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SYSTEMS BIOLOGY

Demystifying Disease, Democratizing Health Care

UNSUSTAINABLE COST INCREASES THREATEN THE GLOBAL HEALTH CARE SYSTEM, and further progress is stymied more by societal than technological factors. Only by engaging health care consumers (that is, patients) as pioneers who provide both health-related data and insights into pathophysiology can we meet these societal challenges and thus accelerate the pace of biomedical innovation.

In March 2014, the Institute for Systems Biology will launch a longitudinal, Framingham-like study (www.framinghamheartstudy.org) of 100,000 (100K) healthy individuals that we believe will be instrumental in bringing predictive, preventive, personalized, and participatory (P4) medicine to patients. Participatory medicine means that patients, researchers, physicians, and the entire health care community join forces to transform the practice of medicine to make it more proactive than reactive—and, in turn, less expensive and more effective (*1*).

PEOPLE POWER

A systems approach is necessary for the effective management of complex diseases (*1*). This fundamental component of P4 medicine is built on two central features. The first is a conviction that, in 5 to 10 years, each patient will have a dynamic data cloud consisting of billions of diverse types of data points and that medicine will be informed by computational analyses that reduce high-dimensional data to actionable hypotheses designed with the intent of optimizing wellness and minimizing disease in individual patients. The second feature is that integration of patient data will reveal biological networks that specify health and are altered in disease, and that through an understanding of these differences, one can gain fundamental insights into disease mechanisms. Such insights are essential for developing more effective diagnostic and therapeutic approaches. Indeed, such an approach has already provided powerful new technologies and strategies (*2*) that have brought us to the brink of P4 medicine (*3*).

At its foundation, P4 medicine is about quantifying wellness and demystifying disease. Individual data clouds will let us predict future wellness and disease. The preventive element focuses on how well we can improve individual wellness and take actions to stop or delay predicted pathologies. The personalized component acknowledges that each individual is genetically and environmentally unique and must serve as their own control over time ($n = 1$) to characterize individual transitions from wellness to disease. The participatory aspect—perhaps the most challenging to execute—involves (i) the education of patients and the medical community about the concepts of P4 medicine, (ii) aggregation of individual data clouds into integrated and deidentified datasets that enable mining for actionable knowledge to drive predictive medicine (while addressing issues of security and privacy), and (iii) the creation of patient-driven social networks, which are the key to convincing health care systems to adopt P4 medicine (*1*).

So how do we bring this vision into the current health care system? We believe that the most effective way to initiate this effort is to launch a pilot project that embodies all of the principles of P4 medicine.

A "FRAMINGHAM" STUDY FOR THE DIGITAL AGE

The 100K project will enroll 100,000 individuals, follow them longitudinally for 20 to 30 or more years, and capture a variety of health-related data types that allows us to observe three broad categories of responses: (i) some individuals will remain well (or perhaps further optimize their wellness), (ii) some will transition into a disease state, and (iii) some will transition back from disease to wellness. In a population of this size, we expect to observe transitions to common diseases (such as cardiovascular, cancer, and neurodegenerative). This study will generate a personal data cloud of billions of data points for each individual and a database of wellness and disease transition parameters. The enabling critical step will be to develop the computational tools that permit analysis of the individual data clouds, includ-

ing data integration, development of predictive models to optimize wellness and minimize disease for each individual, and aggregation of these individual clouds into large, minable data sets to serve as a foundation for the predictive medicine of the future.

Initially, we plan to gather six different types of data at regular time intervals: (i) Whole-genome sequence (once in a lifetime) to identify "actionable" genomic variants; (ii) clinical chemistries (three to four times a year), with a focus on informing nutrition and on data that have actionable consequences; (iii) quantified self-measurements (continuous), including heart rate, respiration rate, amount and quality of sleep, weight, blood pressure, and calories expended; (iv) personal traits that represent ongoing health changes in the individual's life (for example, colds, changes in eating or exercise habits); (v) gut microbiome quantification (three to four times a year); and (vi) organ-specific blood proteins arising from brain, heart, and liver, which will permit the identification of early-stage wellness-to-disease transitions (or vice versa) in these organs.

