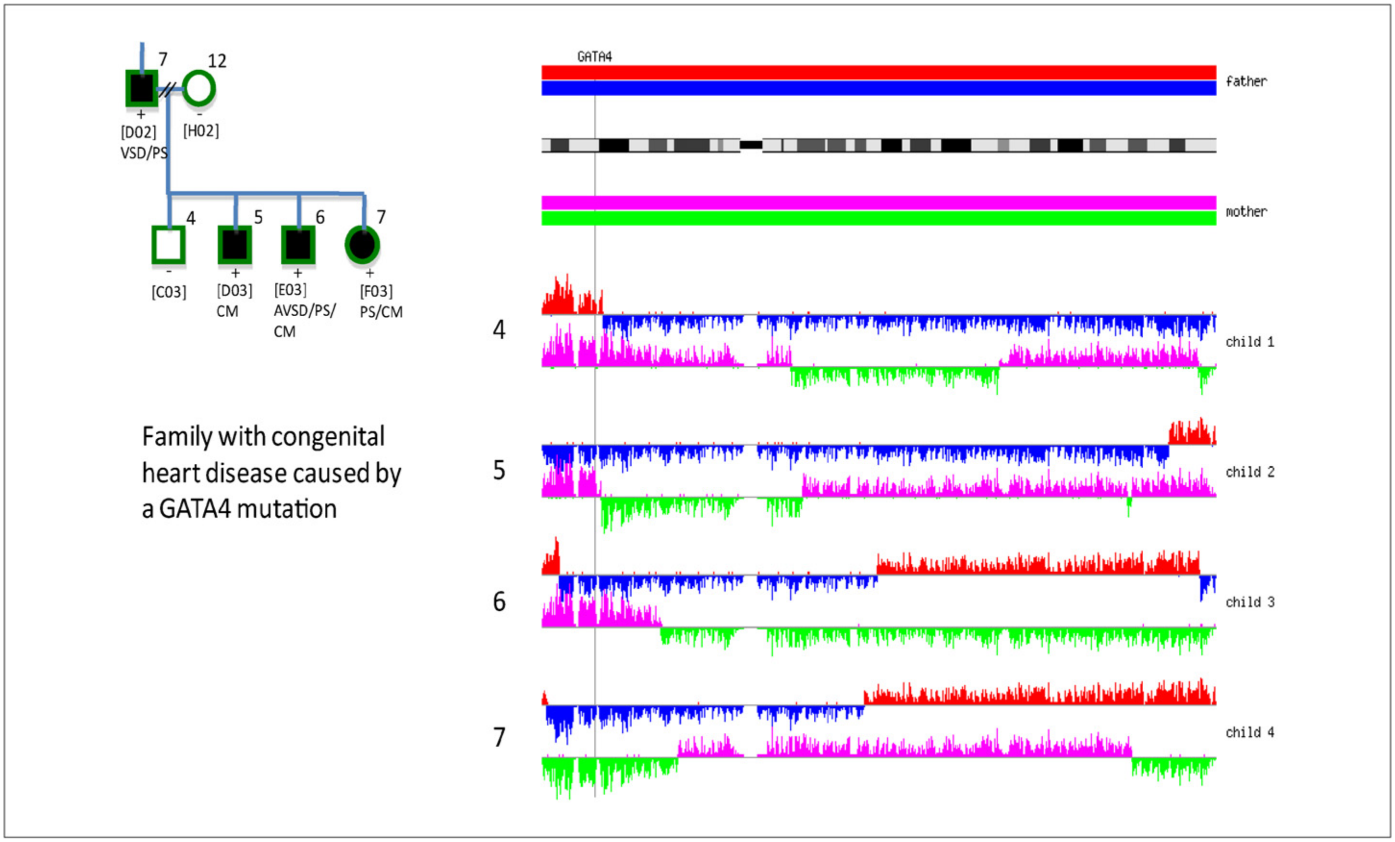

FIGURE 5

A schematic depicting the haplotypes of the members of a family of 6. The family tree is indicated at the left. The four parental haplotypes (two for each parent) are indicated by four different colors. The portions of the parental haplotypes that are passed on to each child are indicated by the same colors. Each color change denotes a site of chromosomal recombination. Family genome sequencing permits one to determine these recombinational sites with great precision. The important point is that the genes that cause particular diseases must reside in areas of shared haplotype by those individuals in the family exhibiting the disease.

medical data by other elements of society such as employers or insurance companies. In this regard, it is interesting to note that all of us made available our entire financial histories to three credit agencies for the convenience of having a credit card. Surely patients will recognize the benefits of being able to mine their collective data to pioneer the future of P4 medicine.

