THE PERSONALIZED HEALTH PROJECT

Identifying the gaps between discovery and application in the life sciences, and proposed solutions

January 2011

Ewing Marion
KAUFFMAN
Foundation

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by

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with

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Expert panel

Thanks to the expert panel that provided input for this study and reviewed the final draft. The panel of thirty-six life science leaders was chosen to represent a wide range of specialists, stakeholders, critics, and points of view.

Adam Gazzaley, MD, PhD, neurologist and neuroscientist, University of California at San Francisco
Anthony Atala, MD, board member, Regenerative Medicine Foundation; director, Wake Forest Institute for Regenerative Medicine
Arthur Caplan, PhD, bioethicist, University of Pennsylvania
Atul Butte, MD, PhD, geneticist and bioinformaticist, Stanford University Medical School
Brook Byers, MBA, venture capitalist, Kleiner Perkins Caufield & Byers
Christopher Austin, MD, neurologist; director, Chemical Genomics Center, National Institutes of Health
Daniel Kraft, MD, PhD, oncologist; stem cell researcher, Stanford University Medical School
David Agus, MD, oncologist, proteomics researcher, entrepreneur, University of Southern California; co-founder, Navigenics
David Ewing Duncan, journalist and life science policy analyst; director, The Center for Life Science Policy, University of California at Berkeley
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Edward Abrahams, PhD, president, Personalized Medicine Coalition
Eric Schadt, PhD, biocomputationist; chief scientific officer, Pacific Biosciences; cofounder, Sage Bionetworks
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Frank L. Douglas, MD, PhD, president and CEO, Austen BioInnovation Institute in Akron, Ohio; founder and first executive director of the MIT Center for Biomedical Innovation, Massachusetts Institute of Technology; former chief scientific officer, Aventis
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George Church, PhD, molecular biologist, professor of genetics, and director, Center for Computational Genetics, Harvard Medical School
George Poste, PhD, researcher, policy analyst, and former pharmaceutical executive; chief scientist, Complex Adaptive Systems Initiative; professor of Health Innovation, Arizona State University; former president, R&D, SmithKline Beecham
Greg Simon, JD, senior vice president for worldwide policy, Pfizer; former president, Faster Cures; former chief domestic policy advisor to Vice President Al Gore
Gregory Stock, PhD, MBA, founding CEO, Signum Biosciences; founding director, Program on Medicine, Technology and Society, University of California at Los Angeles School of Medicine
Hank Greely, JD, professor of law, Stanford University; director, Center for Law and the Biosciences

James Heywood, cofounder and chairman, PatientsLikeMe
James Thomson, VMD, PhD, stem cell scientist; director of Regenerative Biology, The Morgridge Institute for Research, University of Wisconsin School of Medicine and Public Health
Joshua Adler, MD, physician, chief medical officer, University of California at San Francisco Medical Center
Lee Hood, MD, PhD, molecular biologist and bioinformaticist; founder and director, Institute for Systems Biology
Linda K. Molnar, PhD, entrepreneur, personalized medicine and nanotechnology expert; founding principal, LKM Strategic Consulting
Margaret Anderson, executive director, FasterCures
Martyn Smith, PhD, professor of toxicology, School of Public Health, Division of Environmental Health Sciences, University of California at Berkeley
Michael Roizen, MD, preventive medicine; director, Wellness Institute, Cleveland Clinic
Misha Angrist, PhD, assistant professor, Duke University Institute for Genome Sciences & Policy
Nathaniel David, PhD, entrepreneur and venture capitalist; venture partner, Arch Venture Partners
Paul Billings, MD, PhD, clinical geneticist; chief medical officer, Life Technologies
Ray Woosley, MD, PhD, president and CEO, Critical Path Institute
Safi Bahcall, PhD, entrepreneur; CEO, Synta Pharmaceuticals Corp.
Stephen Friend, MD, PhD, president, CEO, cofounder, Sage Bionetworks; former senior vice president and franchise head for Oncology Research, Merck
Stephen P. Spielberg, MD, PhD, pediatrician; director, Center for Personalized Medicine and Therapeutic Innovation, Children’s Mercy Hospital, Kansas City, Mo.; former dean, Dartmouth Medical School
Steve Wiggins, venture capitalist and former health insurance executive; managing director of Essex Woodlands Health Ventures; founder and former CEO, Oxford Health Plans
Zack Lynch, entrepreneur; executive director, Neurotechnology Industry Organization

Summary

Background

Recent advances in the life sciences hold great promise to not only improve the health of individuals, but also shift medicine and society away from primarily treating illness toward a greater emphasis on prediction, early diagnosis, prevention, and personalized treatments.[1] Exciting breakthroughs have come in a broad range of fields, including genomics, proteomics, epigenomics, neuroscience, nanotechnology, microbiology, environmental toxicology, and systems biology. Translating these discoveries for patients, however, has been slower than many expected. In part, this comes from a "natural gap" that always occurs between innovation and implementation. Yet many inside and outside of the life sciences field contend that this gap is wider than it needs to be. This study assesses this contention. It also delineates possible causes for what might be termed an "artificially created gap," and offers proposed remedies—many of which are under way, but moving slowly—to shrink the gap and more efficiently facilitate the adoption of new scientific breakthroughs.

Methods

The authors have conducted a survey of major studies and reports addressing aspects and causes of the alleged gap, and a range of proposed solutions and initiatives. We have engaged a group of thirty-six senior leaders from science, medicine, business, government, law, ethics, the media, and patient advocacy to provide input and help assess key features of the gap, and to help formulate proposals to accelerate the application of new biomedical discoveries. The panelists each completed a standard set of eight survey questions (see Appendix C: Project questionnaire).

Conclusions

We are in an unprecedented period of scientific and technological discovery that has placed society on the cusp of a new era of health care. Yet an artificially created gap does exist between innovation and application in the life sciences. (Ninety-seven percent of the expert panel concurred with this assessment.[2]) A key obstacle to shrinking this unnatural gap has been a failure to coordinate and communicate new innovations across disciplines and institutions throughout society—in science, medicine, environmental science, industry, finance, patient advocacy, government, politics, ethics, law, and the media. The current system was assembled to serve a biomedical and health care model that is fast becoming outmoded and incomplete, one that (1) emphasizes the diagnosis and treatment of illness without an equal amount of attention paid to keeping people healthy; (2) traditionally has treated patients according to generalized population data and averages rather than as individuals; and (3) depends heavily on a reductionist approach that has served science and society well, but also has led to a "silo" effect that over-emphasizes details and subspecialties and fallen out of balance with the complementary need to integrate. A restoration of this balance would assist in transitioning to a health care enterprise that is more personalized and

holistic and emphasizes healthy wellness and illness. The authors are confident these gaps will be addressed, but can happen more quickly and coherently if the life sciences community and society establish a more robust plan to accelerate the translational process.

Call to action

This study concludes with a list of action items the authors and panelists believe will remove barriers and hasten the adoption of new discoveries. These include (1) suggested shifts in thinking, and (2) more practical measures—plus an appeal for our society to encourage the same level of intense and fruitful creativity and innovation in the clinic, business, law, education, ethics community, the media, and government as we have applied in making basic scientific discoveries and in developing new technologies.

A note on tone: optimism versus pragmatism

A debate ensued among some members of the expert panel about the tone of this report—whether it should reflect a robust optimism that the new age of personalized health has arrived, as opposed to a sensibility that progress has been slowed by hurdles that must be addressed with a sober pragmatism. The authors have attempted to offer a balance of tone that falls somewhere between the outer edges of both optimism and pragmatism. Of course, the optimists on the panel have suggested that this tone is too pragmatic, while those more strongly in the pragmatic camp consider some parts of the report to be overly optimistic. In other words, all of the panelists are convinced that a new era of health care based on new discoveries in science and technology is on the horizon, but they differ on how close that horizon might be and how difficult it will be to get there.

— David Ewing Duncan, Frank L. Douglas, Linda K. Molnar, Stephen P. Spielberg

I. Life Sciences in the twenty-first century

> We need to understand that we're standing on the threshold of a whole new understanding of human biology, health, and disease—and we need to grasp the opportunity.
>
> — Stephen P. Spielberg, MD, PhD, former dean, Dartmouth Medical School

Where we are

In the past decade, the United States has spent almost $1 trillion on life science research and development in the public and the private sectors, twice the amount spent in the 1990s.[3] This outpouring has resulted in an unprecedented era of discovery and technological innovation. Geneticists have mapped and explored the human genome, assisted by new technologies that now can sequence an entire human genome for less than $10,000—down from hundreds of millions of dollars a decade ago.[4] Biologists are drilling down to understand the inner workings of cells and organisms, making substantial efforts to understand and combat the mechanisms of hundreds of rare and common diseases. Inventors are creating everything from brain implants that forestall epileptic seizures to engineered nanoparticles that may one day target and kill rogue cells in cancer patients.

One measurement of this extraordinary enterprise is the volume of data produced by biologists, which has grown from perhaps ten megabytes (billions) of information stored in computers in 2000 to hundreds of petabytes (quadrillions) in 2010—with a likelihood of crossing the exabyte (quintillion) barrier of data in the very near future.[5] This gusher of information and knowledge has led not only to vast research repositories, but also to thousands of drug candidates and other treatments being developed by hundreds of pharmaceutical companies large and small; and to thousands of genetic and other biomarker candidates being proposed by researchers for use in predicting, diagnosing, and treating patients.

Regrettably, this impressive effort is not being translated into the explosion of approved drugs, treatments, and diagnostic biomarkers that many expected a decade ago when scientists announced the first draft sequences of the human genome. Since the year 2000, the number of drugs approved by the U.S. Food and Drug Administration (FDA) has declined—from a peak of fifty-three drugs approved in 1996 to an average of twenty-one per year between 2005 and 2009.[6] Out of the thousands of biomarkers discovered and reported in scientific journals, the Food and Drug Administration has approved only a handful of diagnostic or predictive genetic tests, though recently it has begun taking serious steps to reorganize how and when it will regulate such tests.[7] Much progress has been made in the realm of personalized health, but much remains to be done.

Inside and outside of government, creative efforts are under way to establish initiatives, proposals, and reforms. These include the "road map" for medical research initiatives at the National Institutes of Health to study and encourage translational medicine[8] and interdisciplinary programs;[9] reform efforts at the FDA that aim to emphasize a new "regulatory science" and bring the agency up to date with the latest science, technologies, and tools;[10] studies such as the National Academy of Sciences 2009 report that calls for "A New Biology for the 21st Century;"[11] the Critical Path Institute, which is dedicated to collaborations that identify best practices in regulation and medical product development; and nonprofit, patient-centered efforts such as FasterCures and PatientsLikeMe. So far, however, these initiatives have not received the funding or support required. For instance, the translational programs at the NIH comprise less than 2 percent of its budget, and the interdisciplinary initiative has a budget of only $40 million over five years. Funding for the FDA was boosted 19 percent by the Obama administration in the 2010 federal budget, yet the $3 billion the agency will spend this year is equal to a mere $10 per American to regulate $2 trillion of the U.S. economy.[12] Funding for patient advocacy groups and nongovernmental initiatives is increasing, but remains a tiny fraction of what is spent on basic biomedical research in the public and private sectors.*

> *"Across biology from neuroscience to organismal biology to ecology, genomics, and bioengineering, the pace of discovery is rapid, making ambitious goals ever more realistic."*[105]
>
> — "A New Biology for the 21st Century," National Academies of Science, 2009.

