P4 medicine: how systems medicine will transform the healthcare sector and society

Ten years ago, the proposition that healthcare is evolving from reactive disease care to care that is predictive, preventive, personalized and participatory was regarded as highly speculative. Today, the core elements of that vision are widely accepted and have been articulated in a series of recent reports by the US Institute of Medicine. Systems approaches to biology and medicine are now beginning to provide patients, consumers and physicians with personalized information about each individual's unique health experience of both health and disease at the molecular, cellular and organ levels. This information will make disease care radically more cost effective by personalizing care to each person's unique biology and by treating the causes rather than the symptoms of disease. It will also provide the basis for concrete action by consumers to improve their health as they observe the impact of lifestyle decisions. Working together in digitally powered familial and affinity networks, consumers will be able to reduce the incidence of the complex chronic diseases that currently account for 75% of disease-care costs in the USA.

KEYWORDS: big data ▪ knowledge network ▪ learning healthcare ▪ new taxonomy of disease ▪ omics studies ▪ P4 medicine ▪ personal data clouds ▪ systems biology ▪ systems medicine ▪ wellness industry

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The vision of medicine that is predictive, preventive, personalized and participatory ('P4') has long been advocated by Leroy Hood and other pioneers of systems medicine [1–3]. As recently as 10 years ago, these pioneers could accurately have been described as voices in the wilderness. However, that is no longer the case. The major elements of this vision of P4 medicine have been largely adopted – albeit incompletely and with different terminology – by a series of reports by the US Institute of Medicine (IOM) and the National Academy of Sciences.

These reports are:

- A New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution. National Research Council 2009 [4];
- Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. IOM November 2011 [5];
- Evolution of Translation Omics. IOM March 2012 [101];
- Best Care at Lower Cost: the Path to Continuously Learning Healthcare in America. IOM September 2012 [102].

While they use different terminology, these establishment reports do an excellent job of laying out the core elements of what we call 'systems medicine': the application of systems biology to the challenge of human disease. However, these elements are not yet connected in a way that can be readily understood as a coherent medical model capable of delivering care that is predictive, preventive and personalized. Nor do these IOM reports sufficiently explicate the crucial role that must be played by patient and consumer participation in healthcare.

This paper argues that new forms of participation by patients and consumers are key to integrating the disparate elements treated in the IOM reports into a practical vision for the emerging transformation of healthcare in the digitally networked era. One of our society's greatest assets is the increasing determination of healthcare consumers to better manage their own health using the internet to gather information and their ability to self-organize using social networking tools.

Networked and activated consumers are increasingly demanding personal information they can use to improve their health and their lives. One in three Americans have gone online to investigate a medical condition [103]. A growing number of 'quantified self' enthusiasts are exploring methods, tools and analytical procedures for a better understanding of their health, activity and well-being [6,104–106]. There are now thousands of mobile healthcare applications, and the number is growing [106]. A growing

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number of activated and networked patients and consumers have the ability to:

- Provide the 'big data' essential to power the innovation cycle of systems medicine;
- Improve health-related lifestyle decisions on a scale sufficient to halt the rising incidence of chronic and complex diseases, such as diabetes, which presently account for more than 75% of healthcare costs in the USA [107].

By combining the scientific and technological power of systems medicine with the active participation of networked consumers, P4 medicine will:

- Provide more cost-effective disease care;
- Reduce the incidence of disease;
- Replicate the innovation cycle of systems medicine on a large scale, as both disease care and wellness support are integrated with discovery science, thereby creating what the IOM calls a "learning healthcare system" [102].

The discussion below first presents a summary of P4 medicine. Then, the following sections describe five key emerging transformations that are collectively making P4 medicine possible, as well as how these transformations were addressed in the IOM reports.

Systems approaches to biology & disease are leading to the emergence of a P4 healthcare system

P4 medicine is emerging from the convergence of three megatrends (Figure 1):

- The increasing ability of systems biology and systems medicine to decipher the biological complexity of disease;
- The digital revolution's radically enhanced capabilities for collecting, integrating, storing, analyzing and communicating data and information, including conventional medical histories, clinical tests and the results of the tools of systems medicine;
- Consumer access to information and consequent interest in managing their own health. Consumers are driving the transformation of healthcare by these megatrends.

The business and academic communities across all economic sectors – particularly retail and finance – are familiar with the opportunities and challenges of the digital revolution. These communities are also increasingly concerned with the impact of active, informed consumers interacting in digitally powered social networks. Companies such as Google (CA, USA), Amazon (WA, USA) and Facebook (CA, USA) are exploring new understandings of social complexity. Systems biology and medicine, however, are as yet largely unknown outside scientific and medical circles.