Participatory

P4 medicine will rely greatly on the positive contributions of activated patients and consumers. Our existing healthcare system is not well adapted to exploit the new capabilities of P4 medicine. Physicians as well as pharmaceutical and medical device companies are compensated solely for delivery of specific procedures and products – hence they have limited financial incentive to deploy new innovations to predict or prevent disease or to maintain wellness. Moreover, the healthcare industry is locked into financial and regulatory models based on large-scale population studies that ignore crucial genetic and environmental exposure differences among individuals. Pressure for change is beginning to be felt as the medical profession faces the looming challenge of increasingly being compensated for outcomes as opposed to service delivery. However, the most important source of pressure for change will be newly activated and networked patients and consumers. Collectively, they will constitute a vital new stakeholder in systems (P4) medicine that is very different from the passive recipients of expert advice characteristic of pre-digital medicine. Activated and networked consumers will do more than demand more effective healthcare – they will help direct the changes to achieve it.

Activated and networked consumers are beginning to push for healthcare that is adapted to their own particular circumstances, including their individual genome (which is static and need to be sequenced only once) and dynamic measurements such as from blood (which change over time and can track changing wellness and disease states). They are also beginning to push for new ways in which to engage with our science-based healthcare system to maintain wellness and achieve life goals as well as treating disease. Because of the reactive nature of the existing healthcare system, which is more accurately described as the disease management industry, the vast bulk of health management in areas such as nutrition, exercise and sleep takes place in the home without the assistance of physicians or other professionally trained care providers. The writers of best-sellers about the latest diet and purveyors of unregulated health products operate largely outside the constraints of science-based healthcare. Today's educated consumers are increasingly conscious of this fact and are beginning to demand that science-based healthcare address their need for assistance in managing their own health. They are stimulating the growth of a new market for devices that deliver increasingly real time data about every aspect of their health, ranging from activity levels to vital signs, and many of them are starting to come to their physicians for help interpreting these data.

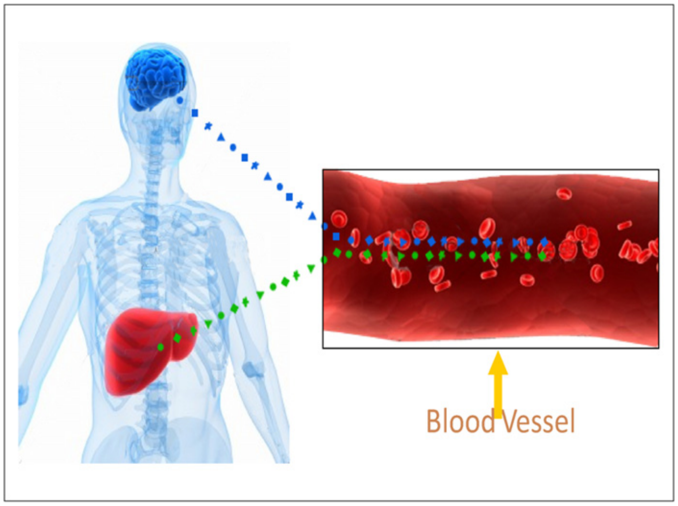

FIGURE 6

A diagram of organ-specific blood fingerprints (collections of organ-specific proteins) from the brain and the liver. For example, in a normal brain, each of the proteins in the brain-specific blood fingerprint will have one set of levels. In a diseased brain, the proteins whose cognate networks have become disease-perturbed will change their levels. Because each disease leads to distinct combinations of disease-perturbed networks – an analysis of the brain-specific protein fingerprints can distinguish healthy from diseased brains, and if diseased can stratify (e.g. distinguish from one another) the distinct types of brain diseases. Thus organ-specific brain fingerprints can provide early detection, a stratification of different types of disease and the ability to follow the progression of the disease (not shown).

