

Systems Biology and Emerging Technologies Will Catalyze the Transition from Reactive Medicine to Predictive, Personalized, Preventive and Participatory (P4) Medicine

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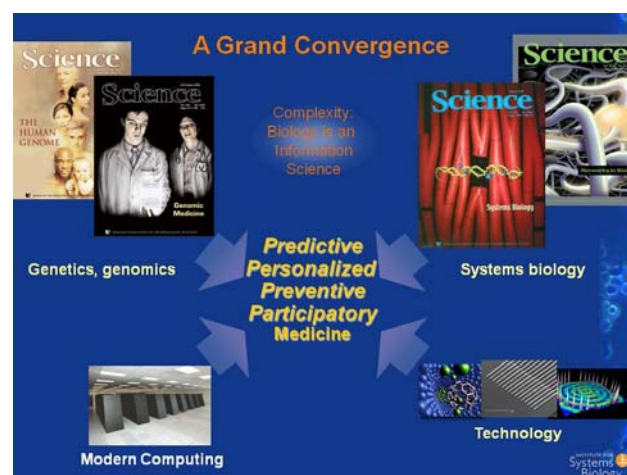
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SYNOPSIS

We stand at the brink of a fundamental change in how medicine will be practiced. Over the next 5-20 years medicine will move from being largely reactive to being predictive, personalized, preventive and participatory (P4). Technology and new scientific strategies have always been the drivers of revolutions and this is certainly the case for P4 medicine, where a systems approach to disease, new and emerging technologies and powerful computational tools will open new windows for the investigation of disease. Systems approaches are driving the emergence of fascinating new technologies that will permit billions of measurements on each individual patient. The challenge for health information technology will be how to reduce this enormous amount of data to simple hypotheses about health and disease. We predict that emerging technologies, together with the systems approaches to diagnosis, therapy and prevention will lead to a down turn in the escalating costs of healthcare. In time we will be able to export P4 medicine to the developing world and it will become the foundation of global medicine. The “democratization” of healthcare will come from P4 medicine. Its first real emergence will require the unprecedented integration of biology, medicine, technology and computation—as well as societal issues of major importance: ethical, regulatory, public policy, economic, and others. In order to effectively move the P4 scientific agenda forward new strategic partnerships are now being created with the large-scale integration of complementary skills, technologies, computational tools, patient records and samples and analysis of societal issues. It is evident that the business plans of every sector of the healthcare industry will need to be entirely transformed over the next 10 years—and the extent to which this will be done by existing companies as opposed to newly created companies is a fascinating question.



Keywords: systems biology, emerging technologies, P4 medicine, health care industry, large-scale integration

The changes of the past decade in science and technology as well as emerging opportunities in these areas can catalyze a major revolution in medicine and healthcare over the next 5-20 years. We use the word *can* here, because there are also still societal barriers to overcome, many of which are economic, ethical, policy and practice issues, rather than technical. What we want to discuss here, however, are the technical issues including new strategies, emerging technologies and powerful computational tools that will transform medicine. The changes in medicine are being initially catalyzed by a new systems approach to studying, understanding and monitoring fundamental biological and disease processes that will trigger the emergence of personalized medicine—a medicine that focuses on the integrated diagnosis, and treatment and prevention of disease in individual patients (Hood et al., 2004; Hwang et al., 2009). The prospective change in medicine is rooted in new science, but science is not enough. The convergence of systems approaches to disease; new measurement and visualization technologies; and new computational and mathematical tools can change our current, largely reactive mode of medicine, in which we wait until the patient is sick before responding, can entirely disappear over the next 10 to 20 years. It can be replaced by a personalized, predictive, preventive, and participatory (P4) medicine that will become more effective for the patient and cost effective for everyone. The healthcare industry, public policy sector, and consumer industries will be required to develop new and creative business models and products because of these new capabilities, and there is a unique opportunity now to enable and accelerate change by eliminating the key barriers that prevent the full realization of the revolution of personalized medicine. We address here what can be accomplished within the next decade. Key benefits of P4 medicine, to the patient and to the system, encompass a number of new medically powerful capabilities, including the ability to achieve the following.