Systems biology & systems medicine

Systems biology is the study of biological systems as collections of networks at multiple levels, ranging from the molecular level, through cells, tissues and organisms, to the population level. The transformative power of systems biology was recognized in a 2009 report from the National Research Council titled 'A New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution' [4]. The Committee reported that years of research "have generated detailed information about the components of the complex systems that characterize life – genes, cells, organisms and ecosystems – and this knowledge has begun to fuse into greater understanding of how all those components work together as systems" [4].

The New Biology report emphasized that quantified systems approaches to study biological networks are a fundamentally new and far more powerful paradigm than traditional reductive science for generating biological insight through studying disease one gene or protein at a time. It concluded that "integration within biology and increasingly fruitful collaboration with physical, earth and computational scientists, mathematicians and engineers are making it possible to predict and control the activities of biological systems in ever greater detail" [4].

Systems medicine is the application of systems biology to human disease [3]. Both systems biology and systems medicine take holistic but quantified approaches to the challenge of biological complexity. Systems medicine uses high throughput technologies – such as DNA and RNA sequencing – to produce global data sets tracking multiple dimensions of dynamic network interactions [3]. Enormous amounts of data obtained by tracking multiple biological networks are integrated to create a 'network of networks' and to yield a comprehensive understanding of human biology. For example, with this information we can begin to understand how an individual's genetic makeup and environment together produce health and disease [3]. Systems medicine requires a new infrastructure summarized herein as the 'five pillars' of systems medicine (Box 1).

In order to take into account the full range of biological complexity and define the range of healthy behavior, these data need to be obtained for as many people as possible in the population – ideally everyone – not just for small test samples. They are analyzed using novel computational tools made possible by the digital revolution (Pillars 1, 2 and 4; Box 1).

Through systems biology and systems medicine, new computational models of multilevel biological networks are being established (Pillars 3 and 5; Box 1). These models decipher biological complexity by showing how all elements in biological systems interact with each other to produce health and disease states. They are being systematically tested and adjusted to become increasingly powerful predictors of each individual's personal experience of health and disease. These models not only demystify disease, they also quantify what it means to be healthy.

Systems medicine will make disease care radically more cost effective by facilitating the stratification of both people and disease into distinct subgroups. Genomic analysis stratifies people into subgroups with different reactions to drugs, different disease risks and other clinically relevant factors. As discussed below, diseases such as breast cancer, which were once classified as single diseases, are being stratified into clinically relevant subgroups based on genetic, molecular and cellular network interactions [7]. Other diseases such as prostrate cancer [8] and Crohn's disease [9] are also being stratified. These stratifications are providing increasingly more accurate diagnoses and cost-effective interventions based on the underlying causes of disease. Surgery and other aspects of traditional medicine will be informed by the stratification of disease and of people where relevant. Focusing on the causes rather than the symptoms of disease will enable intervention to occur much earlier in the disease process, in many cases preventing disease from occurring in the first place.

By deciphering which biological networks are perturbed in diseases, systems medicine will provide a stream of new drug targets for the pharmaceutical industry [2,10]. The drugs developed using these models will be radically more effective because they are targeted to precise stratifications of patients (based on their genetics) and of disease (based on combinations and configurations of disease-perturbed biological networks). These drugs will be cheaper for pharmaceutical companies to develop because patient stratification will allow smaller test populations composed of target populations to be tested with far more effective results. Interventions (including, but not limited to, pharmaceutical interventions) will take place at an earlier stage in the disease process, often presymptomatically, where they are far more cost effective. The impacts of interventions will be more accurately monitored, allowing for adjustments to improve outcomes and reduce costs.