Systems (P4) medicine responds to these growing demands by providing patients and consumers with actionable information which they can use to improve their health. This information can be cost-effectively mediated by clinical institutions using wellness coaches and genetic counselors in addition to physicians. It will be conveyed largely through digitally linked social networks, the most important of which will be family networks. One effective strategy may be to identify family members who are the most active in setting familial health-related standards and in caring for members with health problems and then to work with those highly activated people to help them do a better job. Medicine today systemically approaches patients as statistical abstractions, relying on the efforts of time-pressed physicians to achieve some degree of personalized care. Working with family and social networks will allow P4 medicine to systemically and more effectively deal with the reality of the social context in which patients and consumers are embedded and which largely determines how they eat, exercise and sleep. Activated patents and consumers working effectively within their family and social networks to utilize the increasingly real-time flow of personalized health related data will be able to reduce the incidence of and to better manage complex diseases such as Type II diabetes which account for a huge percentage of total healthcare costs and, of course, to optimize their wellness.

To achieve this goal we need to develop and continually update a 'gold standard' of reliable data, information and explanations of disease and health that will meet the needs of both physicians and activated patients and consumers. Developing and maintaining this gold standard will require a close working relationship between clinical and systems-based scientists. In addition, we need to develop ways to actively counter misinformation that might begin to spread through social networks and to correct misinformation often found on the current medical web sites and in other sources of medical information. While significant, these challenges are outweighed by benefits to be gained by wide dissemination of actionable 'gold standard' of personalized health data reviewed for consistency with the standards of our science-based healthcare system.

Ultimately patients and consumers will be recognized as not only a source of disease problems to be solved but as a source of disease and wellness solutions as revealed by their data. Creative new forms of engagement with networked and activated consumers as active participants in healthcare, as opposed to passive recipients of expert advice, will become a major source of value tapped by the healthcare revolution. Networked and activated participants will find new ways to adjust diet and exercise to move their biomarkers in the direction of better health. Crowd sourcing these problems will yield many benefits. For example, researchers will be able to correlate their behavior changes with biomarker impacts, their genome, their medical histories and other key parameters. Such data from millions or even tens of thousands would provide researchers with deep insights into the effects of nutrition and exercise that have never before been possible. These large scale personalized data sets would be the basis for quantifying wellness, providing society with a far more effective understanding of the effects of diet, exercise and sleep on highly stratified population sectors.

The digitalization of P4 medicine will enable its distribution to all citizens of the world – both developed and third world communities. For example, we remember those who thought the initial large brick-like cell phones of the early 1990s were ridiculous and could not imagine their widespread acceptance in the world (there are more than four billion cell phones world-wide). Today a woman in a rural village in India can make a living for her family with a cell phone thanks to the digitalization of communications with its potential for transforming the economic conditions of even the poor. So we will see a 'democratization of P4 medicine' in the throughout the world as inexpensive and digitalized P4 medicine becomes available (see below).

To summarize, we argue that P4 medicine has two major objectives for each participant – quantifying their wellness and demystifying their disease (Fig. 7). Our feeling is that the quantification of wellness will become increasingly important over time, ultimately dominating as the concern of most individuals. Table 1 provides a striking comparison of proactive P4 medicine with contemporary, reactive evidence-based medicine.

Two big challenges: education and information technology for healthcare

One big challenge for P4 medicine will be the education of consumers, patients, physicians and the members of the broader medical community, including the principal stakeholders in the healthcare industry. This education will present an enormous challenge – and will require ultimately the effective exploitation of social networks for education integrated with new effective information technology teaching strategies. Many individuals will initially want to remain 'old-fashioned patients' letting the doctor tell them what is best. However, once these individuals see the