- To gather billions of data points on each individual patient—and these data will be managed by new approaches to IT for healthcare that will be able to reduce this enormous data sets into simple hypotheses about health and disease for each individual—the emergence of personalized medicine
- To gather extensive longitudinal information about each patient that will allow them to become their own control and monitor their possible transitions from health to disease—thus we will be able to determine by this means a deeper answer to the questions what is health and what is disease
- To detect disease at an earlier stage than previously possible (for example, before any symptoms appear), when it is easier, more medically useful and less expensive to treat effectively
- To stratify patients into disease groups that define more precisely than ever the specific pathological processes involved and that enable the selection of optimal therapies for just those pathologies—this should allow very high therapeutic success rates
- To monitor the effectiveness of therapies to disease in the individual with frequent assessments of multiparameter blood biomarkers that assess the transitions from health to disease in individual organ (through organ-specific blood diagnostic proteins)
- To reduce adverse drug reactions by more effective assessment of individual drug responses using a network approaches both from the relevant organ and the blood to assess both on-target and off-target drug effects
- To improve the selection of new drug target candidates assessing the dynamics of disease-perturbed networks to identify key nodal points (proteins) that by drug interaction could return the network to a more normal functioning—or least abrogate the most deleterious effects of the disease perturbations
- To reduce the time, cost, and failure rate of clinical trials for new therapies by targeting effectively and monitoring precisely

the indicators of key pathological network perturbations

- To shift the emphasis in medicine from reaction to prevention – a fundamental change of philosophy, based in science and with the focus on wellness rather than disease (Hood et al., 2004).

The P4 medicine paradigm will hold the key to more cost effective care, improved patient outcomes, and to empower both the patient and the physician. Having extensive and more accurate, information to be used by the patient and the doctor to make decisions about prevention and treatment can change the relationships of patients to doctors and healthcare providers, and is at the heart of this future medicine. In order to bring the full benefit of the new science and technology to our health care system, however, an interdisciplinary focus is essential. This is systems biology, an integrative, interdisciplinary approach to biological science. Systems biology is built around the concept of close integration of computational methods, technology development and global measurement and analysis of biological systems.

In grappling with the issues of how to bring practical, personalized medicine into being, with its highly diverse technical, policy, economic and societal challenges, the opportunity also arises for unusual strategic partnerships between government, the academy and the commercial sectors. The societal, ethical and healthcare policy issues attendant to the anticipated changes will be profound in all healthcare systems. These changes must also be planned for so that the barriers to delivery of the benefits of the coming technical advances will not prevent their adoption. Another critical point is that the transformation of healthcare will in the end be catalyzed by emerging systems strategies, technologies and computational and mathematical tools. Assessing the nature of the new medicine will require an understanding of these strategies and technologies—as they lie at the heart of what P4 medicine will be able to do.

Science and technology have advanced enormously in the past decade, but more will be required to make the above described future applications to medicine a reality. Among the most important of these needed advances are the following.

- Methods for determining the structures of individualized genomes – personalized genome sequencing. While the advances in this area have been truly amazing in the increase in throughput and the decrease in cost achieved, new methods and approaches are still necessary for us to reach the speed and cost needed to have whole genome sequence become a general medical service. We believe the cost of full genome sequences will fall to less than \$1000 within the next 5 years—certainly affordable for today's medicine—and this will place the genome sequence squarely in the realm of essential data for every individual's health record in the near future. It remains true that we do not know much yet about how to use the information in the genome to improve health—but this will change rapidly as more studies are done in analyzing the relationships between the genotypes and phenotypes of large numbers of individuals.
- Methods for discovering and validating the levels of organ-specific proteins, microRNAs and other molecular biomarkers in the blood to assess health or disease in all major human organ systems by assessing the state of the key biological networks (Wang et al., 2009). The simple hypothesis embedded in a systems approach to disease is that disease arises as a consequence of one or more biological networks in the relevant organ that have become disease-perturbed through genetic and/or environmental pathogenic changes. These networks alter the levels of proteins that they encode—and if these proteins are secreted into the blood—these quantitative changes can be detected. The identification of

organ-specific blood biomarkers is particularly critical as this is the only means for identifying the site of disease that is changing the levels of these biomarkers. Powerful new mass spectrometry techniques have been developed for the discovery and validation of these biomarkers (multiple reaction monitoring (MRM) mass spectrometry is among the most promising) that are perhaps 100 times more rapid and 100 times less expensive than antibody-based procedures. This new approach to fundamental diagnostic strategies is very promising and is already gaining ground in that such blood markers are being discovered. These panels of molecular markers have the necessary information density to provide detailed, specific diagnostics.