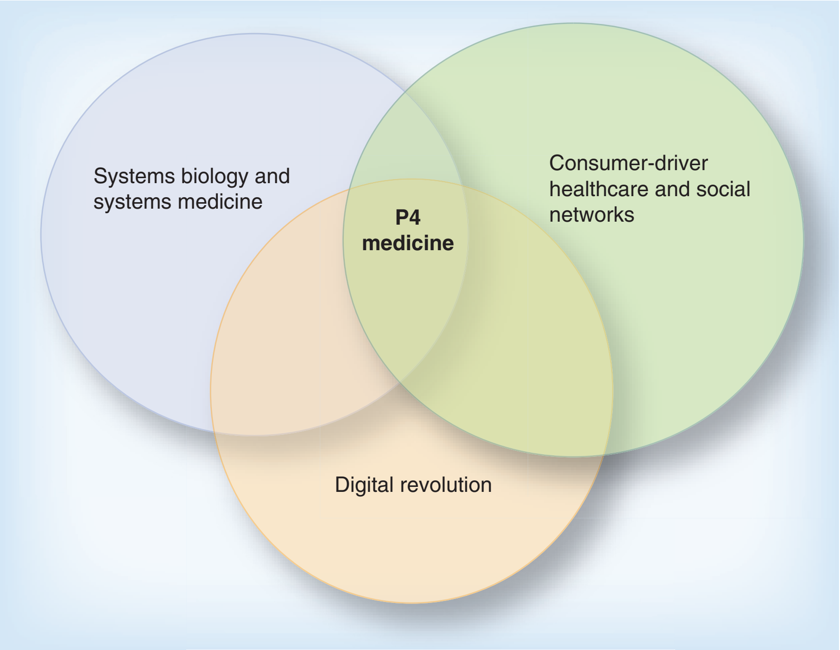

Figure 1. Three converging megatrends driving the transformation of healthcare. P4 healthcare is emerging at the intersection of these megatrends. P4: Predictive, preventive, personalized and participatory.

In addition, in systems medicine, each individual will have a 'personal data cloud'. The personal data cloud will act as a medical record, containing all of the multidimensional health data for each individual collected over time – including one's genome, blood measurements, lifestyle data (activity levels and stress, among others), transcriptome and gut microbiome data. The collection and analysis of this data will produce a stream of highly personalized information about each person's unique health and disease. Furthermore, 'actionable' information can be supplied back to each individual based on the accumulation of data in their personal data cloud. For example, if an individual has a genetic variant that is associated with a high predisposition to Type 2 diabetes [11] and their accumulated blood results show increasing fasting glucose levels, actionable information will be supplied back to the individual about medical and behavioral interventions to avoid the onset of diabetes. Much of this actionable information will center on lifestyle changes. Utilization of this data cloud will require the expansion of healthcare beyond the

Box 1. The five pillars of systems medicine.

Pillar 1

- Cutting-edge technologies for generating data regarding multiple dimensions of each person's experience of health and disease.

Pillar 2

- A digital infrastructure linking participating discovery science and clinical institutions, as well as patients/consumers.

Pillar 3

- Personalized data clouds providing information about multiple dimensions of each individual's unique dynamic experience of health and disease ranging from the molecular to the social. These data will include genetic and phenotypic characteristics, medical history, demographics and other sociometrics.

Pillar 4

- New analytic techniques and technologies from deriving actionable knowledge from the data.

Pillar 5

- Systems biology models for understanding the unique health status of each individual in terms of dynamic network states that can be manipulated by cost-effective strategies.

provision of care by physicians and other professionals to include care provided by individuals for themselves, their families and their communities.

Computational 'machine learning' techniques for training and generalization from data, and cutting edge statistical techniques will play a significant role in analyzing multidimensional data sets generated by the new technologies of systems medicine [12]. However, it has become clear that, alone, these computational tools will not be sufficient to meet the challenge of deciphering biological complexity. Domain expertise in biology is essential, where decades of research can be leveraged to help interpret this data [13]. Without a deep and growing understanding of biological phenomena and networks, it will not be possible to find the critical signals in the tremendous noise generated by vast heterogeneous data. Finding the signal in the noise is a significant technical challenge of systems medicine.

Finally, systems approaches to biology and medicine together create a cycle of innovation; as biological insight drives the development of new technologies, new technologies produce new data and new data drives the creation of new analytic tools that advance biological insight. As discussed below, the integration of discovery science and clinical service in P4 medicine will reinforce this cycle, as individual care and follow-up monitoring generates new data that not only benefits the individual patient, but also is aggregated to generate new insight that helps everyone.

P4 medicine

The strategies, technologies and analytic tools of systems medicine have given us the ability to decipher biological complexity, making it possible to provide care that is predictive, preventive and personalized. By adding the 'participatory' component, P4 medicine maximizes the effectiveness of systems medicine by expanding its application out from hospitals and clinics into homes, workplaces and eventually schools. With the addition of self-monitoring (activity, weight and calorie intake) and self-assessments in the participatory component, new quantities and forms of data will be aggregated and mined to generate new insight into health and disease. These insights will drive the development of new technologies, analytic tools and forms of care.

This societal challenge of deploying P4 healthcare is more daunting than the scientific and technological challenges facing P4 medicine. Existing institutional healthcare stakeholders are locked in a disease care model that is based on reductive approaches to biology, with a restricted arsenal of methods and tools that were tested in limited sample populations [14,101]. Futhermore, physicians are not compensated by insurance companies for most forms of wellness care.