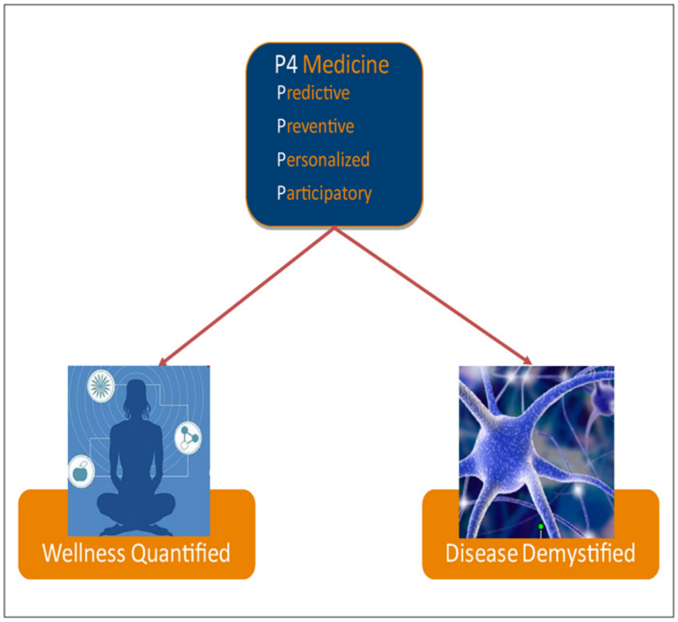

FIGURE 7

A schematic representation of the two major objectives of P4 medicine: quantifying wellness and demystifying disease.

power of consumer-driven medicine to improve individual health they will inevitably accept this new form of healthcare.

ISB has successfully developed modules of systems biology for the insertion of leading-edge biology into high school biology courses and is currently developing similar models for P4 medicine. Early education of consumers/patients is key. Another interesting idea is the suggestion that there be a commercial TV program, hopefully with very broad coverage, along the lines of the forensic CSI TV program, to explore solving the problems of P4 medicine in a well-written and compelling manner – that brings a knowledge of P4 medicine to the average viewer, just as CSI has brought insights in crime forensics to a broad audience. Another possibility is that one could use computer-game like strategies to bring the principles of P4 medicine to patients, physicians and members of the healthcare community.

Another challenge is how to produce an information technology (IT) for healthcare that can handle the enormous multi-scale data dimensionality that will arise from P4 medicine – for in the end P4 medicine is defined by the interconnected 'network of networks' – genetic networks connected to molecular networks, to cellular networks, to organ networks, to the networks of individuals in society, for each provide unique insights into the complexities of disease (Fig. 2). We must understand the individual in the context of all of these integrated networks, as this is the only way to capture both the digital information of the genome and all of the diverse environmental signals impinging on the individual from many different sources. This requirement places enormous demands on the need to develop an effective IT for healthcare. Healthcare IT must be comprehensive, interoperable, data-driven (e.g. bottom up), biology-driven and, we believe, fundamentally open source. It is probably beyond the capacity of any single organization to fashion a comprehensive IT for healthcare that goes beyond medical records to encompass the collection and distribution of the entire heterogeneous data cloud at the heart of systems (P4) medicine. Yet, that is what is required and an effectively orchestrated open-source approach could transform IT for healthcare. We must be able to capture the deep insights that will come from various patient social networks.

Impact of P4 medicine on society

P4 medicine will have an enormous impact on society and healthcare.

1. P4 medicine will transform the practice of healthcare in virtually every way. Table 2 provides a summary list of the powerful new strategies and technologies P4 medicine will employ.
2. P4 medicine will require that all healthcare companies rewrite their business plans in the next 10 years or so. Many will not be able to do so and will become 'industrial dinosaurs'. There will be enormous economic opportunities for the emergence of new companies tailored to the needs and opportunities of P4 medicine.
3. P4 medicine at some time in the future will turn around the ever escalating costs of healthcare and will in fact reduce these costs to the point P4 medicine can be exported to the developing world, hence enabling a 'democratization of healthcare' unimaginable even five years ago. These savings will arise from the early diagnosis and therefore more effective treatment of disease; the stratification of each major disease (e.g. breast cancer) into its major subtypes to achieve a proper impedance match for each individual against a drug effective for his or her subtype of disease; the ability to identify genetic variants that cause drugs to be metabolized in a manner dangerous to the patient (this is termed pharmacogenomics and more than 50 such validated variants have been identified to date); the ability to 're-engineer' disease-perturbed networks with drugs to generate a powerful and less-expensive rationale for drug-target selection; an increasing focus on wellness for each individual; and the emergence of striking near-term advances in modern medicine. These advances include an increasing ability to deal effectively with cancer, the use of stem cells for replacement therapy as well as new approaches to diagnostics and understanding disease mechanisms, an understanding of aging that will allow individuals to optimize and extend their effective mental and physical health routinely into their 80's and 90's, an understanding of the metagenome (e.g. population of microbes) of the gut and other body surfaces that will provide deep insights into one incredibly important manner in which the microbes of our environment influence our health, and finally the emergence of a deep understanding of neurodegeneration to avoid the personal and societal tragedies of diseases such as Alzheimer's Disease and Parkinson's Disease.
4. P4 medicine, through its driving of the emergence of new technologies and computational techniques, is pioneering the digitalization of medicine. The 'quantified self' will provide the data that will enable each individual to optimize his or her own health. This digitalization of medicine will also provide the data to empower P4 medicine to revolutionize healthcare through consumer-driven social networks (Fig. 8). The digitalization of medicine through the generation of big data sets for each individual – allowing one to sculpt with exquisite