The promise of personalized health and medicine

Despite the gaps and the slow pace of change, this study's expert panel is optimistic that recent discoveries in the life sciences will become the basis for a new era of health care. The broader field is called "personalized health," which includes predictive tests and technologies for individuals and for society, and also science-based strategies to prevent or mitigate disease and poor health. A subset of personalized health is

"P4" Medicine

1. ***Predictive Medicine*** *denotes the creation of therapeutics that will prevent a disease that a person is assessed to have a high probability of developing.*
2. ***Preventive Medicine*** *refers to the development of a probabilistic health projection for a person based on his or her DNA and protein expression.*
3. ***Personalized Medicine*** *refers to treating an individual based on his or her unique human genetic variation, completing the predictive and preventive efforts above.*
4. ***Participatory Medicine*** *denotes patients' active, informed involvement in their medical choices and care, acting in partnership with their health providers.*

— Lee Hood, MD, Institute for Systems Biology

* For more information see Appendix B: Selected linkage projects already under way.

"personalized medicine," which refers to therapies that can be tailored to an individual's own genetics and physiology. The following is a synopsis of major discoveries and trends in personalized health:

Predictive tests, risk factors, and early detection

Researchers have located thousands of genetic and molecular markers that may provide clues to an individual's health in the present and in the future. The most significant gains have been made for genetic markers associated with rare and often severe disorders such as Tay-Sachs Disease, Fragile X Syndrome, and Down Syndrome.[13] Mutations linked to these rare maladies almost always signal that an individual has or will acquire the disease. A deeper understanding of these mutations' role in these diseases and in the development, in some cases, of new drugs to treat them has been one of the great successes of the Human Genome Project and the "new biology" of the last decade.

Similar success remains elusive, however, for the thousands of DNA markers that geneticists have associated with common diseases such as cardiovascular disease and diabetes. Most markers for these disorders come from "genome-wide association studies" (GWAS) that scan the DNA of a test population to search for genetic differences that seem to increase the risk for a specific disease. GWAS, however, are mostly statistical comparisons that have not been clinically tested to see if the risk factors are accurate predictors for an individual of contracting a disease. Even when validated, the increased risk detected by these variants tends to be statistically small, often in the10 percent to 30 percent range above the average risk.[14] For instance, a frequently cited marker for heart attack on chromosome 9 (rs10757278[15]) confers only a 23 percent greater risk for those carrying the high-risk alleles, which is a small addition to the average risk of about 45 percent chance for heart attack for all men over fifty years old.[16] Current GWAS methods and technologies also fail to take into account that common diseases or conditions are likely the result of interplay among many genes and environmental variables; they also can miss rare gene variants that likely interact with more common variants to cause or influence disease.

So far, only a handful of genetic tests for common diseases have been approved by the FDA or are routinely used in the clinic. FDA-approved tests include Roche Diagnostics Amplichip CYP450, which analyzes two genes, CYP2D6 and CYP2C19, that greatly influence a person's ability to metabolize antidepressants, cardiac drugs, and many others.[17] Variations in these genes can cause a person to be a poor, intermediate, extensive, or ultrarapid metabolizer of widely used drugs such as Prozac and other serotonin reuptake inhibitors. Another biomarker pattern widely used in the clinic is Myriad Genetics' DNA test that detects a high risk for a rare form of hereditary breast cancer that

> *"The ten years since [the sequencing of the first human genome] have brought astounding technological and intellectual advances. But ten years from now, when the story of the genome's first two decades is being told, it should include equally astounding applications to human health."*
>
> — *Nature* editorial on the tenth anniversary of the sequencing of the human genome

occurs with variations in the BRCA1 and BRCA2 genes.[18]

Despite the preliminary nature of most GWAS data, several companies have launched direct-to-consumer websites that offer to genotype customers and provide results and information on genetic markers for dozens of diseases and traits based mostly on published GWAS findings.[19] These companies—23andMe, deCODEme, Navigenics, Pathway, and others—have received substantial media attention in spite of resistance and criticism by much of the scientific community, and by many physicians and ethicists concerned about the preliminary nature of the science, the lack of clinical validation for these tests, and privacy issues. To date, only about 100,000 people have signed up for the services, though this may have as much to do with the cost ($400–$2,000) as with the other concerns.[20] Multiplex studies sponsored by the NIH are collecting data on healthy individuals ages twenty-five to forty who have been genotyped for fifteen genes that play roles in type 2 diabetes, coronary heart disease, high blood cholesterol, high blood pressure, osteoporosis, and other diseases to ascertain if the information provided is useful for these individuals, and if they act on high-risk variants to change their lifestyles or to take preventive actions.[21] Preliminary results suggest that the several hundred subjects tested have found the information useful, and, in some cases, have used it to alter their behavior.[22]

Lately, legal and regulatory issues have added more layers of uncertainty about the use of many GWAS markers for disease. In spring 2010, a U.S. District Court judge reversed key elements of the patents held by Myriad for its BRCA breast cancer tests, ruling that genes are naturally occurring entities not covered by patent law.[23] Myriad is appealing the ruling, and plans to challenge it all the way to the Supreme Court if necessary.[24] This has left the question of whether or not DNA and other molecular entities inside organisms can be patented in limbo—and has exacerbated an already-existing legal gap in implementing new discoveries.

In May 2010, the FDA issued letters to direct-to-consumer (DTC) genetic testing companies, warning them that medically oriented genetic tests will need to be approved under a still-unspecified set of rules.[25] In July, the FDA held two days of hearings and workshops that began a process of establishing regulations that will include new requirements providing safety and efficacy for some genetic tests.[26] Also in July, the U.S. House of Representatives Subcommittee on Oversight and Investigations, part of the Committee on Energy and Commerce, held hearings that included an investigation prepared by the Government Accounting Office, which found numerous serious drawbacks with the tests provided by DTC genetic testing companies.[27]

Genetics is not the only field of biomedical research that is producing new predictive and diagnostic tools and treatment options.[28] For instance, molecular biologists are developing novel tests in the realms of proteomics and other molecular arenas such as epigenetics, and neuroscientists are developing predictive and informational tests for the brain using MRI scanners and other technologies. Pioneering scientists and biocomputationalists are beginning to create complex risk models that link tests and results from multiple fields and technologies—genetics, proteomics, environmental toxicology, scanning technologies, and more—to create potentially powerful algorithms and profiles of a person’s proclivity for disease.

Biomarkers and targeted therapeutics

In the 1990s, scientists at Genentech (now part of Roche) discovered that a candidate breast cancer drug called Herceptin was effective only on patients who have a genetic mutation that causes them to overproduce the HER2 protein.[29] The company developed a molecular test that identifies these patients in what was hailed as the first true personalized medicine test that combined predictive biomarkers with targeted drugs. When Herceptin was approved by the FDA in 1998, advocates of personalized medicine assumed it would be the first of many such personalized pharmacogenomic tests that soon would arrive to link patients with drugs using their genes and physiology. Unfortunately, the HER2-Herceptin link remained only one of a handful of these tests for several years. Recently, a small number of other biomarker-drug pairs also have been flagged as important indications by the FDA—including a test that links certain mutations in the KRAS gene to whether or not two common drugs used to fight colorectal cancer will work.[30]

Another example is a genetic test that can identify patients who face a potentially lethal side effect of warfarin, a blood thinner primarily used after surgery to avoid clotting. In 2006, the FDA added a “black box” warning to physicians to consider a genetic test before administering the drug.[31] The most recent update in the package insert for warfarin contains a dosage table developed by a team led by Larry Lesko, Director of the Office of Clinical Pharmacology in the FDA’s Center for Drug Evaluation and Research.[32] The instructions center on the two genes—CYP2C9 and VKORC1—that impact a person’s sensitivity to warfarin and recommend dose ranges based on a patient’s genotype for the two genes.

“The ranges are needed (rather than a specific dose) to adjust for environmental variables such as diet, concurrent diseases, and other medications,” notes panelist and coauthor of this study, Stephen P. Spielberg. “This label is really key since it’s the first that provides explicit recommendations based on pharmacogenetic information.” Studies have shown that the use of biomarkers for warfarin has reduced hospitalizations and complications from excessive or inadequate warfarin doses. A report by the AEI Brookings Joint Center for Regulatory Studies estimates that integrating genetic testing into warfarin therapy could reduce health care costs by as much as $1.1 billion in future years.[33] Other biomarker-drug pairings are being developed and tested, though so far the number of these tests in wide use remains small.

Tools and software

The dramatic increase of less expensive and more efficient tools for sequencing DNA is another success story emerging from the new biology. By marrying the fields of computing and bioengineering with genetics, the costs of sequencing a complete human genome has fallen from millions of dollars just two or three years ago to less than $10,000 today. At this rate, genomes soon may cost less than$1,000.[34]

Sequencing technologies, however, produce only the raw data of a person’s As, Cs, Ts, and Gs. Several other steps are needed to understand and make use of this data,

including the clinical validation of predictive markers; the development of analytical tools and algorithms to assess markers as part of multivariable risk profiles for individuals; and a better understanding of how individual and polygenetic markers fit into molecular pathways and biological systems that impact health and disease. Efforts are under way to address each of these issues at universities, institutes, and companies, although there is no systematic plan to validate, analyze, and interpret the thousands of genetic GWAS markers identified to date. Some notable efforts to make sense of genetic data include the NIH's plans to develop a Genetic Testing Registry by 2011.

> *"The generation of genomic data will have little value without corresponding phenotypic information about individuals' observable characteristics, and computational tools for linking the two. The challenges facing researchers today are at least as daunting as those my colleagues and I faced a decade ago."*
>
> — J. Craig Venter, PhD

"The registry is expected to include information about the availability of genetic tests, indications for testing, test accuracy, validity and utility," read an NIH news release announcing the program.[35] The NIH also is expanding its Pharmacogenomics Knowledge Base (PharmGKB) program that catalogs, annotates, and curates data on links between human genetic variation and drug responses.[36] In 2009, working with a worldwide consortium, PharmGKB researchers took a leading role in using their DNA protocol to better predict the optimal dose of the blood thinner warfarin, which is tricky to administer because of differences in how patients respond. Their work has led not only to a black-box warning, but also to a large-scale clinical trial sponsored by the NIH's National Heart, Lung, and Blood Institute that is testing the validity and usefulness of genetic markers associated with warfarin.[37] Many other efforts are under way both inside and outside of government to make sense of the data and knowledge generated by the new biology over the past decade or two.

Another crucial development in tools and software is the move to digitize medical records in the United States, where only one in five physicians and one in ten hospitals have even a rudimentary system for keeping electronic medical records (EMR). Having these records available has the potential to improve care for patients by making their records available whenever and wherever they interact with the health care system. Anonymously accessing this information also will provide researchers with a rich stream of data on the progression of disease in people and populations that will greatly improve society's ability to predict and prevent disease, and potentially track down environmental contributions by revealing patterns according to geography, diet, and other factors. Adoption of EMRs in the United States received a

> *"It is more important to know what kind of patient has the disease than what kind of disease the patient has."*
>
> — Sir William Osler, MD, 1905
>
> *"It is equally important to know what kind of patient has the disease as it is to know what kind of disease the patient has. The new biology enables us to do both."*
>
> — Frank L. Douglas, MD, PhD, 2010

boost in 2009 with the Obama administration's allocation of more than $20 billion toward the effort, and the FDA has launched efforts like the Sentinel Initiative to use electronic records to detect adverse events, though much more funding and effort is needed for this and other tools to collect, organize, and analyze personalized health information and make it useful for patients.