It has become clear that the driver of an emerging P4 healthcare system will be information consumers can use to better manage their health. This demand is being met by the emerging digital health industry, providing personalized data about activity levels, sleep and nutrition, along with limited data analysis [108]. These 'first adopters' will be the essential pioneers of P4 healthcare.

P4 healthcare will be implemented as the data from the digital health industry, particularly lifestyle data, is integrated with data generated by clinical institutions. Leading groups in healthcare are experiencing the benefits of combining self-monitoring and participatory care with standard clinical care [109]. Traditional medical records will need to be combined with genomic, metabolomic, transcriptomic and proteomic data, along with data about sleep, activity, diet and other lifestyle data.

The knowledge generated by aggregating and mining these vast personalized data clouds is already beginning to transform the healthcare industry. A new information commons will emerge as a digital infrastructure is even now being created by a multitude of efforts to mine these data by connecting widely disparate data sources. Qualcomm Life (CA, USA), for example, has created an open-sourced digital infrastructure called '2Net' capable of integrating health data from devices from multiple sources (such as digital health devices and blood data) marketed by many different companies [110]. This privately developed utility, or others like it, will eventually be available for use by clinical and research institutions, and physician practices.

Systems medicine is already beginning to transform the healthcare sector in five fundamental ways that are laying the foundation for the emergence of a P4 healthcare system:

- Transformation 1: reliance on averaging data from limited test cohorts is being eclipsed by mathematically sophisticated 'big data' analyses of billions of data points generated for each individual in the population;
- Transformation 2: diseases are being diagnosed and treated with far greater cost–effectiveness based on their molecular and cellular origins in each individual rather than categories of symptoms (e.g., the DNA sequencing of tumors to search for driving mutations that might effectively be treated by known drugs);
- Transformation 3: a new cycle of accelerating biomedical innovation is emerging as discovery science is integrated with disease care and wellness care to create, for example, new companies in the wellness space;
- Transformation 4: science-based healthcare is moving beyond disease care in the clinic to include the active preservation and enhancement of wellness by consumers in their homes and workplaces;
- Transformation 5: a new wellness industry is beginning to emerge that will become a major source of economic growth in the 21st century. Indeed, we predict that in 10–15 years, the wellness industry will accede in size the current healthcare industry.

The IOM's treatment of each of these developments in three reports issued within the last 13 months is discussed below. The first three transformations – the direct results of systems medicine – are acknowledged as important developments that must be accelerated. Each of the five pillars of systems medicine are acknowledged as key developments in the transformation of medicine. Transformations 4 and 5 arise out of P4 medicine and are not explicitly analyzed to any significant extent in these IOM reports. However, it is clear that the last two transformations are inherent in the first three.

The five transformations of healthcare & society

Transformation 1: big data & biomedical innovation

By analyzing the aggregated data clouds of vast numbers of individuals, we will begin to have the statistical power to stratify states of health and disease [15]. The stratification of health and disease will facilitate cost-effective personalized healthcare (Box 2) [16].

The challenges of big data analysis in systems medicine were the subject of a March 2012 IOM report titled 'Evolution of Translational Omics: Lessons Learned and the Path Forward'. This report recognized that tests based on characterization of global sets of biological molecules such as DNAs, RNAs, proteins and metabolites

Box 2. Controls for big data.

- Traditionally, the gold standard for biomedical studies has been highly controlled double-blind clinical trials that take place in a laboratory setting. Control populations are essential for conclusions regarding cause and effect.
- Establishing control populations in laboratory studies is not the only way to generate controls. Controls can also be created by analyzing massive heterogeneous data sets generated in real-world conditions. By these means, subpopulations can be identified that serve as controls for testing hypotheses.
- In fact, one can find and analyze more controls by analysis of big heterogeneous data sets than one could possibly build into the design of any laboratory study. The larger the data set, the more control data sets are likely to be available. Furthermore, analyses of big data give scientists an unparalleled opportunity to identify patterns that can generate new hypotheses to be tested.

(omics-based tests) have opened a new era in biomedical science. In addition to these cutting-edge technologies, the report recognized the importance of developing new computational tools and mathematical techniques, along with a digital infrastructure to facilitate data accumulation and analysis. As discussed below, the report's analysis highlighted the need for data on large numbers of people in the population from diverse locations. The report also expressly recognized that systems paradigms can be advantageous in finding the signal in the noise of the biological complexity reflected in the large heterogeneous sets of omics data. In short, all five pillars of systems medicine are discussed in that report.

