

HUMAN HEALTH

Precision medicine: Beyond the inflection point

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A confluence of biological, physical, engineering, computer, and health sciences is setting the stage for a transformative leap toward data-driven, mechanism-based health and health care for each individual.

Despite staggering and persistent inequalities in health care access and clinical outcomes, there is no doubt that the past century's growth in our understanding of mechanisms that underlie biological processes and the application of such knowledge to medicine have steadily advanced human health and longevity. Now, early in the 21st century, convergence of the technological and health sciences has created the opportunity for a transformational leap forward in the way health care decisions are made for all individuals.

Biomedicine now sits at an inflection point, poised between what futurist Ian Morrison calls the first, or incumbent, curve marking steady progress and a second, or nascent, curve that would transform and

dramatically accelerate progress (1). The first curve depicts biomedical scientists' incremental progress through iterative reductionist approaches loosely coupled with the advances of clinicians in diagnosis and treatment through the use of periodic patient histories, physical examinations, signs and symptoms, personal expertise and experience, and risk factors assigned to statistically defined groups.

We suggest that the second curve will be defined by precision medicine (2), in which scientists, clinicians, social and behavioral investigators, and patients collaborate to generate and use massive data networks that access, aggregate, integrate, and analyze information from huge patient cohorts, healthy populations, and experimental organisms in order to determine mechanisms of normal and disease processes and provide precise health advice, diagnoses, and treatments for each individual.

POISED FOR PRECISION

Humans are not hardwired by their genomes. Rather, we sense and respond to internal and external signals, and the combinatorial output of likely hundreds of complex contributing factors and interactions defines one's overall health status as well as the onset and course of a disease. While capturing the excitement and promise inherent in the \$1000 human genome, a defining assertion of precision medicine is that genomics—no matter how powerful or economical—is far from sufficient to understand human physiology and pathophysiology. Myriad other components—molecular, developmental, physiological, social, and environmental—also must be monitored, aligned, and integrated in order to arrive at a meaningfully precise and actionable understanding of disease mechanisms and of an individual's state of health and disease.

The 2011 U.S. National Academy of Sciences (NAS) report entitled "Toward precision medicine: Building a knowledge network for biomedical research" (2) used the analogy of Google Maps to illustrate the value and necessity of aligning and integrating diverse, often unstructured, data sets into a comprehensive knowledge network if we are to understand the complexities of human health and disease (Fig. 1).

Precision medicine, as named and detailed in the NAS report, is not a new field of study or a subspecialty but, rather, an

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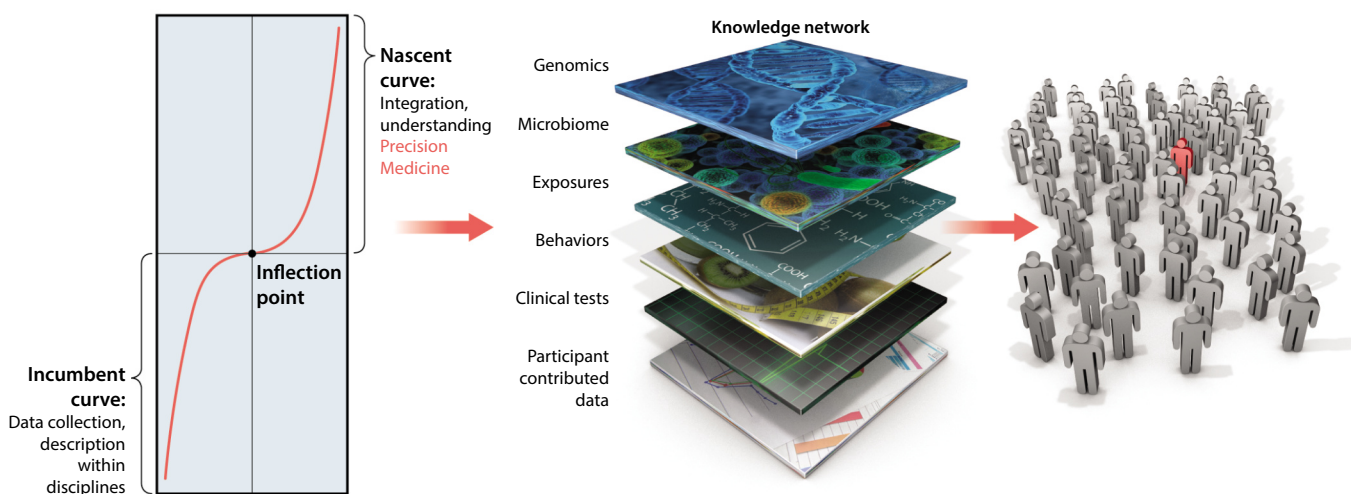


Fig. 1. Surpassing single-layer health care. An inflection point marks an opportunity or moment of dramatic change between the first, or incumbent, curve, marking steady progress, and a second, or nascent, curve, indicating transformation and accelerated progress. In biomedical research, health, and health care, we are at an inflection point, poised for precision medicine. Whereas Google Maps links layers of transportation, land use, and other data, precision medicine aims to integrate and apply data from biomedical research, clinical practice, social/behavioral studies, and participant-contributed observations toward better diagnosis, treatment, and preventative strategies.

Table 1. Precision medicine approaches and pilot studies.