- Correlate these molecular blood fingerprint panels with health and disease states in patients. Establish which molecular profiles reflect the key states of the involved disease-perturbed biological networks, which will allow us new measures and mechanistic understanding of the disease phenotypes. When diagnostic methods are available that reflect the states of the underlying networks in the organs the medical interpretation of the patterns observed from blood data will become increasingly rich and informative. A great deal of work is required to construct and verify the networks, the related pathological and normal states, and extensive patient-based studies are essential to this effort.
- Develop new blood protein measurement technologies. This requires two new technologies. First, the application of microfluidic approaches to make many, inexpensive and rapid measurements from small amounts of blood is required—and several new approaches are being developed in this regard. Second, new specific protein-capture agents, are required to provide the essential molecular identifiers, currently only provided by antibodies (Agnew et al., 2009). The use of antibodies must be replaced because of the difficulty in obtaining a large number of highly specific, tight-binding antibodies, and the fragility of these molecules in extensive everyday use. New readout methods are also required that will work rapidly and simply on very small volumes of blood (Fan et al., 2008). The barriers to achieving these technical breakthroughs are substantial, but it is likely they will come about within a few years.
- Develop new mathematical and computational methods for extracting maximum information from molecular information on individuals (including their genomes), and from other clinical data and history—as well as integrating all of this information into predictive models (Carter et al., 2009). Develop new computational techniques are needed for building dynamic networks from massive amounts of integrated genomic, proteomic, metabolomic and higher level phenotypic data. Many of these problems are unsolved or at most partial unsolved, but the way is reasonably clear to approaching the problems and we would predict that methods will be available in the next few years (Heath et al., 2009). This is the heart of the new medicine: new methods for interrogating and understanding the interaction between the environment and the genome of the individual.
- Drug perturbations of biological networks to be understood in a predictive sense. The technical problems here are very hard, mostly because of the enormity of the number of variables and the sparseness of the data. With enough data, including enough data that enables the genetic deconvolution of the relevant network perturbations, they are all approachable. The problems are both in the experimental design and measurement and computational arenas.
- Therapeutic perturbations of biological networks which re-engineering their behavior with drugs (diseased back to normal). We have no idea how to do this yet, but the advances in understanding the critical networks are impressive and increasing. We will likely learn how to do this in specific cases within a few years.
- Among the great opportunities for new technologies are new methods for creating pluripotent cells (stem cells) from normal, differentiated cells from each individual patient and then have the capacity to differentiate these stem cells from each individual to differentiated tissues that are relevant to the disease of the patient. These relevant tissues can be studied with large-scale data generating techniques *in vitro*—e.g. global measurement of genomics, proteomics, metabolomics, phenotypes, etc. parameters to come to understand better the nature of the disease-perturbed networks for each individual patient. The practical methods for doing this are developing rapidly, but the understanding the correlations of genotype and phenotype will be even more challenging—but very rich in opportunity for science and medicine. The ability to create stem cells with a given individual's genome enables us to begin to interrogate the details of the relationship of genetic variations in the genome and subtle differences in specific cell type functions. This technology will be remarkable, but understanding the results will be revolutionary.
- Single cell analyses. We believe that one of the major new opportunities in biology and medicine will be the advent of the ability to analyze in a comprehensive manner the contents of individual cells. We envision a time when the entire genome can be sequenced inexpensively from a single cell; when the transcriptomes, micRNAomes and proteomes from a single cell can be quantified; the single relevant cells from the patient can be perturbed with drugs to identify the optimal treatment; when the molecules secreted from single cells can be analyzed to assess environmental perturbants; when the key feature of immune blood cells can be determined to assess past and present immune capacities (e.g. the VJ and VDJ junctions of 1000 B cells or 1000 T cells), etc. Moreover, we can see a time in the not too distant future when the transcriptomes and/or miRNAomes of 1000 cells may be bar-coded and analyzed simultaneously in a single sequencing run. The new sequencing technologies will expand this capacity rapidly. These approaches will generate an enormous amount of data on individual patients that could be very powerful in choosing the proper therapies—or indeed in designing strategies for prevention.
- Imaging molecular disease indications. New *In vivo* molecular imaging methods and analysis methods to follow disease, drug response, drug effectiveness, drug dosage determinations, etc. This technology is developing rapidly. Integrating this kind of data with all the other measurement data to make predictions and diagnoses is an important challenge.
- Handling the enormous personalized data sets—policies, security, quality control (validation), mining, reporting, modeling, etc. These will be technically challenging and requiring significant investment and effort, but are completely achievable. The challenges here are large, but they include the challenge of making transparent interfaces for researchers, basic and clinical, to mine, analyze and visualize this data. All these are essential for its effective use in future. Finally, there's the great challenge of how key information can be presented effectively to physicians, practitioners and patients.
- Education of patients and physicians about P4 (predictive, preventive personalized and participatory) medicine. For the full effect of the changes discussed here to be felt there will be an acute need for patients to be well informed about the meaning of available information and their personal choices. This challenge is an enormous one, as it requires a change in attitude, a shift in educational levels of the general population and a substantial national effort. At least as important is also the essential, profound change in the way that physicians understand the medical issues (therefore medical school education must be radically changed) and how they relate to