The Translational Omics report emphasizes the value of omics-based analyses that reveal the underlying causes of disease and thereby provide new opportunities to improve patient care. For example, Oncotype DX® (Genomic Health, Inc., CA, USA) is a multiparameter gene expression test that predicts whether or not early-stage breast cancer patients are likely to benefit from chemotherapy. This test and others have stratified breast cancer into as many as 15 different subtypes with different prognoses and treatment regimes. The ability to intervene in disease progression based on these stratifications is opening the door to radically more cost-effective disease treatment. However, omics-based tests pose unique challenges because they are derived from complex high-dimensional data: that is, the number of variables measured in each patient exceeds the total number of patients in the study cohort. There is a significant risk of 'overfitting', resulting in tests that perform well on the samples used in discovery research, but not on other samples taken in a different context. Most of the omic tests that have been generated in the past 5 years have turned out to be clinically ineffective for just this reason.

Omics-based tests are powerful tools for revealing the full range of biological complexity in any given sample, as well as the complexity introduced by variations among different laboratories (technical complexity). The problem of 'overfitting' arises from sample populations which "typically correspond to a relatively homogeneous set of patients, collected at one or a few institutions, which were run on the same machine at approximately the same point in time" [101]. Hence, these samples tend not to capture the full range of biological and technical complexity of particular diseases. As a result, tests based on these limited samples often do not work on other samples.

To deal with this challenge, the Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials, Board on Health Care Services and Board on Health Sciences Policy, Institute of Medicine specified best practices strengthening omics-based test development and guiding their use in clinical trials. It recommended that at the end of the discovery phase, the test should be precisely defined in terms of molecular measurements, intended use and 'locked-down' computational procedures (meaning that neither the test nor the computational procedure can be changed at all during the validation stage for the accuracy estimate to be valid). Neither the molecular measurements nor the computational procedures for analyzing those measurements should be changed without a protocol amendment and discussion with the US FDA. To ensure accuracy, the Committee recommended that candidate omics-based tests be confirmed using an independent set of samples not used to generate the locked-down computational mode. In the best case, these independent samples should be gathered at one or more sites that differ from those used in the discovery phase in order to provide a strong basis for validation relevant to clinical use scenarios.

The Committee noted that systems approaches for integrating multiple data types in mechanistic models can lead to more robust and clinically useful tests by reducing the number of variables in the data through constraints on possible relationships between the variables. As the Committee pointed out, the signal in the noise of omics data can also be enhanced by removing measurements believed to be noise, by using pathway databases and other sources to guide model construction and by aggregating individual measurements, often across data types, to integrate multiple sources of evidence to support conclusions. These and other uses of prior biological knowledge approach can all help to reduce the danger of 'overfitting' and to enhance the mechanistic relevance of omics-based tests. As an example, the Committee pointed to a study of prion-mediated neurodegeneration, in which data from five mouse strains and three prion strains were used to identify transcripts, pathways and networks commonly perturbed across all genetic backgrounds [3,17,18].

The Translational Omics report performed a valuable service in recognizing the importance of big data approaches to biological complexity and establishing guidelines for carrying them out [101]. It confirmed Transformation 1 above. However, it shied away from discussing the obvious social implications of its analyses – the solution to 'overfitting' lies, in part, in obtaining data from many more individuals from diverse locations with the appropriate legal protections in place to make broader data-sharing attractive. This changing data regime (FIGURE 2) will have profound implications for healthcare and society. As discussed below, it both opens the possibility of accelerating biomedical innovation and raises the multiple challenges involved in engaging large segments of the population in radically enhanced forms of active participation in healthcare.

Transformation 2: from symptoms to causes

In the current healthcare system, diseases are largely classified, diagnosed and treated primarily on the basis of symptoms rather than on a deep understanding of the molecular and cellular origins of disease and health in each individual patient [5,111]. In November of 2011, the IOM released a report titled 'Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease' [5], which provided "a framework for developing a more precise and more accurate classification of disease based on molecular biology" [5]. This 'New Taxonomy' of human disease promises to revolutionize disease diagnosis, therapy and clinical decisions, leading to more individualized treatments and improved outcomes for patients. The Committee concluded that: "Dramatic advances in molecular biology have enabled rapid, comprehensive and cost-efficient analysis of clinical samples, resulting in an explosion of disease-relevant data with the potential to dramatically alter disease classification. Fundamental discovery research is defining at the molecular level the processes that define and drive physiology. These developments, coupled with parallel advances in information technologies and electronic medical records, provide a transformative opportunity to create a new system to classify disease."

