The Emerging Landscape of Medicine and Health Care**

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Summary
Advances in genomic and systems technologies have led to the emergence of personalized medicine as a paradigm shift in health care. Rapid sequencing of DNA and proteomes has facilitated a systems approach to medicine that allows the identification of the multiple variables contributing to health and disease. Technologies under development will allow more rapid diagnosis of diseases at increasingly granular and individual levels, which will in turn provide opportunities for more personalized, effective, and less expensive treatments. The combination of these factors has created what has been termed P4 medicine — predictive, preventive, personalized, and participatory. If society and policy makers are able to fully capitalize on the opportunities offered by P4 medicine, the quality of health care can be improved, costs can be reduced, and innovation will be catalyzed to fuel wellness and health care for the future.

Current realities

The landscape of medicine has changed profoundly in the past 10 years with the emergence of personalized medicine. Over the 40-some years of my career, I have participated in four paradigm changes in the biological sciences that have led to profound changes in medicine and biology.

First, I brought engineering to biology by inventing five instruments that allowed one to analyze and synthesize the fundamental molecules of life: protein and DNA. These advances heralded the revolution of "big data" that is so essential to personalized medicine. Second, I was one of the leaders of the human genome project, due to my invention of the automated DNA sequencer, which enabled genome (DNA) sequencing. The genome project both provided a complete parts list of all human genes (necessary for systems medicine) and opened the possibility of personalized medicine by enabling the analysis of the genome sequences of individual patients and their cancers.

Third, I founded the Institute for Systems Biology, the first institute to use systems or global approaches for studying biological complexity. To illustrate, consider how one might understand how a radio converts electromagnetic waves into sound waves. One must not only identify all the parts in a radio and understand what they do individually (as biology has done for the past 40 years with individual genes and proteins), but must then assemble these parts together into their circuits and study, individually and collectively, how the circuits enable the conversion of radio to sound waves. So it is also with living organisms, which have circuits or networks that manage biological information whose components, circuits, and dynamics need to be described to decipher biological complexity.

Finally, I was one of the early advocates of taking a systems approach to disease, otherwise known as systems medicine. There are three central features of systems medicine. First, disease arises from two types of biological information: mistakes in the digital genome and pathogenic environmental signals (such as infectious organisms). The challenge is to be able to identify and assess the relative contributions of both of these types of information to disease. Second, in five to 10 years, each patient will be surrounded by a virtual data cloud of billions of data points, and the analytic tools will exist to reduce this enormous data dimensionality to simple hypotheses about optimizing wellness and minimizing disease for each individual patient. These individual data clouds will enable the assessment of both the genomic and environmental contributions to disease. Finally, each patient has a biological "network of networks", which are biological networks that operate at many different levels of information — molecular, cellular, organ, and social — each of which are seamlessly integrated in each patient. In disease, these networks become "disease-perturbed" and alter the information they generate. A systems approach permits us to identify this altered information that, in turn, explains disease mechanisms and provides new insights into diagnosis and therapy.

Scientific opportunities and challenges
Systems medicine has reached a tipping point and is transforming the practice of medicine through a number of advances.

Revolutionizing DNA diagnostics. New genetic approaches, such as the sequencing of the genomes of families, are enabling physicians to more readily identify disease and wellness genes. These approaches have been used to identify interesting disease genes for a variety of neurodegenerative diseases, bipolar disease, and some metabolic diseases. The human genome sequence currently has about 300 "actionable gene variants" — variants that, if identified, can lead to behaviors to improve the health of the individual. For example, in the case of a person who developed osteoporosis in his late 30s, genetic analyses found he had a defective calcium transporter, and as a result he was able to reverse the disease by taking 20 times the normal amount of calcium. Without being able to act on this information, he might have spent the rest of his life in a wheelchair. As the numbers of actionable genes increases, a person's genome sequence will be able to be checked each year against new actionable variants — an investment in health that will continue the rest of the person's life. In addition, there are 70 mutant genes that block patients from responding effectively to certain drugs, so knowing whether a patient has one of these genes before drug treatment is very important. Certain individuals cannot effectively utilize common drugs because of genetic defects.