Preventive health

The purpose of developing a robust science of predictive medicine is to foster preventive measures that are based on evidence and targeted profiles of individual risk factors. Preventive measures always have been a part of medicine. Whenever a physician counsels, say, an overweight patient to avoid fatty foods and to exercise more, he or she is predicting that the patient will not attain optimal health or prevent unwanted outcomes without taking certain actions. More recent low-tech measures to mitigate or prevent bad outcomes include smoking cessation courses and counseling. For instance, Medicare recently agreed to pay for seniors to get antismoking counseling—which can improve even an elderly person's health, and costs less than a third of what is spent on medical care for those who keep smoking.[38] Recently, the new biology has provided a deluge of possible tests, tools, and protocols that aim to predict risk factors for a person's future health outcomes, good and bad—which also is expected to lead to more personalized and precise lifestyle and behavioral adjustments. For instance, a recent clinical trial in Taiwan found that genetically screening all users of a common epilepsy drug would cost $5 million, but would save $35 million in treatments by detecting a mutation associated with Stevens-Johnson syndrome, a rare side effect of the drug.[39]

Wide-scale adoption of predictive and preventive tests will present several challenges, including a need for everyone, including patients and health care providers, to get used to using complex patterns of risk factors in making predictions and diagnoses. For instance, a slightly elevated genetic risk factor for heart attack will have to be considered—and understood—along with other risk factors provided by family history, lipid chemistry, diet and smoking status, a carotid ultrasound scan, and other measurements. Society also will need to understand that predictive tests and preventive protocols are subject to change and reassessment according to the latest findings.

An example of this changeability came recently with the announcement that mammograms may not be necessary for women between the ages of forty and fifty. The finding was based on epidemiological data that showed the test was not cost effective for most women under fifty years old.[40] Though based on sound epidemiological data, the findings upset many patient advocates and physicians who have worked for years to convince women over age forty to take this test. They took the position that even if only a few breast cancer cases were caught for women under fifty, the test was worth it. They accused the researchers of putting statistics and costs above women's lives—a reaction that caught the research community by surprise. (One solution for this dilemma is to work hard to develop a molecular test that can better identify patients under fifty years old who might benefit from the test). Similar controversies have developed around the PSA test for assessing a patient's risk factor for prostate cancer. The high number

of false positives—which often lead to unnecessary biopsies—and the very slow progression of the disease even if one gets a true positive have created difficulties for physicians and patients in assessing the value of this predictive test.

Impact of the environment

What occurs inside our cells and body is only part of the equation in assessing an individual human. For most disease, the impact of our environment—sunlight, air, chemical toxins, smoking, food, and water—is the primary source of common diseases and other deleterious traits. Modifying one's environment has been estimated to reduce the risks of stroke, colon cancer, coronary heart disease, and adult onset diabetes by as much as 90 percent.[41] Studies of twins indicate that the risk attributable to genes for many cancers is as low as 10 percent, and GWAS suggest that the heritability of many common diseases is considerably less than the impact of the environment.[42] Lately, scientists have learned that the environment can cause epigenetic changes—changes that impact how a gene behaves, but don't change the makeup of the gene itself—that can activate the advent of disease.

Given the environment's enormous impact on disease, a substantial gap exists between the attention lavished on genetics and the comparatively scant attention given to how environmental factors interact with genes and human biology to cause outcomes. In 2006, the U.S. Congress approved a $40 million pilot project, the Gene Environment Initiative, to study the interaction of specific environmental toxins and genetics and pay for the development of biomonitoring technologies to better collect data on environmental exposures, including more sophisticated methods of identifying levels of toxins in people.[43] Other small-scale projects at the NIH, and in the Environmental Protection Agency and other agencies, have begun to apply technologies designed to screen drug candidates for toxicity—such as high throughput screening and cell assays—to investigate the impacts of environmental toxins at the molecular level.

An example is the Tox21 collaboration among the NIH's Chemical Genomics Center (NCGC), and the National Human Genome Research Center, and the National Institute of Environmental Health Sciences' National Toxicology Program. More recently, the FDA joined in. They plan to test the impact of 10,000 pollutants and chemical toxins on human and animal cells.[44] They are using NCGC's robotic screening and informatics platform, which normally is used to test toxic effects of drugs on cells. NCGC head Christopher Austin, who also is a member of this study's expert panel, describes the effort as a method for directly testing systemic effects on human cells rather than depending on animal models. (Ethically, humans cannot be directly tested for chemical toxicity). "This systems-wide project is designed to develop in-vitro assays that will be more predictive; and because they're

> *"Recent increases in chronic diseases like childhood asthma and autism cannot be due to major shifts in the human gene pool. They must be due to changes in the environment, which may produce disease in genetically predisposed persons."*
>
> — Francis Collins, MD, PhD, Director, NIH

more predictive, and mechanistic, and cheaper, and faster, it will make the animal studies no longer necessary," Austin said.

The NCGC project, however, is just the beginning of a long and complicated effort needed to better understand the impact of environmental chemicals and their interaction with the human organism. One idea to accelerate this field has come from panelist Martyn Smith, a toxicologist in the School of Public Health at the University of California at Berkeley. He has called for a Human Exposome Project: "…to discover the major contributors to disease risk, agnostic approaches are needed to classify *all* important environmental exposures." In a recent "big think" proposal to the NIH, he wrote:

> What we need are environmental analogs of GWAS to characterize the "exposome" and open the door to discovery of the environmental causes of disease. High throughput technologies that work on small amounts of biological material should be developed to characterize all internal tissue exposures via top-down exposomics strategies focusing upon biobanked samples.[45]

In spring 2010, the first-ever "EWAS"—Enviroment-Wide Association Study—was published by panelist Atul Butte, a physician and researcher at the Stanford University Medical School. His lab ran statistical analyses linking data collected by the Centers for Disease Control and Prevention on what Americans eat and their exposure to environmental toxins with the prevalence of diseases such as asthma and diabetes.[46] As a proof of concept, the researchers investigated possible links between subjects in national surveys who test positive for type 2 diabetes and a list of 266 chemical toxins that also are tracked by the CDC through levels that show up in blood or urine. They found significant associations between people with diabetes and their exposure to heptachlor epoxide, a pesticide that was partially banned in 1988, and also to gamma-tocopherol, an ingredient in some versions of vitamin E. They also discovered that high levels of beta-carotene were slightly protective against diabetes. Butte's lab is working on linking these findings to potential genetic variations that might increase one's sensitivity risk to environmental toxins.

Like GWAS, the EWAS are mere statistical analyses that need to be tested and validated in real people. But they offer a method for identifying targets in what should be a broader and more coordinated effort to understand the environment's impact on human health.

Rise of the patient consumer

At one time, patients tended to defer to their physicians for most matters concerning their health. In recent years, this passivity has given way to a movement among many patients who want to have a more active role in their own health care—whether it is perusing medical information websites on the Internet or seeking out nontraditional opinions and treatments. This has led to a thriving alternative medicine industry that embraces everything from acupuncture to the latest fads in diet and herbal supplements. Last year, the diet and supplements industries alone earned more than $24 billion.[47] Despite this, traditional physicians and biomedical researchers have

shown little interest in testing or validating widely used alternatives, or in taking more seriously the increasing demand of healthy patients to make lifestyle changes that can maximize their health potential. This is despite efforts made by organizations such as the National Center for Complementary and Alternative Medicine (NCCAM) at the NIH, which for eighteen years (called The Office of Alternative Medicine for the first seven) has sought to apply scientific rigor to, say, the use of green tea to protect against rheumatoid arthritis (may work);[48] the use of *Ginkgo biloba* to protect from cancer or to treat dementia (doesn't appear to work);[49] [50] and the consumption of flaxseed to reduce some risk factors for cardiovascular disease (may work).[51] The center has produced some 2,500 studies to date on how diet, lifestyle, and supplements impact health, although its budgets have been too small for any sort of systematic study, even though the money available to the NCCAM has gone up from $2 million in 1992 to $128.8 million in 2010.[52]

"Living a healthy lifestyle is crucial to good health," said panelist Michael Roizen, a physician and wellness specialist at the Cleveland Clinic, "but this has not been properly studied." Congress also has decided not to require vigorous testing or scientific proof of efficacy for most supplements and diets.

As the gap between discovery and application grows, patient-centered groups such as FasterCures, PatientsLikeMe, and the Multiple Myeloma Research Foundation have moved in to demand and, increasingly, pay for efforts to connect research and application. "Emphasis on speed or direct responsiveness to health needs is spotty," concludes a recent paper published by FasterCures, "and the time from initial discovery to dissemination and commercialization can sometimes be measured in decades—an outcome that is simply unacceptable to the citizens who fund this research and expect to benefit from it."[53] Still, only a small fraction of overall health R&D funding is spent by these groups—$918 million out of $131 billion spent by government, companies, and nonprofits on life sciences research and development in 2008.[54]

> *"We believe that the Internet can democratize patient data and accelerate research like never before. Furthermore, we believe data belongs to you, the patient, to share with other patients, caregivers, physicians, researchers, pharmaceutical and medical device companies, and anyone else that can help make patients' lives better."*
>
> — Jamie Heywood, Cofounder, PatientsLikeMe

Not everyone on the expert panel agreed that patients always should be responsible for their own health and decisions about their care. "I do not believe in this model," said bioethicist and panelist Arthur Caplan of the University of Pennsylvania. "Too many people cannot do it—children, the mentally ill, the chronically ill, the senile, non-English speakers, the very poor, and others. This is ideology pretending to be ethics." Clearly, provisions will need to be made in a world of personalized health to acknowledge that health care by its nature impacts many who are vulnerable because of illness, ignorance, or age, and to create strong provisions to protect and assist these people.

How we are doing: outcomes and costs

It is not entirely fair to offer up gross medical outcomes data as an assessment of "how we are doing" in the larger enterprise of biomedicine in the United States. The new biology we are discussing in this study is in its early stages and, even if all gaps were narrowed or closed tomorrow, it still would take many years for this mass of new discoveries to truly revolutionize health care in America and the world. However, after a decade or more of massive expenditure and effort centered on biomedical research and discovery, it may be useful to offer a few metrics that can serve as health care benchmarks for where we stand as a society now compared to the recent past—and as we move forward into the future.

In gross terms, lifespan in the United States has increased over the past decade by about 3.6 percent a year, to 78.8 years for Americans in 2010.[55] This growth rate is nearly three times higher per year than the annual growth in lifespan between 1970 and 2000, which increased by about 1.5 percent a year. The number of people living longer than eighty years has increased, too. In just the six-year period between 2000 and 2006, this cohort grew by an astonishing 20 percent.[56] Yet these gains most likely came from breakthroughs occurring in the latter three decades of the last century rather than what has happened since the year 2000.

Globally, the U.S. lifespan last year ranked twenty-third out of twenty-seven countries in the Organisation for Economic Co-operation and Development (OECD)—which includes the United States, most of Europe, Japan, Korea, Turkey, Australia, New Zealand, and Canada.[57] This is a drop from fifteenth place in 1970. Mortality rates in the United States for some medical conditions, such as strokes and cancer, ranked among the best in OECD countries—meaning fewer deaths. Yet the United States ranked toward the bottom in mortality rates for diabetes and obesity, and was twenty-sixth, or second to last, for infant mortality. It should be noted that a number of issues contribute to the high United States infant mortality rate. These include the exclusion of very premature babies in some countries other than the United States from neonatal mortality rates. There also are substantial racial and ethnic disparities in the United States that don't exist in many OECD countries that contribute to the neonatal mortality numbers.