TABLE 1

A comparison of the current reactive, evidence-based medicine with proactive P4 medicine

Reactive medicine – evidence-based medicine	Proactive P4 medicine
Reactive-respond after a patient is sick (symptom based)	Proactive-responds before a patient is sick (based on pre-symptomatic markers)
Disease-treatment system	Wellness-maintenance system
Few measurements	Many measurements, including complete genome sequencing, high-parameter blood diagnostics, many longitudinal omics measurements
Disease-centric, with standard of care associated with population-based disease diagnosis	Individual-centric, with standard of care tailored more fully to multiple measurements on the individual
Records not highly linked	Deeply integrated data that can be mined for continued improvement of healthcare strategies
Large-scale diffusion of medical information mediated mostly through physicians alone	Social networking of patients to enhanced shared experiences and diffusion of knowledge in consultation with their physicians
Drugs tested against large populations – 10s of thousands to develop statistics for FDA	Stratification of disease populations into small groups, 50 or so, that can be effectively treated to achieve FDA approval
Science based healthcare takes place almost entirely in clinics and hospitals	Science based healthcare takes place in the home as well as the clinic as networked and activated healthcare consumers use the information made available from systems biology and wireless measuring devices to do a better job of managing their health
Discovery science and medicine are largely separate spheres of activity which communicate primarily through publication of articles in peer reviewed journals	Discovery science and the practice of medicine are integrated through digital networks and heterogeneous databases that capture data from every clinical encounter for discovery purposes and quickly and efficiently distribute information about stratified diseases and populations to physicians on an ongoing basis

TABLE 2

A summary of the principal opportunities that P4 medicine will bring to medicine and healthcare

Systems approaches provide fundamental new insights into disease mechanisms
The human genome through actionable variant genes provides a means to begin optimizing human health and deal with disease
Blood as a window into health and disease – disease diagnostics, drug toxicity assessment, wellness assessment, among others
Stratification of diseases into their subtypes for a proper impedance match against a patient's disease and discovery of the proper drug
Assessment of multi-organ response in a disease
New approach to drug target discovery – re-engineering disease-perturbed networks to behave normally with drugs
Digitization of individual human parameters offers the opportunity for focusing on wellness, optimizing patient treatments and mining for the predictive medicine of the future create metrics for assessing and optimizing wellness

specificity wellness and appropriate responses to emerging diseases – is one of the transforming aspects of P4 medicine. Another important implication arising from the digitalization of medicine is the fact that personal data will become incredibly inexpensive (e.g. it is estimated that the first human genome sequence cost about a billion dollars, today it costs a few thousand dollars and in a few years genome sequences will cost perhaps a \$100) – thus digital technologies and their exponentially declining costs will contributing significantly to reversing the escalating costs of healthcare.

5. P4 medicine will bring increased wealth to the healthcare systems, communities and nations that practice it. The decreasing costs of healthcare have been mentioned above. Many economic opportunities will evolve from the knowledge of P4 medicine through the transformation of the healthcare industry. Additionally, we predict that a new science-based 'wellness industry' will emerge over the next 10–15 years that will in time far exceed the size of the healthcare industry. P4 medicine is an area replete with economic opportunities.
6. The patient (consumer), through social networks, will drive the emergence of P4 medicine. Because of intrinsic conservatism and sclerotic bureaucratic systems, physicians, healthcare specialists and the healthcare industry will take a back seat to the power of patient-driven social networks in bringing change to the healthcare system. Indeed, patients may be the only driving force capable of truly changing our contemporary healthcare system to the proactive P4 mode.