The Precision Medicine report explained how this new disease taxonomy is emerging from a new data network that integrates cutting edge research on the molecular makeup of diseases with clinical data on individual patients. This new network is essential to handle the vast data sets essential for translational omics. The Precision Medicine report advocated creating a 'Knowledge Network', allowing researchers, healthcare providers and the public to share and update these integrated research and clinical data sets in a new 'information commons'. The Knowledge Network would integrate academic research laboratories with clinician offices to improve clinical care and advance discovery in a real-time innovation cycle: "The Knowledge Network would impact all aspects of biomedicine and healthcare. By analyzing connections between information sets (for example between the genome and environmental exposures) basic scientists would be able to formulate and

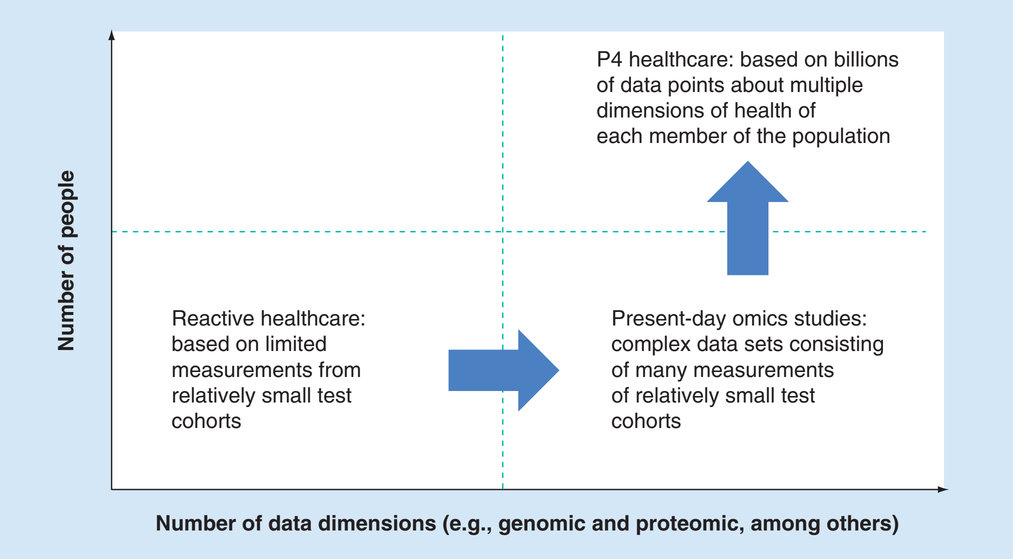

Figure 2. The evolution of data regimes. Healthcare's data needs can be characterized by two variables: the number of people measured and the number of measurements taken. We are moving from a limited-data regime of few measurements of few people to vastly increased measurements of few people. The future points to a regime of billions of data points for all members of the population. P4: Predictive, preventive, personalized and participatory.

test disease mechanisms, and clinicians could develop new treatments based on unique features of a disease and tailored to each patient. The availability of more diverse information about each disease would allow insurers and healthcare providers to more precisely define disease subtypes" [5].

The IOM used the term 'precision medicine' in a way that is descriptive of one of the principal benefits of systems medicine – stratification of diseases and people based on genetic, molecular and cellular markers relating to the causes rather than the symptoms of disease. It should be recognized, however, that systems medicine is the key underlying driver of the new stratifications. There can be no greater recognition of the power of systems medicine than the IOM's conclusion that science is now in a position to begin to systematically reclassify all diseases based on the causes of disease. The black box of biology has been pierced, and it is now essential to harness this knowledge for the benefit of patients.

The term 'precision medicine' is not particularly useful, as 'precision' is generic and does not really in any way describe the 'new medicine'. It is clear that all medicine or biology is trying to achieve precision. Systems medicine is largely focused on integrating diverse data sets (genomic, transcriptomic and behavioral, among others) for each individual to better quantify their health and for a population of individuals, to stratify health and diseases into distinct subgroups. The components of systems medicine are:

- Systems approaches;
- The deployment of the analytics of big data;
- The power of patient-driven health management.

The 'new medicine' employs these three features to create a medicine that is regarded as P4. The personalization aspect is addressed by 'precision medicine' only insofar as the patient population is better stratified than in traditional medicine. The other three important components (prediction, prevention and participation) are not addressed by the term 'precision medicine' at all. We therefore propose that a far more accurate and precise designation for this new medicine is 'P4 medicine'.

Transformation 3: an emerging cycle of accelerating biomedical innovation

Systems medicine establishes a cycle of discovery and innovation, and reduces the reliance on serendipity. The data produced through systems medicine generate a stream of hypotheses that are continually tested and refined to bring them closer and closer to reality.

The application of systems medicine establishes this cycle of innovation as new biological insights drive the development of new technology, which, in turn, drives the development of new analytical tools. At each turn of this innovation cycle, new technologies, new analytical tools and new concepts emerge, any one of which can be the fuel for creating new opportunities for commercialization and improved healthcare management.