America ranks first in one important category, however: health care spending per capita, which, at $7,500 a year, is nearly twice what most other major Western countries spend. Here, the impact of new technologies is unambiguous, according to the Congressional Budget Office. In 2008, that office issued a report claiming that new technologies have been responsible for half the increase in spending on health care for several decades.[58] This is to be expected when new drugs and technologies can treat or cure previously untreatable diseases, although most of this technology also is available in countries where health care costs considerably less.

One argument for aggressively developing and applying new advances in predictive and preventive care is to reduce health care costs. Proof of savings, however, remains poorly studied and therefore difficult to quantify. A 2008 report issued by the Congressional Budget Office concludes that "examples of new treatments for which

long-term savings have been clearly demonstrated are few."[59] Many new technologies for treating disease increase costs, said the report. However:

> Future advances—in molecular biology and genetics, in particular—may one day offer the possibility of savings if they make curative therapies available. Continued advances in understanding the genetic origins of disease offer the credible possibility that future providers will accurately predict the health risks faced by individual patients and design therapies tailored specifically to them.[60]

A more thorough discussion of health and spending patterns in the United States is beyond the scope of this study. However, the OECD rankings presented here do have relevance for one crucial reason: because even if a society is rich in innovation and scientific achievement, it must devise systems and methods for effectively utilizing these discoveries to both improve health and avoid onerous costs. Arguably, this has not occurred as efficiently as it might have in present-day America.

II. The nature of the gap

> This 'gap' might have been considered normal five years ago when the translation of these discoveries to applications in clinical practice was new. But now this gap is avoidable and almost a crisis because patients are not getting to the best treatment decision and medicine possible.
>
> — Brook Byers, Kleiner Perkins Caufield & Byers

Describing the gap

Innovation by its nature takes time to be adopted, with gaps between discovery and application often taking decades or even centuries. For instance, the gap was sixteen years between Alexander Fleming's discovery of penicillin as an antibiotic in 1928 to its first wide-scale use in 1944, when it saved thousands of Allied lives in the final bloody year of the Second World War.[61] The gap between the birth of the Internet in 1969—when the Department of Defense commissioned the creation of ARPANET—and its broad adoption by hundreds of millions of people took three or four decades. [62] On the other hand, the gap between the invention of technologies allowing records to be stored electronically was available as early as the 1950s (earlier if you count the first crude computers in the 1940s), with most industries fully adopting these innovations by the 1990s—the major exception being the health care industry, which today, more than a half-century later, remains overwhelmingly in the paper world of the early and mid-twentieth century.

> *"We've all been following the remarkable advances in biomedical sciences led by the NIH with great enthusiasm for years. However, much more can be done to speed the progress from new scientific discoveries to treatments for patients."*
>
> — Kathleen Sebelius, Secretary of Health and Human Services

These examples illustrate the three most common gaps that occur between new discoveries and technologies, and their application. First are those caused by the need for further testing and refinement (penicillin). Second are those that lack the complementary infrastructure and investment required to make them work (the Internet needed servers, personal computers, and a network of websites). Third are those gaps caused by a failure of imagination in a society or an industry that is unable or unwilling to grasp the importance of new discoveries, or properly encourage and facilitate their adoption (digitization of health care records).

All three "gaps" are complicit in the artificially created gaps that now are occurring between discovery and application in the life sciences. This section, however, will concentrate mostly on the third cause of technology gaps: a failure of imagination. It is under this heading of "imagination"—of understanding and overcoming the hurdles to change—that we will describe some key philosophical shifts that are framing the drive toward an era of personalized health. We then will describe ten specific categories of gaps.

First, however, we will ask if the gap is worse than it should be, and address a major cause of this and many other technological gaps in history: the “complexity conundrum.”

Is the gap “natural”?

Nearly all of the experts consulted for this project agree that the current gap between discovery and application has natural components in common with, say, the development of penicillin and the Internet. However, they disagree on the size of the gap. Panelist and biocomputationist Eric Schadt calls it a “very significant gap that I believe has more or less disabled molecular biology’s ability to impact clinical medicine.” According to panelist and stem cell researcher James Thomson: “Gap is a bit of a strong word ... A lag time to widespread adoption is unavoidable, but clearly one might try to optimize the transfer rate from discovery and use.” Nearly all agree, however, that the gap is more profound than it should be, and that this gap can be reduced if we unleash the force of our collective imagination.

The “conundrum of unexpected complexity”

In 2000, when President Bill Clinton stood alongside geneticists Francis Collins and Craig Venter to announce a draft sequence of the human genome, he voiced the prevailing sensibility that this achievement would “lead to a new era of molecular medicine, an era that will bring new ways to prevent, diagnose, treat and cure disease.”[63]

This conviction on that balmy summer day in 2000 already was fueling a biotech investment craze that had committed billions of dollars to “pure play” genomic companies such as Celera and Millennium Pharmaceuticals. Two years earlier, in 1998, Congress had approved a Clinton administration initiative to double the budget of the NIH in five years in the belief that more basic research along the lines of the Human Genome Project would hasten the arrival of drugs and treatments based on the new science characterized by the Human Genome Project. Instead, as we earlier noted, the era of megafunding for basic R&D has seen a shrinkage in the number of new drugs approved by the FDA—from an average of thirty-five per year in the late 1990s to around twenty-one per year since 2005. Likewise, only a handful of the thousands of genetic markers and other biomarkers identified by researchers as being associated with disease have resulted in a direct health benefit.

> *“The truth is we have little idea of the underlying causes of common human diseases.”*
>
> — Eric Schadt, CSO, Pacific Biosciences

Many blame this substantial gap in expectations on a realization that the human organism is substantially more complex than many thought a decade ago. Indeed, as

researchers drill down ever deeper into the details of cells and molecules, a "conundrum of unexpected complexity" has arisen that is frustrating efforts to fully understand biological mechanisms and to develop new treatments.

In *Nature*, science writer Erika Check Hayden recently wrote an essay on complexity in biology to mark the tenth anniversary of the draft human genome, noting that

> as sequencing and other new technologies spew forth data, the complexity of biology has seemed to grow by orders of magnitude. Delving into it has been like zooming into a Mandelbrot set—a space that is determined by a simple equation, but that reveals ever more intricate patterns as one peers closer at its boundary.[64]

The new biology was supposed to allow drug makers to better target mechanisms of disease, eliminating the trial and error method of drug discovery and ushering in an age of "rational drug development" that would create drugs that were more effective, cheaper, and personalized. Regrettably, this expectation also has been thwarted by the conundrum of unexpected complexity, with the cost of each drug approved soaring from $802 million per drug in 2003[65] to over $2 billion today.[66] Drug prices also were supposed to go down with smarter R&D techniques. Instead, they have soared, with some "new biology" cancer treatments costing tens of thousands of dollars per patient, and some treatments for rare diseases costing hundreds of thousands of dollars per year. These treatments are lifesavers for patients who need them, but the process to create them has hardly been efficient or cheap.

In many cases, the conundrum of unexpected complexity in science is to be expected. New discoveries almost always turn out to be more complicated than first thought, whether one is trying to understand the mechanisms and progression of a tumor or forecast the course of a hurricane in the Gulf of Mexico. There comes a time, however, when enough is known to start applying the knowledge to real-life situations, even as researchers continue to delve deeper. While this may seem self-evident, there exists a powerful impetus in life science research to aim toward elegant, detailed explanations and discoveries. As former Intel CEO and Parkinson's disease activist Andy Grove has commented: "Scientists are so caught up in doing the best science that they are failing to translate that science into anything useful. When we set out to develop the microchip, we did not try to make the best chip, but one that worked for as little cost as possible."[67] If one chip idea didn't work, he said, they tossed it and built a better one, learning from their mistakes. Grove, who is seventy-three years old and has Parkinson's disease, suggests that bioscientists should follow the same example. He and others have called for a "cultural revolution" that rewards curiosity, risk taking, and lessons learned from failure, rather than the current paradigm that rewards work pleasing to peer reviewers, takes few chances, and retains an ivory tower mentality that puts elegant science above finding speedy treatments that work.[68]

An example is the argument in the 1980s and 1990s over methods during the quest to sequence the first human genome. Many biologists opposed the idea of assembling a "rough draft" of the genome rather than a complete and highly accurate sequence using

what was then the gold standard: the Sanger Method. After years of heated debate, the Human Genome Project leaders went for fast and cheap, using technologies eventually developed by Craig Venter and others. This produced an incomplete haploid genome that made many reductionists squirm. But it was enough to allow businesses and labs to mine the genome more quickly while scientists continued to fill in details missing in the rough draft.

Conceptual gaps

The primary conceptual themes driving the gap between discovery and application are mostly a matter of balance—or a lack of balance—between illness and healthy wellness, one-size-fits-all medicine and personalized health, and reductionism and integration. We will address these three yin-yang elements separately, although clearly they overlap each other. For instance, the need to accentuate healthy wellness is dependent on a greater stress on personalized health for individuals and integration among the various disciplines in biomedicine, and in a more holistic focus on the human organism. Neither can a focus on the individual or integration be fully realized without an equal emphasis on healthy wellness. Diagram A illustrates the relationship among the three themes.

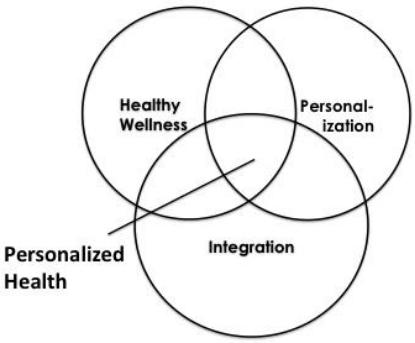

Diagram A: Key elements of personalized health

The predominance of illness

For most of human history, healers could do little for patients who were ill. “God heals,” said Benjamin Franklin, “and the doctor takes the fee.”[69] In the past century, science has provided us with an astonishing medical toolkit for treating the ravages of many diseases. Some past scourges, like smallpox, have been eradicated. The effort continues as society devotes unprecedented resources to keep improving treatments and cures for the ill. The time has come, however, for a complementary effort to devote substantial resources, expertise and energy to keeping people more broadly well. By healthy wellness, we don’t mean simply the absence of illness, but, instead, an active effort to stay healthy by using traditional good sense in terms of diet and lifestyle, and by using new discoveries and technologies for the prediction and prevention of disease. Healthy wellness cannot forestall all disease and will not prevent aging and death. Yet it makes sense in terms of individual health and societal

> *“Having good health is very different from only being not sick.”*
>
> — Seneca the Younger, 50 AD

well-being—and cost—to reduce as high a percentage of diseases, both acute and chronic, as possible.

Millions of patients, both healthy and sick, in the self-help segment of our society already are embracing healthy wellness. This is despite the absence of a serious effort by the biomedical community to apply rigorous scientific testing and study to diet, supplements, exercise, and other “wellness” treatments. Changing the mindset to concentrate on both the science and application of healthy wellness is an obvious need in an age of personalized health, but will be difficult to implement in a health care system where medical education, policy, investment, business, reimbursement, regulation, and infrastructure overwhelmingly are aimed at waiting until a person gets sick and shows symptoms before action is taken. But the demand is certainly there. So are the technologies and methods for testing and validating what might be termed “lifestyle science.” The impetus now is on the biomedical community and policymakers to connect these two dots.