How to bring P4 medicine to patients

The challenges of bringing P4 medicine to patients and consumers have two crucial dimensions – technological and societal. The latter is far more complex. At the Institute for Systems Biology in conjunction with Ohio State Medical School, we have created the P4 Medicine Institute (P4MI) – a non-profit organization that is committed to creating a network of six or so clinical centers with ISB to employ the strategies and tools of P4 medicine in pilot projects to prove the power of P4 medicine. Striking pilot project success will be crucial in convincing conservative physicians, and a healthcare industry that is locked into disease-focused business models, of the potential of P4 medicine. P4MI is also interested in bringing relevant industrial partners to this clinical network. In addition, P4MI has established a fellows program to begin delving into some of the societal challenges of P4 medicine, eventually through 'white papers' on economics, the 'gold standard of healthcare information', ethics, regulations, among others. Strategic partnerships are a crucial component for bringing P4 to patients worldwide and gaining its widespread acceptance in the national and international medical communities.

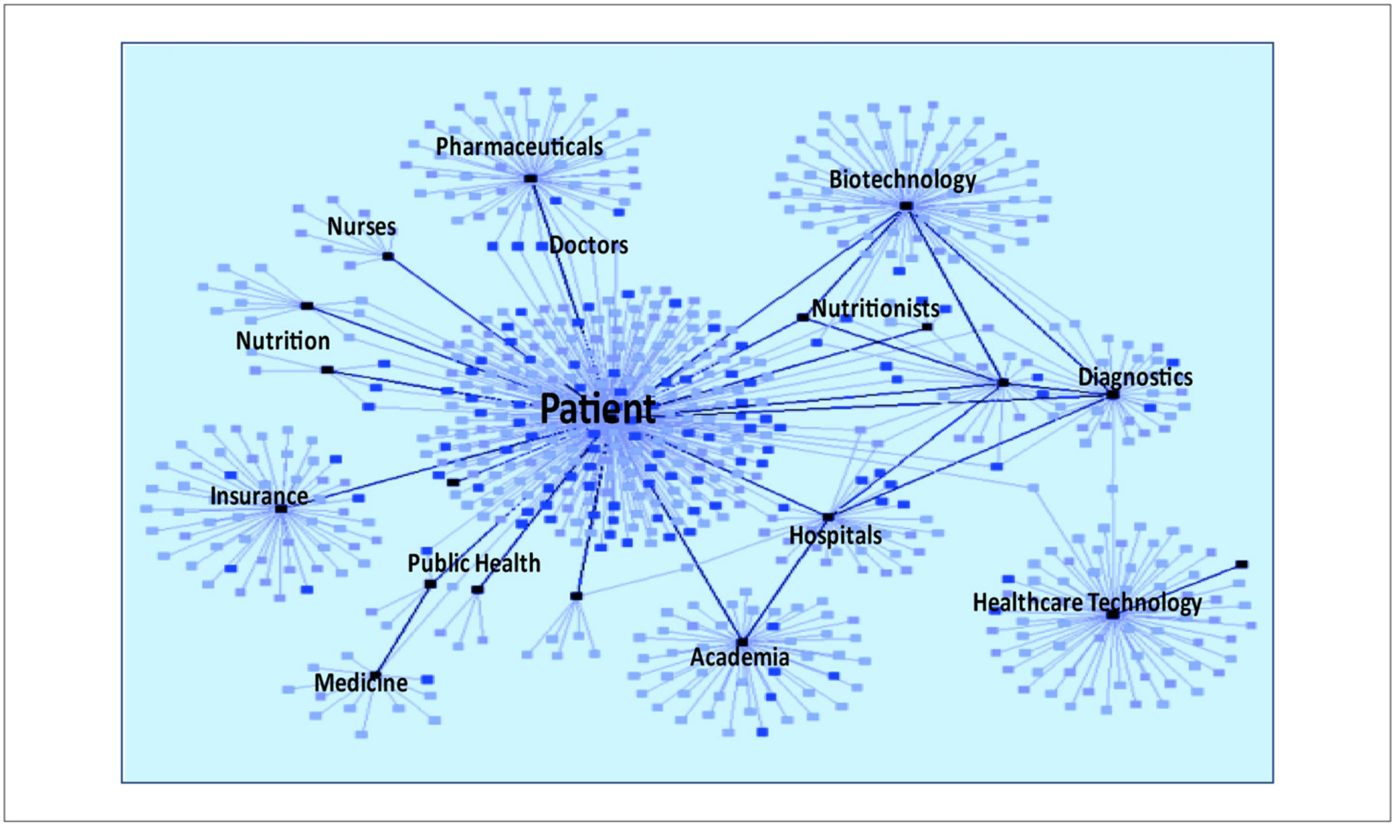

FIGURE 8

A network depicting the interacting components of the healthcare system indicating the dominant role that patients will have in advancing P4 medicine through their consumer-driven social networks. Networks allow one to organize and model data and are important in dealing with the signal to noise problem of large data sets.