In September 2012, the IOM released 'Best Care at Lower Cost: The Path to Continuously Learning Healthcare in America'. The report argues that a "learning healthcare system" is both necessary and achievable. It would require the alignment of science, informatics, patient–clinician relationships and culture to promote and enable continuous improvement in both the effectiveness and efficiency of care. As described by the IOM, the key characteristics of a learning healthcare system include:

- Capturing all relevant data from the care experience on digital platforms;
- Applying computing capacity and analytic approaches to develop research insights from populations of patients;
- Engaged and empowered patients who contribute their unique knowledge and data;
- The alignment of incentives to encourage continuous improvement;
- The creation of positive innovation feedback loops as care drives science that creates 'evidence' driving improved care.

The report goes into significant depth on a number of important topics relating to a learning healthcare system; for example, managing increased clinical and administrative complexity, generating and applying knowledge in real time, and the greater engagement of patients in clinical decision-making and research. The report also outlines the key roles of the NIH and other research institutions in building the evidence base used by the learning healthcare system and aggregating study results into systematic reviews and clinical guidelines.

However, the IOM vision of a 'learning' healthcare clearly rests on the importance of big data analyses as outlined in the Translational Omics report and on the creation of digital networks to carry out these analyses on a scale sufficient to reclassify disease based on causes as opposed to symptoms, as outlined in the Precision Medicine report. However, the 'Best Care at Lower Cost: The Path to Continuously Learning Healthcare in America' report contains no significant discussion of either of these two reports. Hence, the underpinnings of the learning system advocated in that report are not as clear as they could be, and the connections between the five pillars of systems medicine and the vision of healthcare as a learning system are not explained.

Transformation 4: expanding the delivery of science-based healthcare into homes & workplaces

Systems medicine will supply individuals with detailed and personalized data for better quantification of their wellness. It has been shown that when supplied with actionable and meaningful information of their health status, individuals and their social networks are more likely to have positive behavior changes [19–21]. The delivery of science-based healthcare will no longer be the exclusive domain of physicians: individuals and families in the information age will increasingly learn to apply the personalized knowledge generated by systems medicine to better care for themselves and the people they love.

An important limitation of the Translational Omics report is that it did not consider whether clinical care will suffice to generate data necessary to exploit the full potential of systems medicine. For example, nutrition, activity levels and sleep are vital in analyzing personalized health trajectories. It is unlikely that clinical care will generate sufficient data to support systems approaches to big data analyses, connecting these critical factors to molecular and cellular data. To provide the full range of data necessary to support systems approaches to wellness and the prevention of disease, it will be necessary to engage the population – both patients and people who are not yet sick – in the process of data collection and analysis long before they need disease care.

It is economically imperative to move beyond disease care in clinics to wellness care in homes and workplaces. Today, the ongoing management of chronic disease accounts for more than 75% of healthcare costs in the USA. Even if disease care becomes significantly more cost effective, these gains will at some point be swamped by the rising incidence of disease. The scientific and technological capabilities of systems medicine have the potential to significantly reduce costs through paradigm changes in how medicine is provided. Our society cannot afford to ignore this potential.

Transformation 5: the emerging wellness industry

Individual behavior in homes and workplaces affects health and its management. Capturing the medically relevant information about such behavior is challenging and will require the development of a new wellness industry. This development will be driven largely by consumer demand. A large educated sector of the population now has the ability and desire to obtain a vast array of health information through the internet [103,112]. They are coming to their doctor's offices armed with this data, seeking diagnoses and treatments that are tailored to their own unique circumstances. Increasingly, consumers seek to have the relevant information delivered directly to them in their own homes and in real time.

Many new businesses have been developed to meet this demand, including direct to consumer genetics companies (e.g., 23andMe [113]) and information services (e.g., WebMD [114]). In addition, there has been a deluge of new consumer products (e.g., Fitbit All in One™ [CA, USA] wireless activity and sleep monitor, Withings Smart Body Analyzer™ [Issy les Moulineaux, France], Jawbone UP™ [CA, USA], Nike+ FuelBand™ [OR, USA]) that track personal health-related information, ranging from physical activity metrics to sleep patterns. Already, companies such as Health Diagnostics Laboratory (VA, USA) have been formed to take extensive longitudinal blood measurements and provide coaching services to help consumers use these measurements to iterate their lifestyle for better health.

By helping consumers become better caregivers not only for themselves, but also for the people they love, the new wellness industry will begin to address the challenge of reducing the incidence of chronic disease and its associated costs. It is becoming increasingly apparent that both health and disease spread through social networks. Social relationships impact health in three principal ways:

- Behavioral;
- Psychosocial;
- Physiological [22].