Coauthor of this study, physician, and educator Stephen P. Spielberg stresses that a greater emphasis on healthy wellness should not be seen as a panacea.

“I ponder the confounded realities about health and disease,” he said. “So much ‘disease’ is actually ‘self-limited illness’—viral infections that last for days or a week, injuries that heal themselves regardless of what we do. For so many commonplace illnesses, nihilism, a little chicken soup, and comfort do fine. As for prevention of serious illness that now requires medical care, certainly many afflictions can be prevented by diet, lifestyle, etc. Equally clear, many cannot, and effects of diet, exercise, etc., are not uniform in the population. We often then end up blaming patients for ‘not taking adequate care of themselves’ when their best efforts may, in fact, have been futile at either preventing or managing disease. Also, predisposition and risk of disease from environmental exposures varies dramatically within the population; benefit of diet, exercise, [and] lifestyle as preventive measures varies, and obviously treatment of existing disease varies, as well.”

One size fits all

Genetics has proven that humans are remarkably similar, sharing as much as 99.9 percent of their DNA, but it also has shown that even a 0.1 percent difference between one person and another can have a sizable impact on everything from how we look to what diseases we are likely to get. Add in a person’s specific family history, lifestyle, and environmental factors, and it’s no wonder that some people don’t respond to a generalized approach to diagnosis, disease, and treatment. Yet modern medicine is built largely on standardized diagnoses and treatments, and on epidemiological averages and means that attempt to fit a patient’s symptoms, test results, and presentation into designated categories of health and illness (and also categories for reimbursement). This system was a triumph of science and medicine in the twentieth century that replaced an earlier system based mostly on the subjective perceptions of physicians. Yet it has a core weakness in being unable to adequately account for the outliers in a distribution curve, which, in medicine, can mean that entire subpopulations

of patients do not easily fit into a one-size-fits-all diagnosis or response to a drug. For instance, serotonin reuptake inhibitors to fight depression appear to have little or no effect on up to half the people who take them.[70]

The converse happens, too, where some treatments are given to many and work for only a few. For instance, the FDA recently announced that it might rescind approval for Genentech's drug Avastin for breast cancer because it has failed to increase the average survivability rate for patients. Yet a small percentage of patients do respond, in a few cases well enough that they survive for several years. Patient advocacy groups, therefore, have protested this proposed action.

"We recognize the benefits of Avastin overall are modest for women with metastatic breast cancer," said Susan G. Komen for the Cure® founder Nancy G. Brinker in a letter to the FDA. "However, we do know that, for some women, Avastin offers a greater-than-modest benefit."[71] The future of this drug for breast cancer is complicated by the fact that it costs up to $80,000 per regimen.[72]

For both cases—serotonin reuptake inhibitors for depression and Avastin for breast cancer—the solution is for scientists to identify which patients respond best, and which don't, by finding an appropriate molecular marker. Roche Diagnostics has developed its Amplichip CYP450 genetic test for calling out patients who don't metabolize SSRIs and other drugs, although few physicians or patients use it. Genentech scientists, however, have tried to find biomarkers that would identify those breast cancer patients most likely to benefit from Avastin, but so far have been unsuccessful.

Even without a conscious effort to push personalized health, medicine has been making efforts to better understand obvious differences in patients. For instance, for hypertension, physicians know that some populations respond better to different agents, with African Americans reacting better to diuretics, and worse with ACE inhibitors, on average. Researchers have spent years trying to find out why.[73] However, much more will need to be done to understand and acknowledge human variation if we are to move into a true period of personalized health.

The pluses and minuses of reductionism

Since at least the seventeenth century, when Rene Descartes and other Enlightenment thinkers articulated a reductionist approach to understanding the natural world, biologists and other scientists have been delving ever deeper into the minutiae of life. This method has been and continues to be crucial to the scientific advancements of the modern era, and has allowed us to acquire a deep understanding of how the human organism works. Less helpful has been the tendency of reductionism to encourage an ever-more-narrow process of specialization that, 400 years after Descartes, has created a universe of experts whose knowledge has gone from the macro to the micro to the nano, and beyond. In Erika Check Hayden's essay in *Nature*, she asks:

> *"A major problem of the reductionist approach is that it leaves little room for serendipity."*
>
> — Frank L. Douglas, MD, PhD

> With the ability to access or assay almost any bit of information, biologists are now struggling with a very big question: Can one ever truly know an organism—or even a cell, an organelle, or a molecular pathway—down to the finest level of detail?[74]

The emphasis on the infinitesimal has come to so dominate the life sciences that few experts are trained or rewarded for the necessary complement to reductionism, which is integration. One striking example we mentioned earlier is the failure of molecular biologists to systematically study and integrate the impact of environmental factors such as diet and chemical toxins on genes and other molecular components of the human body. Our society needs and greatly values specialists with a detailed knowledge of a subject. But we also need to develop systems for rapidly and effectively moving their discoveries into applications. This will require the establishment of equally valued experts in integration, and an acknowledgement that society cannot function smoothly unless both reductionism and integration are embraced, rewarded, and practiced.

Specific gaps

The current gap between discovery and application in the life sciences can be broken down into the following specific areas. These are presented as a blend of data, impressions, and comments from our expert panel.

Gaps in tradition and culture

As Thomas Kuhn wrote in *The Structure of Scientific Revolutions*, the transition to new scientific paradigms first must overcome resistance to traditional methods and thinking he calls “normal science”:

> That enterprise [of normal science] seems an attempt to force nature into the preformed and relatively inflexible box that the paradigm supplies. No part of the aim of normal science is to call forth new sorts of phenomena; indeed, those that will not fit the box are often not seen at all. Nor do scientists normally aim to invent new theories, and they are often intolerant of those invented by others.[75]

Today, as the life sciences begin to edge into a new paradigm of personalized health, the state of “normal science” is not this rigidly anti-new, although Kuhn’s description is apt for many of the key institutions in science and medicine. The sheer size of these endeavors and their multibillion and multitrillion dollar budgets over the past few years—and the millions of workers and the vast complexes of labs, hospitals, clinics, and payers—make it difficult to foster change even when new paradigms beckon. We already have given the example of health care’s slowness to embrace electronic medical records, which is as much a failure of tradition and culture as it is one of cost. Individual institutions must contend with the dismantling and replacement of personnel and tried-and-true systems of record keeping. Apparently, the momentum to retire this tradition is accelerating with the Obama administration’s commitment to spend $20 billion of the 2009 economic stimulus funds on projects to digitize medical records. Health and Human Services Secretary Kathleen Sebelius recently detailed her

department's plans to use this money to train IT workers, assist providers in finding the right IT system, and motivate providers with cash rewards—"up to $44,000 in Medicare or almost $64,000 in Medicaid for individual providers, and millions of dollars for hospitals."[76]

One positive trend impacting the tradition gap in the life sciences is the sense that one of Thomas Kuhn's paradigm shifts already is well under way, as the numerous translational and integrative projects attest—even if they have yet to reach a critical mass that would shift the personalized health movement into a "revolution" from normal science to something new.

Gaps in basic science

The proliferation of specialties in this latter-day age of reductionism has led to an atomization of specialties that have their own streams of funding, conferences, journals, awards, traditions, and technical languages. In 2007, a team of researchers in Finland found that more than 23,000 peer-reviewed or juried academic publications in all fields were published that year on thousands of specialized subjects containing over 1.3 million studies.[77] The impact of this specialization has been a sequestering of researchers into their own fields, with too little interaction among specialists. For instance, says panelist Stephen P. Spielberg, molecular biologists have little contact with scientists who study metabolism and biochemistry. They, in turn, have little contact with cell biologists or environmental toxicologists, much less clinicians caring directly for patients.

"Within basic science, people tend to be trained with 'blinders,'" said Spielberg, "and faculty are promoted by peers from their specialty for 'individual' accomplishment, usually within the narrow confines of their field." An example of the silo effect is in genetics, where Spielberg and others report a serious gap between the characterization of a genotype and its phenotype, which is the actual observation of the trait or disease. "This risks a garbage-in, garbage-out situation when trying to apply genomics in the clinic," he said.

Spielberg also points out that universities often base promotion systems on first author publications and focused scientific effort, with little incentive to contribute to "group" science, or to work in complex, multidisciplinary areas as part of a team.

"The grant structure at NIH similarly reinforces the 'rugged individual,'" he said, "although new translational programs have attempted to move toward integrated, cross-disciplinary science and systems that try to expand recognition and promotion systems in this milieu alongside science driven by individual curiosity. We clearly need both, and not in opposition to each other, but rather interdisciplinary dialogue raising hypotheses through creation of validated products and interventions."

Within specialties, the model favors the individual investigator operating largely on his or her own, typically devising one-off experiments without any larger plan to independently

replicate the findings, or to integrate the research with related specialties or clinical applications.

“We need replication studies and a better understanding of who would benefit from tests,” said panelist Michael Roizen of the Cleveland Clinic. Independent research with the sole aim to further knowledge should be a key part of the biomedical enterprise, but not when it predominates over more targeted research. A healthy system would encourage and provide funding, tenure, and prestige in equal measure for independent initiative, and for efforts to integrate with other scientific disciplines and with strategies that aim for purely scientific outcomes and for those related to a clinical need.

Selected comments from the expert panel:

Anthony Atala: “Right now, discovery is generally a product of hypothesis-driven, single-investigator research. Scientists work in silos and, even if they are part of a virtual center, they often don’t communicate with each other. For example, if a team is studying a particular cell type, the scientists who are looking at cell biology, physiology, and genetics may be located in separate departments and buildings.”

Anthony Atala: “One reason [for this gap] is that scientists work in very specific areas, making micro-discoveries, and may not realize the impact of what they’ve done. Understanding how these micro-discoveries relate to the entire fund of knowledge is a process that takes time…”

Atul Butte: “After a discovery, a researcher has to decide how to spend future effort, on the long road toward application, or back to the bench for another discovery. As the road gets longer toward application/product realization, I think staying at the bench is viewed as the path of least resistance. Investigators are not valued (i.e., by universities, academic settings, etc.) for pursuing both novel discoveries and applications at the same time.”

Christopher Austin: “Lastly, there is a scientific cause for the gap—the reason the time is so long and so much structure is needed is that the failure rate is so high at each step, and this failure is due directly to our lack of understanding of the scientific principles underlying most steps of translation. This lack of understanding leads to a high degree of empiricism, which is fraught with failure.”

Dietrich Stephan: “Chaperoning a discovery from the lab to the commercial sector is a skill set that is not taught to our scientists, and is extremely disruptive to the work-flow of academic research. We need to educate and support our entrepreneurial scientists.”

Greg Simon: “[Gaps are] unavoidable because ‘discovery’ and the practice of medicine are not practiced by the same people, funded by the same institutions, or even talked about at the same conferences.”

Stephen P. Spielberg: “The miracle of the modern age to me is that we’ve done as well

as we have with molecules that address one or another target that play a role in an illness. I think that this has been because drug development has traditionally focused on modifying a phenotype. Today's approach, highly targeted to a given locus, holds huge promise, but also suggests that one drug may not do the trick and that we will need more poly-pharmacy and 'environmental' interventions to more effectively treat conditions. Older drugs were discovered because they 'worked,' and we were pretty 'dirty' in terms of targets. Newer drugs are much better targeted, but will they 'work?'"