Study type	Description	Reference
Basic discovery	An experimental strategy has been devised that combines genetic, proteomic, structural, and computational approaches to proceed from patient-based systems data, such as genome-wide association studies, to functional complexes, to pathways, and ultimately to predictive networks. The approach reveals disease mechanisms and has implications for therapeutic decisions and drug development.	(7)
Clinical discovery	BRCA pathway mutations, known to be causative in certain breast cancers, have also been implicated in ovarian and pancreatic cancers thought previously to be unrelated. This common mechanism predicted correctly that therapies for BRCA pathway-defective breast cancers, such as poly (adenosine-diphosphate-ribose) polymerase (PARP) inhibitors, could be efficacious for other cancers with related defects.	(8, 9)
Social and behavioral discovery	Analysis of genomic data linked to clinical records of a diverse cohort of >100,000 Californians has revealed genomic variants linked to prostate cancer, diabetes, and other diseases; uncovered molecular features related to aging; and provided insight into the relation between genetic ancestry and social categories of racial and ethnic identity.	(10)
Disease prevention	Health eHeart is a large study that seeks to harness data from smart phones, biosensors, and other wearable devices in order to collect longitudinal blood pressure, activity, sleep, diet, and other data on 1 million subjects to define patterns that will be informative and predictive and motivate behavioral changes so as to prevent cardiovascular disease.	www.health-eheartstudy.org

approach to knowledge acquisition that integrates across the spectrum of biomedical research and clinical practice; it is a computation-enabled platform for organizing, synthesizing, and rationalizing information in ways that fundamentally change how we conduct biomedical research and patient care. The success of this approach will depend on the engagement of wide stakeholder communities, notably including both patients and healthy people who become convinced that their contributions will benefit their own health and well-being as well as that of their children and grandchildren. U.S. president Barack Obama's precision medicine initiative, announced in January 2015 (3), gives voice to this complex task with his call to create a million-citizen cohort, assembled largely from existing cohorts, to contribute and share their health data while maintaining privacy and security.

BUILDING THE KNOWLEDGE NETWORK

In the 4 years since the release of the NAS report, work has progressed at different velocities within distinct data layers ranging from cancer-gene atlases to exchanges of clinical data in electronic health records to a growing appreciation, through metagenomic analyses, of the diversity and complexity of microbial communities resident in and on our bodies. Of course, progress has been slower in discerning correlations, patterns, and relationships between data layers and over time as well as in aligning health data collected in the ordinary course of care or in the course of daily life. The defining of such linkages will be the hard-fought product

of insightful research designed to achieve a measure of understanding that moves us through the inflection point, extending beyond the collection of data to the creation of new knowledge. This is the work of decades, demanding sustained effort, effective partnerships, and a broad base of support.

For example, in April 2015, California governor Jerry Brown announced the California Initiative to Advance Precision Medicine, which provides funding to motivate diverse stakeholders to participate and contribute resources (<http://gov.ca.gov/news.php?id=18921>). Collaborative teams are currently designing and launching demonstration projects that take advantage of the state's diverse demographics, deep intellectual resources, and energetic entrepreneurial culture to illustrate the power of precision medicine and build tools with which to drive its application.

When contemplating the daunting challenge of such a massive endeavor as precision medicine, we can perhaps take heart in the assertion of Microsoft cofounder and philanthropist Bill Gates, who remarked that "most people overestimate what they can do in one year and underestimate what they can do in ten years" (4). However accurate or flawed the trajectory projections of Morrison's nascent curve for precision medicine may be, this approach has a crucial redeeming characteristic: Creation of the knowledge network need not be complete to demonstrate contributions to our understanding of the diverse natural histories and mechanisms of disease and to the impact of new knowledge on human health. Individual pixels of success

derived from adding a single new data layer to those traditionally used to interrogate a disease mechanism or inform a therapeutic decision can have substantial impact. Indeed, the progressive merging of these pixels will begin to reveal the full image. At the University of California, San Francisco, where precision medicine is central to our overarching institutional vision, numerous pilot projects are under way across basic, clinical, and social and behavioral discovery research as well as in disease prevention studies (Table 1), and our knowledge network, initially rooted in oncogenesis/cancer and neuroscience/neurological disease, is expanding across a range of disciplines and disease areas. Our efforts, although still at an early stage, are already providing valuable insights and reinforcing the perception that we have entered a transformative period in life-science research, health, and health care.

PERSPECTIVES

Precision medicine is a bold approach that broadly integrates the endeavors and advances of biomedical science, physical science, and engineering research with health outcomes and health care. Although grand in overall scope, precision medicine can succeed iteratively and likely can move forward only through pilot studies—some that will establish standards and best practices and some that will be scalable, illuminating routes toward larger and broader efforts. Individual biomedical communities can and should undertake different pilot projects that are tailored to their strengths, resources, cultures, and environments.

The NAS “Toward precision medicine” report (2) envisioned a national or international enterprise, surely an audacious aspiration. However, success, even in much smaller increments, would demonstrate how insights gained from integrating many data elements—some drawn from engaged citizens seizing a new social contract (5)—will bring advances through data manipulation, modeling, and testing of predictions, toward a more intricate mechanistic understanding of fundamental physiological principles and processes. This knowledge—evidence-based and predictive in nature—will, in turn, promote new strategies for prevention, early diagnosis, treatment, and cure of diseases. Moreover, if the nascent curve of precision medicine yields a healthier, more productive workforce; better control of chronic disease; smaller, faster, and more successful clinical trials; and avoidance of unnecessary tests and ineffective thera-

pies, the slope of the health care–cost curve could decline—a welcome consequence for the United States, in which health care costs account for 17.4% (and growing) of the gross national product (6). Thus, precision medicine holds promise for improvements in health, reduction of disease, and broad impacts—scientific, societal, and economic.

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