The database that will arise from the 100K project will create several powerful opportunities: (i) to integrate and model the individual data clouds in order to optimize wellness and minimize disease for each individual; (ii) to mine the data from those individuals who maintain wellness (or exhibit increased wellness) for metrics that will, for the first time, provide a quantitative foundation for the currently vague and incomplete definitions of wellness; and (iii) to identify early transition stages from wellness to disease, so that appropriate therapeutic responses to early-disease mechanisms can be deployed so as to thwart the disease transition at the earliest point possible. The principal value of these data is to identify actionable data features that provide consumers with opportunities to improve their health (or avoid disease) by taking action. The actionable possibilities may come from individual data or from the integration of multiple types of data. Two pioneers in making longitudinal self-measurements are Larry Smarr (identification of inflammatory bowel disease; http://lsmarr.calit2.net/repository/Biotech_J._LS_published_article.pdf) and Mike Snyder [identification of insipient diabetes after a viral infection; http://www.cell.com/abstract/S0092-8674(12)00166-3]. In both cases, appropriate actions could ameliorate these diseases. Our belief is that most individuals will have multiple identifiable and actionable opportunities that will improve their health or permit them to avoid disease.

For practical reasons, the practice of medicine and most biomedical research have focused on later stages of disease. In contrast, the proposed approach could transform our ability to design early-disease interventions. In fact, the only way to pinpoint early disease transitions and map the natural history of diseases is through longitudinal studies of a large patient population. This database will become increasingly valuable as data accumulate, and it will be a powerful source of innovation through the creation of a new industry focused on maintaining wellness and therapeutic targeting of disease transitions.

How are we to achieve such an ambitious program? Our approach will be to take a series of successive steps—starting with 100 individuals (Pioneer 100) for a 9-month study that launches in March 2014 under Institutional Review Board oversight. The study will then expand to 1000, 10,000, and ultimately 100,000 participants in a 20- to 30-year study. At each step, we will evaluate the results and then apply relevant insights to design of the next phase of the study.

The goals of the first study (Pioneer 100) are to establish assay and analytical platforms and to train coaches who will serve as interfaces between actionable opportunities arising from the data and the individual participants, with appropriate guidance from physicians.

The cost of many personal health assays is on a steep decline, frequently compared to Moore's law. We predict that, in fewer than 5 years, many of these assays will cost 5% of what they do today. An example of a transformational assay technology is a microfluidic platform that identifies wellness-to-disease transitions by quantifying 2500 organ-specific blood measurements (50 organ-specific blood proteins from each of 50 major organs) from a droplet of blood in 5 min at the doctor's office—or neighborhood drugstore.

We will include several families in this study, which will generate more actionable information for a family member than will an analysis of one individual alone. These families constitute social networks that will be counseled in the use of personalized actionable information and the adoption of behavioral changes that enhance wellness. We will also determine how often individuals benefit from actionable opportunities uncovered by comprehensive longitudinal measurements. Our prediction is that most individuals will have actionable opportunities to improve their health.

DEMOCRATIZATION OF WELLNESS

The 100K project has the potential to bring P4 medicine to health care systems around the world and, in turn, transform health care and society. With its focus on wellness, P4 medicine should reduce the enormous social and financial burdens caused by simply managing diseases. The costs of generating and analyzing personal data clouds will diminish over the next 5 years, while our ability to generate and effectively use personalized actionable information will increase. Early detection and the ability to understand disease mechanisms and manage the transitions from disease back to wellness should make clinical care more cost-effective.

However, clinical care is only a minor determinant of public health. Wellness care in homes and workplaces through participatory medicine, in which people work together in networks to improve their health with the assistance of professional coaches, has the greatest potential to reduce the societal costs of disease. Indeed, the 100K project will help foster a new culture of wellness based on the use of personalized actionable information, bringing the benefits of 21st-century science out of hospitals and clinics and into everyday life.

P4 medicine will drive the digitization of medicine—that is, the ability to make many different types of digital measurements (molecular and imaging) rapidly and inexpensively. The digitization of communications has made it possible for a woman in a rural village in the developing world to support her family with the use of a cell phone (there are 5 billion cell phones worldwide)—so, too, will the digitization of medicine make it possible to bring P4 medicine to the developing world.

P4 medicine will drive companies in health care systems to reconsider their business plans—and to adapt them to the mandates and opportunities of P4 medicine. Many will not succeed—thus opening business ecological niches for new companies (and progressive existing ones) that are positioned to take advantage of the opportunities P4 medicine is bringing to health care. Countries whose health care systems adopt P4 medicine will realize savings that come from optimizing wellness and avoiding disease—and from innovative new business opportunities, such as those arising from the newly emerging wellness industry. We predict that in a 10- to 15-year period, the value of the wellness industry will far exceed that of the disease-oriented health care industry. Indeed, companies that will create the wellness industry are being spawned today—and enormous opportunities exist to grow the future "Googles" of wellness.

Society's resources are being drained by the rising costs of disease management and of incremental improvements to our existing health care system. We need to take immediate action to reverse these trends. The longer we wait, the fewer resources we will have to transform health care in the coming decade.

– Leroy Hood and Nathan D. Price

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