Gaps in the clinic

"There is … a gap between clinicians and patients on the one hand, and molecular scientists on the other hand in understanding the potential use and applicability of recent advances," said panelist Joshua Adler, an internist and the chief medical officer of the University of California at San Francisco Medical Center. Few gaps under review in this report seem more significant than this one, according to the expert panel. Partly, this comes from the natural tension and differences in training between scientists devoted to pure research and clinicians whose focus is on patient care. However, many panelists agree with Adler that there should be "…better coordination between clinical leaders and scientists in tailoring questions to answer through molecular biology in order to increase the clinical utility of the answers." He and others on the panel talked about the lack of a concerted effort to target high-impact discoveries for patients.

Panelist Stephen P. Spielberg also has observed that physicians are not adequately trained in the new biology and lack a mechanism to keep them up to date on new findings that are relevant, or could be relevant, to the clinic.

"The rate of accrual of new science, technologies, even the language of science leaves many who care for patients unable to understand and even fearing the explosion of new knowledge," he said. "They lack training in pharmacology, therapeutics, and genetics, or in the sort of quantitative thinking that is crucial for understanding predictive and risk-based testing and profiles." Working as doctors do, one patient at a time, places a dynamic tension between those who study populations and those who care for individuals.

In a recent paper, the nonprofit patient advocacy group FasterCures detailed some of the prevailing gaps between science and the clinic, including:[78]

- a highly specialized, reductionist approach to scientific inquiry;
- little funding or reward available for high-risk research;
- a focus on individual organizational challenges instead of collaborative approaches to "big picture" problems;
- increasing conflict-of-interest challenges arising in public-private partnerships;
- a lack of public understanding of the challenges facing the disease research endeavor;
- insufficient focus on translating basic research into clinical application;

- inadequate dissemination of previous research efforts—especially failures; and
- failure to aggregate funding across organizational lines to achieve larger-scale impact.

Selected comments from the expert panel:

Adam Gazzaley: "There seems to be minimal communication between basic and clinically directed researchers. This may in part be due to inherent differences in any specialized pursuits, but perhaps is also the result of undeveloped infrastructure."

Dietrich Stephan: "We need to meet our physicians halfway. Physicians do not know how to run or interpret data from a mass spectrometer of ELISA assays, yet the results are commonly used to guide clinical care. This is no different than genetic readouts—it is in the packaging."

Eric Schadt: "I think confusion around how results should be interpreted and around how data should be integrated to get to something that is more clinically relevant are big problems. That is, it takes a long time to get something accepted by practicing physicians—as we saw with CRP [the C-Reactive Protein test that measures levels of this protein for an indication of inflammation in the body] being accepted as a risk marker for heart disease. Clinicians require the evidence-based paradigm, versus a more proactive path for demonstrating the utility of a discovery. But beyond that, there are debates that need to be had around what type of model should be used in making a prediction, how it compares to other models."

James Thomson. "A fundamental problem is that doctors don't have the bandwidth to keep up with all the latest developments that might be applicable to the complexity of an individual patient. Similar to the current approach to drug development, then, there is a certain 'one-size-fits-all' approach necessitated, in part, by the number of hours a doctor has in a day."

Joshua Adler: "Another factor, however, is the fact that there is highly variable clinical value associated with new discoveries and ineffective filtering. This has caused those responsible for supplying resources (insurers, delivery systems, government) to be very cautious when evaluating new discoveries for coverage/funding decisions."

Stephen P. Spielberg:
"Systematic education is needed for scientists and physicians in a basic understanding of each other's fields, and how to integrate molecular biology with the clinic."

"Given what physicians know from their encounters with real patients, and the expanding science of 'personalized medicine,' the crucial question for all future studies is *not* 'what is the drug of choice,' but 'what is the drug of choice *for whom*.' The focus of personalized medicine brings the hope of refocusing outcomes on individuals and, in

the long run, is probably more understandable and meaningful for clinicians. The direction of the science, thus, may help bridge some of the current gaps."

Gaps in technology

Gaps in technology fall into two categories. One is the gap that occurs whenever a major new innovation is invented at the bench that is not yet ready for application—but could be with the proper funding and attention.

"It is one thing to develop an assay that works in the lab," said Lee Hood, "and quite a different thing to develop one that works in the clinic. Ideally, the latter requires low-cost, automated, highly parallelized, accurate measurements from samples that are readily available—blood, skin, etc. Imaging techniques also present similar challenges." Many nascent technologies for personalized health, however, have difficulty getting funding and support to develop ideas and discoveries into products. In part, this is because many personalized health products by their nature are intended to serve a small, highly-targeted subpopulation, which makes them individually difficult to scale. Indeed, trying to fund and develop hundreds of small-scale innovations as stand-alone efforts seems challenging, if not impossible, in the absence of a strategy to integrate them into a comprehensive plan where each is a part of a whole. For instance, individual products, tests, and discoveries could be grouped and funded around a specific disease or protocol.

The other gap occurs when certain discoveries and technologies race ahead while other complementary technologies don't. For instance, there is the gap between progress in speeding up and reducing the costs of sequencing, which has been dramatic, and the understanding and management of the data produced, which is lagging behind. (This gap is similar to what happened with the Internet, which needed to wait for other technologies to catch up and enable it). Currently, the race to sequence full genomes is exacerbating this gap by producing extraordinary quantities of genetic data that cannot yet be interpreted. "Knowing what any biological part is doing has become much more difficult, because modern, high-throughput technologies have granted tremendous power to collect data," wrote science writer Erika Check Hayden in *Nature*. "Unfortunately, say some, such impressive feats don't always bring meaningful biological insights."[79] The sequencing-interpretation gap has momentum building to correct it, yet many other such gaps exist and will continue without a comprehensive plan to address them.

> *"The goal of getting your genome done is not to tell you what you will die from, but it's how to learn how to take action to prevent disease."*
>
> — George Church, PhD, Harvard

Selected comments from the expert panel:

Christopher Austin: "This time-gap has been exacerbated by the avalanche of new discoveries in the last decade (HGP [Human Genome Project] is but the most obvious example), which has created an enormous feed for a translational infrastructure that is,

for the most part, static or shrinking in size (the latter in biopharma), creating a scientific traffic jam of historic proportions."

Eric Schadt: "I think the pace of discovery at this point is astonishing, with the literature growing so fast that even in areas where one is expert it is difficult to keep up. As of yet, there are not really great efforts to capture all of that knowledge represented in papers, so it is difficult for broad cross sections of people to understand what is there. If the research scientist can't keep up, how in the heck can we expect the practicing physicians to keep up, given they are working nonstop to treat patients and the last thing they have time for is reading the scientific literature?"

Stephen P. Spielberg: "Radical improvements are needed in the use of IT for huge data management/informatics *and* for patient care, and integration—also, for electronic record hazards: increasingly IT is used for billing, *not* Dx [diagnostic] validation—diagnostic/descriptive richness need to be recaptured for research, patient care, and physician education."

Stephen P. Spielberg: "Validation of new diagnostic assays requires both evaluation of the assay per se, and validation of the clinical 'condition' being addressed if the diagnostic test is to add increased precision in patient diagnosis or prognosis."

Gaps in education and ethics

During the European Renaissance, the imperative for a learned person was to know everything about everything. As the accumulation of knowledge made this impossible, the effort was amended to having experts learn everything there was to know about their fields: for biologists to learn everything known about biology and physicians to learn everything about medicine. As the accrual of knowledge has continued, the urge to further specialize in order to command all or most knowledge about a nanospecialty becomes not only compelling, but necessary for a society that needs experts on each crucial detail of our science and technology. But so does the need to integrate these specialties back into a holistic model.

One of the most conspicuous gaps in medical education is the lack of emphasis on personalized health. Such an emphasis would start with a sharper focus on the whole patient, working backward to teach about the various organs and local systems, rather than the tendency of many programs to teach medicine the other way around. In most cases, programs don't emphasize healthy wellness and an understanding of new developments in molecular biology and other fields that support predictive and preventive care. More than this, perhaps, is a failure to instill a philosophy of continuing education to learn about new discoveries and technologies so that physicians can stay current. We understand the challenges in reducing these gaps for curriculums that are already jam-packed and take many years to complete, and for practicing doctors who barely have time to deal with patients, paperwork, and all the rest. Yet we have no choice. As discoveries and information increase, a system must be created and followed to enable physicians to keep up. As panelist and bioethicist Arthur Caplan said: "Train, train, train, train health care providers!"

A second major structural gap in education has grown around the need to train a corps of scientists to be integrators, not only among the branches of science, but also with physicians and with the rest of society.

“We need to modify incentives, promotion, recognition, and job satisfaction,” said Stephen P. Spielberg, “and to modify departmental structures. Not by abandoning in-depth expertise and disciplinary excellence, but by integrating across disciplines, and by focusing on advancing knowledge of human biology and improving health outcomes more than disciplinary survival.”

In addition, the expert panel emphasized a need to better train physicians and scientists in translational medicine—in being partners or instigators of moving discoveries into clinical applications. Gaps also exist in educating patients and society about personalized medicine, including the use of technologies such as genomics for prediction and prevention, and for understanding and embracing healthy wellness.

The advent of personalized health technologies and protocols carries certain ethical risks and dangers. These include the challenge of keeping individual patients’ health data private and protected from those who might use it to discriminate against individuals. The Genetic Information Nondiscrimination Act (GINA) passed by Congress in 2008 forbids health insurers and employers from using genetic information to discriminate against individuals. This is a start, although GINA does not offer protections against the use of genetic information by government and law enforcement, life insurers, researchers, and others. GINA also does not cover other emerging technologies in personalized health such as proteomics and neural scanning that can provide risk assessments and diagnoses for disease and behavioral traits.

Other ethical concerns raised by the expert panel include who will get access to new protocols and treatments; who will pay for them; and how we can be sure that new discoveries and technologies will not cause inadvertent or deliberate harm to humans or the environment. Bioethicist and panelist Arthur Caplan also makes the crucial point that society will need to rearrange its priorities far beyond anything the life sciences can influence to make personalized health and wellness a reality.

“The life sciences are not going to organize anything about wellness,” said Caplan. “This is a job for social science, business, theology, ethics, government, etc. We need shifts in advertising … and incentives to promote health-enhancing products. Wellness is not asking an individual to do better in a sea of ads touting fast food, drinking, and drug use.”

Selected comments from the expert panel:

Eric Schadt: “Another reason [for gaps], I believe, is a complete lack of training in medical school and residency for physicians to understand the data pouring out, and what it means regarding disease, drug response, etc. Take CYP2C19 as an example.

For the last four years it has been known that variations in that gene affect the metabolism of warfarin. Patients with the fast-metabolizing allele should immediately be started on double the dose. This will save lives and yet today it is not done since most physicians are not even aware of this finding. The same goes for the hepatitis C association that came out of Duke regarding treatment with interferon and the length of treatment one should undergo. I think there are many such examples."

James Thomson: "[There are] structural educational issues. For example, in basic sciences, an entirely new field has a certain built-in lag time to general adoption (by other basic scientists, not just in practical application) inherent in the time it takes for students to complete PhDs or postdocs, and to go out and populate the world. It is worthwhile to look at the growth in publications around a specific high-impact area, like mouse ES cells. Very few papers in the first decade (lag) are followed by exponential growth, followed by saturation. This curve, in part, reflects the training cycle, which takes years. A similar curve likely describes the transfer/adoption of basic science discoveries into practical applications, in part because of the length of training time required for complex areas. For complicated genomic issues, or even dietary recommendations based on epidemiologic studies, MDs generally don't have the required training, so even if useful, practical results are available, it does not always reach patients. The question is, given structural time issues, how much could the lag phase really be contracted?"