and interact with their patients. The patient physician relationship will undoubtedly change dramatically.

The science is advancing at a remarkable rate, but to keep it advancing we will need to make a shift to a real systems approach to medicine – longitudinal, global high information content measurements of different information types (DNA, RNA, protein, metabolic molecules, etc.) and their integration into predictive models that will enable an understanding of network perturbations and their consequences. All of this will require new, sophisticated computational analyses. The burden of realizing this change falls first on the scientific community to develop the technologies and methods, achieve the understanding, and begin to apply these advances to important medical problems. The research community must, however, begin to work much more closely with the providers of medical care, the developers of new diagnostics and therapeutics and the regulators of new medical products, among others, who can work with us to bring about the exciting and effective new medicine that our new view is making possible.

It is worth noting that we believe the emergence of P4 medicine will occur gradually over the next 10-20 years. P4 medicine, with its emerging technologies, will lead to a digitalization of medicine— analogous to the digitalization of information technologies and communications. The digitalization of medicine means that disease-relevant information may be obtained from a single molecule, a single cell, a single tissue or the individual patient—from each of the successively higher levels of biological information. The meaning of this digitalization, together with the systems revolutions in diagnostics, therapeutics and prevention that will come from P4 medicine, is that the escalating costs of healthcare will turn sharply around in the future and decline sharply—to the point that P4 medicine will be exportable to the developing world—and indeed will be the new foundation of global medicine.

We also believe that P4 medicine will necessitate fundamental changes in the business plans of virtually every sector of the healthcare industry—drug companies, medical instrument companies, IT healthcare companies, payers, providers, medical diagnostics companies, etc. The fascinating question is how effectively will preexisting companies with bureaucracies honed by past experiences be in adapting to this new world. It is also clear that the medical centers and the medical academic world (medical schools, public health schools, etc.) will also have to adapt in major ways to the new world of P4 medicine.

The challenges and opportunities of P4 medicine are enormous. At our Institute of Systems Biology we have taken on P4 medicine as a major vector in our future strategic plan. As noted above, the challenges to realizing P4 medicine are both technical and social. Over the past five years we have begun exploring global partnerships that might help us accelerate the emergence of P4 medicine—taking into account that the societal challenges must be faced as well as the technical challenges. We are convinced that such strategic partnerships could transform the more incremental approaches to this problem that are enabled by the usual, generally

modest, federal grants and contracts. Recently we have established a partnership between ISB and the country of Luxembourg to attack some of the most fundamental challenges of P4 medicine. This partnership includes establishing a sister institute of systems biology in Luxembourg, taking on two of the most fundamental challenges in P4 medicine—translating the genomes of individuals from families and integrating this genome information with a systems analysis of their individual phenomes—for \$100 million over the next five years and establishing with Luxembourg and U.S. investors a company that will aspire to be the platform company for future P4 medicine. We are now seeking to establish additional strategic partnerships to bring academic medicine and many different sectors of the healthcare industry into alignment to accelerate the achievement of P4 medicine. It will be fascinating to follow the roles emergence of global scientific partnerships in catalyzing the acceleration of P4 medicine—and to follow how these global partnerships bring into alignment academia, industry and government efforts. It will also be interesting to see how many other countries will follow the bold and courageous lead of Luxembourg in initiating a powerful new strategic partnership that could have the potential for transforming healthcare. In this regard, there are other major areas of opportunity for strategic partnerships in biology (bio-energy, agriculture, nutrition, etc.). Strategic partnerships offer the opportunity to approach the challenging biological and medical problems of humanity's future in a bold, global and focused manner that integrates systems approaches, technology and computational/mathematical tools.

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