Revolutionizing blood diagnostics. Systems approaches have made blood a window into health and disease by pioneering procedures to identify blood biomarkers that can diagnose virtually any disease. For example, biomarker panels can distinguish benign from cancerous lung nodules. This information could save the American health care system billions of dollars a year by avoiding surgical procedures on the 95% of patients with benign nodules, and bring "peace of mind" to these patients. Individuals having posttraumatic stress disorder (PTSD) can be distinguished from those who do not. These new blood biomarkers will be able to (i) distinguish sick from normal patients, (ii) detect disease early, (iii) follow the progression of disease (future treatments will, in part, be determined by the stage of the disease), and (iv) follow the response to therapy. The systems strategies for blood diagnostics can easily be extended to most other diseases. Each of these diagnostic opportunities will reduce the cost of health care by making disease management more effective.

Stratification of disease into different subtypes. This is important because each disease subtype will require a unique therapy and will have a unique prognosis. Diseases that have been stratified include several types of cancer, such as breast cancer. With the stratification of diseases, optimum impedance matches (i.e., most potent response) can be identified between the subtype of disease and effective drugs.

*More effective targeted use of drugs***.** Drugs can be targeted to treat patients' individual cancers. By sequencing the genome of cancers, the specific genes that are mutated can be determined and an appropriate drug that will be effective for these mutations can be identified. This approach can be effective for some melanomas, colon cancers, breast cancers and many other cancer types.

Invent cheaper and more effective drugs. Knowledge of disease-perturbed biological networks can be used to select drug targets that will optimize the ability to re-engineer these networks back to normal. This is a novel and powerful strategy for selected drug targets. Drug companies are effective at developing drugs, but not at choosing drug targets. Thus, the marriage of the systems approach to identifying drug targets with the pharmaceutical industry's ability to make drugs will lead to drugs that are far less expensive to develop.

Focus on optimizing wellness for each individual. Increasingly, there will be a focus on optimizing wellness for each individual, rather than just worrying about disease. Once again, this behavior will lead to enormous savings for the health care system.

The convergence of systems medicine, big data and its analytics, and patient-activated social networks has led to a new type of medicine termed P4 medicine — predictive, preventive, personalized, and participatory. The predictive and preventive aspects have been described above. Personalized indicates that each patient is genetically different from other people and hence must act as his or her own control for analyzing personalized data clouds. Participatory suggests that patients will become more involved in optimizing their own health and thus in minimizing disease. Such patient-activated social networks will be one of the major driving forces in bringing physicians and the health care system to accept systems medicine and P4 medicine.

Policy issues

P4 medicine will transform health care by improving the quality of care, strikingly decreasing costs, and promoting innovation to create the companies fueling wellness and health care for the future. As a result, there are a number of implications of P4 medicine for society.

- P4 medicine will reduce the ever-escalating costs of health care to such an extent that advanced health care can be exported to the developing world, thus generating the possibility of a democratization of health care that was inconceivable even five years ago. There should be substantial societal investments in P4 medicine to speed up this process. Moreover, facilitating wellness-relevant, patient-activated social networks will facilitate the acceptance of P4 medicine in the face of the conservative nature of health care systems and practitioners.

- P4 medicine is leading to a digitization of medicine that will reduce enormously the cost of personalized data clouds. One can see this with devices that permit "quantified self" measurements (e.g., sleep, weight, and fitness measurements). Just as the digitization of communications and information technologies led to enormous reductions in costs in these sectors, so too will the digitization of medicine lead to a reduction in the cost of health care. Economic incentives will be needed to facilitate this digitization of medicine.

- Each industrial sector of the health care system will have to rethink its business plans according to the challenges and opportunities of P4 medicine. Some companies will be unable to accommodate the new imperatives of P4 medicine, thus opening up exciting new space for the creation of new companies that are structured to take advantage of the opportunities of P4 medicine. P4 medicine will facilitate health care innovation in conducive policy environments.

- P4 medicine will create significant wealth for the countries that adopt it early. For example, the market capitalization of the wellness industry will potentially far exceed that of the current health care industry within 10-15 years. Thus, we now have the opportunity to create the companies that will fuel a major economic sector of future industry. The question of which policies will best facilitate this process will be a key one for policy makers to address.

- P4 medicine will advance most effectively by making personalized data clouds available for analysis by qualified scientists to generate the medical advances that will transform the health of future generations. Policies will be required to balance this imperative with issues of security, privacy, and ethics.

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