Gaps in funding

The outpouring of spending in both the government and the private sector over the last ten years is likely to slow down in an era of austerity in Washington and downsizing in the pharmaceutical industry. Federal budgets for life science R&D have been flat for several years after the doubling of the NIH budget between 1998 and 2003, and may go down as the next Congress is expected to look for places to trim the budget and reduce the federal deficit. Where these cuts might come is anyone's guess.

Large pharmaceutical companies already are making substantial cuts, reversing years of growth in research budgets. These cuts have come in the wake of increased spending on research and early development that has failed to produce the hoped-for abundance of new drugs. For instance, Pfizer is eliminating thousands of jobs and slicing its R&D budget by $2 billion to $3 billion by 2012.[80] And AstraZeneca says it will cut back by $1 billion in the next four years. Big companies now are turning to a strategy that has them investing in milestone and licensing deals with smaller biotech companies, which have been more successful at coming up with drug candidates in the research phase of the drug development pipeline. According to common wisdom at the moment, this is because "little pharmas" have less bureaucracy and complications. They also are driven by a chronic fear of underfunding that compels them to be more nimble and creative. At the other end of the pipeline—late-stage human clinical trials and manufacturing, sales, and marketing—"big pharma" tends to be more adept.

Potential cuts by Washington and further cuts by big pharma makes it all the more urgent to push an agenda for translational medicine programs. With the lion's share

of federal funding going to basic research, it will be harder to defend to members of Congress a $30 billion NIH budget, plus the roughly $9 billion spent by other federal agencies for R&D, if there isn't a more aggressive plan in place to prioritize treatments and cures. The good news is that this does not mean reinventing the wheel, since several translational and integrative programs already have been initiated at the NIH and in other programs. Funding for these programs, however, represents an investment of only 2 percent of the institutes' budget.[81]

Most of the experts consulted for this paper were adamant about the need to reprioritize funding toward translational medicine, which includes translating promising discoveries and technologies in personalized health. Safi Bahcall spoke for many when he said the biomedical establishment should be "shifting NIH resource allocation to place a greater emphasis on translational research." This won't be easy, however, since Congress is unlikely to approve new funding for translational programs. Paying for these programs by shifting money from existing programs will be highly unpopular in the research community, and is likely to get stiff opposition from powerful defenders of the status quo in universities and institutes, some patient advocacy groups, and in the NIH itself. Yet as panelist and patient advocate Margaret Andersen said, "Good ideas cannot advance through the pipeline if we don't figure out how to reengineer the pipeline."

Selected comments from the expert panel:

Christopher Austin: "There is a lack of dedicated resources to the translational/early product-development work required, which fits neither the academic nor the biopharma reward structure."

Gregory Stock: "Greatly increase peer-reviewed government funding for early stage clinical trials in all major diseases [is needed]."

Margaret Anderson:
"Focus on the translational research 'Valley of Death,' where funding for the steps between basic discovery and clinical research is shrinking."

"There is a need to continuously modernize the research environment, including enhanced resources and capacity at the FDA, more innovation at NIH, and improved support for translational research across a variety of settings."

Michael Roizen: "More dollars are needed for translational repeat studies."

Safi Bahcall: "Creating/elevating translational centers that focus specifically on investing in institutions' earlier-stage concepts is required so that they reach the point where they become more attractive, stronger packages for out-licensing to industry."

Zack Lynch: "There is a lack of funding for coordination and dissemination of emerging technologies directly into translational labs."

Gaps in commerce

Few industries are more volatile than biotechnology, which has seen substantial fluctuations in investment streams, market caps, and other financial metrics since the industry's birth in the early 1970s. For brief periods, the promise and, at times, the hype around new discoveries—fueled by both a hope for curing disease and for profits—has caused an irrational exuberance in the commercial promise of the new biology of the sort we saw in the late 1990s with the excitement around the Human Genome Project, and in the early 1980s with the enthusiasm around the commercialization of recombinant DNA, when Cetus and Genentech launched IPOs that each broke records for first-day trading on the NASDAQ even though both companies were years away from profitability. Big pharma, too, has seen its share of ups and downs in blockbuster drugs coming on and off patent, and with market caps that have been on a roller coaster ride in recent years.[82]

This volatility arises from the phenomenal risks associated with a drug R&D effort in which close to 90 percent of all compounds that enter human trials fail, and successes take ten to fifteen years and cost the industry over $2 billion per approved drug.[83] The device and diagnostic markets have more rational metrics, but also are risky in terms of being accepted by physicians and payers. For early stage life science companies, the cost of capital (time value of money and risk of not getting money back) is as high as 20 percent, compared to an average of 10 percent for all publicly traded companies in all sectors.[84] Moreover, a recent study by Cambridge Associates of 1,606 deals found that 44 percent of biotech exits were a full or partial loss. Those who successfully exited averaged a10.7 percent IRR, but two-thirds of these companies took five years or longer to be realized, and another 1,223 investments have yet to pay out.[85] Overall, IRRs in the life sciences have been dropping, from around 17 percent in 1989 to only 6 percent, on average, in the years between 2003 and 2008, to an unfortunate −16 percent in 2008 as the economy imploded.[86]

Industry observers and study panelists provide several reasons for the high rate of failure and burgeoning costs. These include the high cost of clinical trials; the blockbuster model of drugs that pushes too hard to develop compounds that will impact millions of people and bring in $1 billion or more in revenues; the short-term thinking of Wall Street investors and analysts; regulators that are too slow, underfunded, and overly strict; and the difficulty of the science itself.

There may be a more fundamental problem at work, however, that contributes to the widening gap between discovery in the lab and the successful commercialization of drugs and diagnostics—and also for predictive tests. This is how compounds and other discoveries are selected to move into a commercialization phase. First, there is no comprehensive plan at work in society to study and prioritize which therapeutic areas need to move forward, and which are most promising. The current ad hoc system depends on a mix of innovation, market forces, the savvy of scientists in attracting investors, and luck. For most technology-based industries, this formula works well enough. For pharma, however, the enormous lead times and costs place a stronger

impetus on the system making the right decisions on which "products" go forward in the beginning, and then at critical junctures all along the pipeline. Second is a dependence on a model inspired by the IT industry, whereby investors put up capital for new ideas using a "shots on goal" mentality that depends on a small percentage of investments to pay off and cover the larger number of failures. This has worked well for businesses that will know within months, or one or two years, if they will be successful, and for industries whose products can massively scale to millions of customers. Biotech is neither fast to fail nor, in most cases, massively scalable, two fundamental drawbacks to the prevailing VC model for an industry that lately has seen venture funding decline again for early stage companies.

> *"One lesson we've learned is to make sure we're more externally focused, whether it's a basic research capability or relationships with the public and private sector. It's an important lesson that as a company you can become too arrogant at times if you don't step back and reflect on your position within the system."*
>
> — Richard Clark, CEO, Merck & Co.

The recent surge of big pharma companies setting up more licensing and milestone deals with a broad range of small and medium-sized biotech companies is a version of the shots on goal method of investing.[87] By focusing on more mature companies with products that have survived the early stages of development, and by delaying substantial payouts until the drugs prove themselves farther down the pipeline, companies are reducing their risk, costs, and exposure, hoping to increase the odds of success.

One final cause of the discovery-to-commercialization gap is the push by academic institutions, entrepreneurs, and investors to commercialize very early discoveries. Going to the trouble of creating a company that will require substantial capital even in the early phases of R&D, and tie up talent and personnel and limited life science investment funds, seems like overkill if a discovery has not yet reached at least the proof-of-concept phase. Other discoveries such as solid-state electronics, telecommunications, and the Internet typically were developed out of small-scale efforts funded by the government through agencies such as DARPA—the Defense Advanced Research Projects Agency—which then passed on the discoveries to the private sector. This approach of providing preliminary funding is another variation of the shots on goal method that has made sense for other industries, and costs comparatively little per project.

Selected comments from the expert panel:

David Agus: "I am in the cancer arena and we apply things more aggressively and quickly than many other fields because of the nature of the disease. Even in that setting getting discoveries in diagnostics to the application phase is very difficult because the capital markets have put little value on the application side. All value is on the therapeutic side. There is no clear business model for diagnostics."

Dietrich Stephan: “Researcher-entrepreneurs need to learn how to package their results, to learn the language of the venture community. They need to learn about technical risk, market risk, and building commercialization teams. This handshake is often the difference between successful commercialization and discoveries dying on the vine.”

Eric Schadt: “Pharma companies have no incentive at this point to see markets stratified using genomic or other markers, because if they can stick with the one-drug-fits-all model, then it makes their potential market bigger; one can use all of the other speculative arguments they want about why a pharma should be incented—higher compliance if you target the right population, higher efficacy if you target the right population so easier to get through trials, etc.—but all of the evidence points to the contrary.”

Eric Topol: “We need a complete reboot of how clinical trials are done with individual molecular information guiding the intervention to be tested ... pharmaceutical and biotech companies have shown a relatively poor overall ability to develop new molecular entities in a streamlined fashion for more restricted applications.”

Frank L. Douglas: “Translation has the three components: proof-of-concept studies, synergistic use of available technologies, and novel applications, or looking for the ‘ah-ha’s.’”

Frederick Frank: “There is: (a) too much focus on ‘shorter term’ issues—i.e., developing fast-follower drugs, not first-in-class new therapeutic agents; (b) not enough collaborative effort between academic researchers and company researchers; and (c) a tendency to stop research after a ‘failure’ rather than asking ‘what did we learn?’ and starting a new research foray addressing the challenge(s).”

Gregory Stock:
“A swing by the industry toward high-potency, high-specificity pharma candidates was thought to be needed to fight off disease. But the war-against-disease mentality has not achieved its promise, in part because diseases of aging like heart disease, cancer, neurodegeneration and such are not problems of invasion but of disregulation and breakdown of our own systems.”

“Moreover, by moving down a pseudo drug-design path, we have increasingly neglected the many botanicals and natural products that have so often been the inspiration of, if not the source for, critical drugs. The biotech revolution should be making these traditional products (with all their problems and uncertainties) more, not less, valuable. Robust tools in the life sciences are making it ever more feasible to understand which compounds in these diverse chemical mixtures have pharmaceutical value.”

“High cost of clinical development relative to the availability of capital doesn’t make sense. Capital is not readily available because so much is needed, and the chances of success in today’s environment are low. We have many, many more drug candidates (and INDs) now than the industry can possibly afford to move through phase II and III

clinical studies. The crux of the problem is not early discovery but the challenges and expense of FDA clinical trials."

Raymond Woosley: "Follow the successful model employed by the semiconductor industry in the '80s. Create the equivalent of Sematech where precommercial applied science can be generated by collaborations between government scientists and industry scientists. The U.S. FDA should partner with the Innovative Medicine Initiative in the EU [European Union] and match their investment (2 billion euros) in a coordinated effort to develop the applied science that will permanently establish the infrastructure that can replicate the HIV drug development experience for the many major diseases."

Stephen P. Spielberg: "There should be a radical rethinking of the economic consequences of subdivided marketplaces for medicines linked to diagnostics. While the hope of enhanced Dx and Rx precision will be decreased health care costs, we need to think prospectively of the consequences of multiple 'mini-busters' versus one 'blockbuster' drug."