Hence, it is no surprise that 'peer-to-peer' healthcare is assuming increasing importance as people take advantage of social networking capabilities. A recent survey found that "23% of social network site users, or 11% of adults, have followed their friends' personal health experiences or updates on the site" [112]. "One in four internet users living with high blood pressure, diabetes, heart conditions, lung conditions, cancer or some other chronic ailment (23%) say they have gone online to find others with similar health concerns" [115]. Tapping the power of digital networks to bring people together to learn from one another and care for each other will be an important part of the future of healthcare.

New incentives will be developed that gradually will begin to shift healthcare to a system of compensation for improved health outcomes rather than the sale of products and services. Ultimately, the wellness industry will be able to capitalize on its ability to improve health outcomes and will become a major source of wealth and economic growth in the 21st century.

Integrating science-based care by physicians with wellness care delivered in homes and workplaces by consumers – for themselves and the people they care about – will be a major challenge. The IOM did not directly address this challenge in its reports because they remained largely focused on disease care.

Concerns about P4 healthcare

As recently summarized in this journal, concerns have been expressed that prediction, prevention, personalization and patient participation all present virtues in danger of 'sliding into vices' [23]. Prediction through genetic risk assessments runs the risk of "eclipsing [more important] environmental and epigenetic factors" [23]. Prevention runs the risk of returning to a coercive ethos of reproductive control and subordinating therapeutic goals to the pursuit of socially valued 'enhancements' in human form and functioning." Personalization runs the risk of "reducing a patient's identity to his or her genes" and establishing a rigid genetic social hierarchy. Participation runs the risk of poor decision-making and a misguided demand that "patients have a moral responsibility to become well."

For the most part, these concerns are alleviated by eliminating the undue focus on genetics. As explained above, the scientific and technological foundation of P4 healthcare rests on systems approaches to big data on many different dimensions of health, not just genomic factors. Systems approaches are powerful precisely because they integrate all of these data to delineate how environmental and genetic factors interact to shape individual experiences of health and disease. Quite apart from ethical considerations, systems medicine demonstrates that genetic reductionism is unworkable from a scientific and technological perspective. The remaining concerns boil down to the irrefutable assertion that technological capabilities can be misused. Our challenge as a society is to use them appropriately – a challenge we cannot avoid without turning our back on scientific and technological progress altogether.

One of our society's biggest challenges is to protect patients and consumers who participate in a learning healthcare system delivering P4 healthcare from misuse of their data. The Health Insurance Portability and Accountability Act of 1996 and the Genetic Information Nondiscrimination Act of 2008 go a long way towards that goal. However, significant gaps remain to be filled.

Future perspective

Within the last 13 months, three important IOM reports have acknowledged that systems medicine is leading to a revolutionary transformation of medicine. The IOM has clearly articulated that systems medicine and the digital revolution are beginning to transform healthcare. However, it has yet to develop a vision of the critical role consumers and patients must play in biomedical discovery and population wellness. Accordingly, the IOM stopped well short of exploring the potential for systems medicine to deliver P4 healthcare. This is another compelling reason why the new medicine should be described as P4 rather than as precision medicine; precision medicine fails to describe the most important features of the new medicine – prediction, prevention, personalization and participation by the patient.

The future will bring further progress in each of the five transformations discussed above. As each develops, their essential interconnectedness will begin to emerge more clearly. A new report that builds on these three IOM reports, and the National Research Council's 2009 New Biology Report, would be another important contribution to the development of P4 medicine.

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Executive summary

Three converging megatrends are giving rise to a new healthcare system

- A new healthcare system is emerging (i.e., predictive, preventive, personalized and participatory [P4] healthcare) that encompasses:
  – Systems approaches to biology and medicine.
  – The digital revolution's radically enhanced capabilities for collecting, integrating, storing, analyzing and communicating data and information.
  – Increasing numbers of networked and activated patients and consumers.

The emergence of P4 healthcare is evident in five growing healthcare trends

- Reliance on averaging data from limited test cohorts is being eclipsed by mathematically sophisticated 'big data' analyses of billions of data points generated for each individual in the population.
- Diseases are being diagnosed and treated with far greater cost–effectiveness based on their molecular and cellular origins in each individual rather than categories of symptoms.
- A new cycle of accelerating biomedical innovation is emerging as discovery science is integrated with disease care and wellness care.
- Science-based healthcare is moving beyond disease care in the clinic to include the active preservation and enhancement of wellness by consumers in their homes and workplaces.
- A new wellness industry is beginning to emerge that will become a major source of economic growth in the 21st century.
- These five transformations are mutually supportive, and will form the basis for a new healthcare system.

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