As the P4MI pilot programs become successful and begin demonstrating the power of P4 medicine, an important next step might be for a small country to build a P4 medicine/healthcare system. This country could play a key leadership role in pioneering the new medicine of the 21st century, just as Johns Hopkins Medical School, in the early 1900s, adopted some recommendations of the Flexner Report on the future of medicine (sponsored by the Carnegie Foundation), which included the recommendation that medicine should integrate basic research and clinical medicine. Thus Johns Hopkins propelled itself from a mediocre medical trade school into a world leader in US and world medicine. So there is now a similar opportunity for Institutions (and countries) that pioneer P4 medicine/healthcare to become world leaders. It will take courage, leadership, resources and an effective communication of the vision to the stakeholders to catalyze the revolution in P4 medicine/healthcare. It goes without saying that any nation that assumes a leading-edge leadership role in catalyzing the emergence of P4 healthcare will be in a unique position to transform the healthcare of its citizens, to revolutionize its medical research agenda and to take advantage of the associated economic opportunities associated with the newly emerging world of P4 medicine.

Acknowledgements

Thanks to Kristin Brogaard, Nathan Price and Lee Rowen for advice and counsel in preparing this paper. LH would like to acknowledge the support of the Luxembourg Center for Systems Biomedicine and the University of Luxembourg, the General Medical Sciences Center for Systems Biology GM076547and a Department of Defense contract on Liver Toxicity W911SR-09-C-0062.

References

1 Hood, L. *et al.* (2004) Systems biology and new technologies enable predictive and preventative medicine. *Science* 306, 640–643

2 Price, N.D. *et al.* (2009) In *Systems Biology and the Emergence of Systems Medicine. Genomic and Personalized Medicine: From Principles to Practice*, (vol. 1) (Ginsburg, G. and Willard, H., eds) pp. 131–141, Elsevier

3 Auffray, C. *et al.* (2009) Systems medicine: the future of medical genomics and healthcare. *Genome Med.* 1, 2

4 Weston, A.D. and Hood, L. (2004) Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine. *J. Proteome Res.* 3, 179–196

5 Hood, L. and Friend, S.H. (2011) Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat. Rev. Clin. Oncol.* 8, 184–187

6 Tian, Q. *et al.* (2012) Systems cancer medicine: towards realization of predictive, preventive, personalized and participatory (P4) medicine. *J. Intern. Med.* 271, 111–12110.1111/j.1365-2796.2011.02498.x

7 Hood, L. (2011) Deciphering complexity: a personal view of systems biology and the coming of big science. *Genet. Eng. Biotechnol. News* 31

8 Hood, L. (2011) Acceptance remarks for Fritz J. and Delores H. Russ Prize. *NAE J. Bridge* 41 (Summer (2)), 46–49

9 Hood, L. (2008) A personal journey of discovery: developing technology and changing biology. *Annu. Rev. Anal. Chem.* 1, 1–43
10 Hwang, D. *et al.* (2009) A systems approach to prion disease. *Mol. Syst. Biol.* 5, 252
11 Hood, L. *et al.* (2008) Systems biology at the institute for systems biology. *Brief. Funct. Genomic. Proteomic.* 7, 239–248
12 Roach, J.C. *et al.* (2010) Analysis of genetic inheritance in a family quartet by whole genome sequencing. *Science* 328, 636–639
13 Heath, J.R. *et al.* (2009) Nanomedicine targets cancer. *Sci. Am.* 300, 44–51
14 Shi, Q. *et al.* (2012) Single cell proteomic chip for profiling intracellular signaling pathways in single tumor cells. *Proc. Natl. Acad. Sci. U. S. A.* 109, 419–424
15 Shizhen, Q. et al. (in press) SRM targeted proteomics in search for biomarkers of HCV-induced progression of fibrosis to cirrhosis in HALT-C patients. *Proteomics*.
16 Bonneau, R. *et al.* (2007) A predictive model for transcriptional control of physiology in a free living cell. *Cell* 131, 1354–1365