Gaps in reimbursement

One of the underlying gaps in applying new ideas and technologies is a reimbursement system that lumps patients into categories of sickness with little attention paid to personalization of treatments and to keeping people well. This emphasis on categories in payment codes at the Centers for Medicare and Medicaid Services (CMS) and with many private insurers provides a powerful financial incentive for physicians to treat sick patients with definable diseases, and does little to encourage the use of predictive and preventive tests for individuals, or to emphasize diet, lifestyle, and healthy wellness. Physicians and the health care system cannot be expected to move aggressively into personalized health if they aren't adequately compensated.

Other gaps include a failure to (1) have in place a coherent system to validate or to regulate predictive and diagnostic tests so that they can reach a reimbursement threshold, and (2) use payments to target and encourage innovation in treatments and in diagnostics and preventive care, and in assessing, evaluating, and paying for pilot studies and programs to encourage personalized health. Recently, the FDA and Medicare began a pilot project that aims to get new medical products paid for sooner for the nation's 45 million senior citizens.[88] Under this proposal, Medicare would begin evaluating drugs for payment as they enter the final phases of testing and review at the FDA—a process that should speed adoption and could be applied to personalized medicine tests and treatments being considered for approval by the FDA.

Selected comments from the expert panel:

Arthur Caplan: "There is a lack of reimbursement for testing and counseling."

Brook Byers: "Reimbursement policy and procedures at Medicare are needed regarding new advanced laboratory-developed tests."

Christopher Austin: “On the biopharma side: increased private capital needs to be available to advance projects, particularly in early phases; this will be facilitated by predictable reimbursement and predictable regulatory review.”

David Agus: “We need reimbursement reform for diagnostics.”

Edward Abrahams:

“Reimbursement needs to go from quantity to quality; with an emphasis on preventive care.”

“The science is way ahead of the system to implement it, including reimbursement.”

Frederick Frank: “Provide increased reimbursement for first-in-class drugs by extending patent life by five years.”

Michael Roizen: “Lack of reimbursement exists in the case of lifestyle treatments as treatments that reverse chronic disease … Medicare coverage should more closely follow the science of therapies such as lifestyle treatments.”

Gaps in government and law

Big science could not exist in the United States without a long history of strong support of taxpayers, elected officials, the federal bureaucracy, and the courts. Notable exceptions include a broad opposition to teaching the theory of evolution in the early twentieth century, which continues in some localities today, and the more recent political and legal imbroglio over federal funding for embryonic stem cell research. Still, in the broad sweep of history, the money expended by the United States in both the public and private sectors is unprecedented in any country in history—even if many groups would like more to be spent. In 2008 alone, the federal government spent $38 billion on life sciences R&D, mostly through the National Institutes of Health—up from about $10 billion just twenty years ago (in constant dollars).[89] The private sector spent an additional $75 billion in 2008, a nearly five-fold increase over the same period. Even with funding for the NIH and other federal programs remaining level for the past five years—not including one-time stimulus payments—U.S. federal government spending for life sciences R&D was second only to the $80 billion spent on R&D for defense last year. Though funding is likely to stay flat or go down in the next year or two, the commitment to life science R&D remains strong.[90]

> *“I want to restore faith and trust in the FDA as a science-driven agency. I want to be a vocal advocate for the resources we require. It’s stunning how underfunded we are given the importance of what we do. Twenty-five percent of every dollar spent by Americans is regulated by the FDA.”*
>
> — Margaret Hamburg, Commissioner, FDA

Structural gaps in government, however, have formed in agencies charged with approving, implementing, and regulating new discoveries. Topping the list of reforms needed to narrow this governmental gap include (1) streamlining the testing and approval process at the FDA, which takes

too long and costs too much; (2) modernizing the FDA's information technology and computing infrastructure; (3) increasing the number of highly trained career experts at the FDA; and (4) revamping the categories of medical products and regulatory requirements to better facilitate new discoveries. Another challenge to the FDA has been to respond to concern in Congress and the public about safety issues in drugs and food after recalls of drugs with dangerous side effects and tainted foods that sickened or killed large numbers of people. The classic example is the 2004 recall by Merck of its blockbuster painkiller Vioxx, which was linked to the deaths of several heart patients from a side effect of the drug that Merck scientists allegedly knew about, but suppressed. Several expert panelists suggested that the federal response to this and other scandals was perhaps too heavy-handed, adding new layers of testing that may be further slowing down the approval process.

Another major gap in regulation is the FDA's budget. Even with a 19 percent increase in 2010, the FDA was allocated only $3 billion this year—about $10 per American—to regulate and oversee $2 trillion of the U.S. economy. "There have been increases in resources for the FDA in the last couple of years," said FDA Commissioner Margaret Hamburg in an interview conducted by one of this report's authors, David Ewing Duncan.[91] "It looks like it will be sustained. We're undermining our own best interests if we have a very robust investment in biomedical research and a scrawny investment in regulatory science and support for the FDA." Hamburg also has pushed hard to develop programs for agency professionals to be trained in "regulatory science."

"I think, as a nation, it is critically important that we strengthen our commitment to regulatory science to make it a robust and respected discipline in the broader scientific enterprise," said Hamburg. "This is the key to ensuring that recent scientific discoveries which hold such promise are actually translated into new therapies and treatments."

Gaps have widened in law as the question of how to patent and establish intellectual property for molecular markers and other new biological discoveries remains in flux. We have mentioned the Myriad Genetics case, where a U.S. District Court judge in the spring of 2010 reversed key elements of the patents held by Myriad for its genetic test for breast cancer, claiming that the company's claims to own the BRCA1 and BRCA2 genes and certain variations linked to a heightened risk of cancer actually are naturally occurring entities not covered by current patent law.[92] Myriad is appealing the ruling.[93] This has left the question of whether or not DNA and other molecular entities inside organisms can be patented in limbo—and has exacerbated an already-existing legal gap in implementing new discoveries.

Selected comments from the expert panel:

Daniel Kraft: "So, while many biotechnologies are working on an exponential curve, the regulatory process is actually going in the reverse. I would argue there need to be new mechanisms, pathways, and smart clinical trial designs (outside of the old phase I, II, and III) that for some types of Rx can speed translation, and in a safer way."

Edward Abrahams: “The political systems don’t evolve as fast as the discoveries and technologies.”

Eric Schadt: “I think a new regulatory agency is absolutely 100 percent needed; again, this gap is going to widen exponentially and the FDA will not know how to deal with it.”

Gregory Stock: “Focus the FDA almost entirely on issues of safety and patient education.”

James Thomson:
“Certainly in the case of some new advances (molecular cloning, human embryonic stem cells), the social controversy and political process slowed the basic science, and ultimately the lag time to practical adoption. I think this is generally a minor effect.”

“I think changes in regulatory science will be important for personalized medicine to really impact people’s health.”

Margaret Anderson: **“**Improve the capacity for regulatory science at FDA—not just internally, but through external partnerships and resources. No products will get to patients if [the] FDA does not have clear pathways by which to evaluate them.”

Raymond Woosley:
“We do not have systems in place that can rapidly learn about the value or harm of new therapies. The workhorse of current development, i.e., large, slow, expensive, randomized clinical trials, are designed using out-of-date clinical information and, because the science is moving so rapidly, their findings are often flawed or irrelevant by the time they are completed.[94]

“The current structure at the FDA is a big part of the problem. The regulatory silos (CDER, CBER, CDRH, etc.) are inefficient and inappropriate for the modern science that requires development of strategies that include combinations [of] drugs, diagnostics, and devices. Another flaw at the FDA is the belief that the agency will ever have within its walls the breadth of scientific expertise to adequately evaluate the safety and efficacy of all of the products it must regulate. The EU’s system uses external consultants and is far more appropriately structured and increasingly efficient. Additional flaws in the United States’ regulatory system are (1) the political influences that result from the commissioner’s political appointment, (2) the inappropriately low level of FDA funding, and (3) the reliance on user fees for support of the agency.”

Safi Bahcall: “On the more broad society/government side, the high cost of clinical trials makes it difficult for both industry and academia to test new ideas, drugs, or technologies.”

Gaps in communication and the media

Bioscience communication and the media are in a “best of times, worst of times” situation. On the one hand, thousands of reporters and small armies of communications

experts toil to explain and announce and promote everything from the smallest details of early stage drug trials to company earnings reports and major trends in science. A sizable increase in communications activity in the life sciences over the last decade has been one result of the doubling of R&D budgets since the 1990s, plus the maturing of biotech companies with $1 billion or greater market caps, and the explosion of new media tools and outlets with the Internet, cable television, and other new venues. What is less clear is whether this expansion has enhanced the understanding of the biomedical enterprise for the public and policymakers.

Gaps exist in a number of areas, including lack of education for consumers and patients in the basics of biology, genetics, and statistics, and a lack of training for some science and biotech/pharma reporters in the media. Another gap comes from the fire hose effect in the age of the Internet, when thousands of websites, blogs, feeds, and networking sites deliver information and compete for our attention. This has democratized the web and opened up the discussion for science and the rest of the news to anyone who wants to participate, yet it has diluted the traditional role of newspapers, magazines, and broadcast outlets to editorially filter stories for newsworthiness while maintaining at least a semblance of factual integrity and objectivity.

Another growing gap is the lack of access for the general population and many journalists—and even some researchers—to scientific journals that publish major studies, but only allow access to those who pay substantial annual or per-story fees. The proliferation of journals, which now number in the thousands and collectively can cost tens of thousands of dollars a year, have made it difficult even for small and medium-sized institutions to afford to carry them—which not only works against an open exchange of knowledge, but also against the idea of integration among fields that cannot afford to purchase journals outside of their own field. The open source movement is a reaction to this gap, and is exemplified by the Public Library of Science, which provides free access to studies it publishes.[95] The longtime practice of journals embargoing stories until their own publication date, and punishing researchers and sometimes reporters who break the embargoes, also impedes the free and timely flow of ideas and reporting. A relaxing of this system would allow reporters and others to follow the progress of breakthroughs as experiments and findings develop, rather than when journals say that it's time to write about them. Waiting for publication also creates an "event" atmosphere around major discoveries that gives the impression they abruptly appeared on the scene, which fails to convey the years of hard work and the gradual nature of most scientific discovery.

Selected comments from the expert panel:

Daniel Kraft: "Medical news and related science often make the press—e.g., recently, 'Cancer vaccine cures breast cancer'—however, these are often, while promising, very early basic science (in the breast cancer case, it was curing a batch of mice with a vaccine approach, which was very, very far from the clinic, and we've cured mice of cancer thousands of times). So the lay public has little understanding of the process,

barriers, and other constraints to taking any hot ‘new’ concept or discovery and getting it translated to the clinic.”

Stephen Friend: “It will require a fundamental change in thinking to realize that sharing data is important.”

Gaps: patients and consumers

A major gap has been expanding between patients who demand more involvement in their own health and the medical establishment’s resistance to meeting this demand. Empowered by medical information that is now widely available online (and of varying quality and accuracy) and by alternative health care options, many patients and consumers have simply bypassed traditional Western medicine for most of their health care needs. Tens of millions of healthy Americans, and millions who have manageable and even chronic illnesses, have registered their dissatisfaction by embracing the latest diets, nutriceuticals, and alternative treatments even when they lack a firm scientific grounding. Some patients’ desire to take responsibility for their own health and wellness has pushed them to explore new biology discoveries and technologies such as genomics, even though the current offerings have yet to be thoroughly validated and integrated into meaningful risk assessment models.

In some cases, the ill and dying have sought alternatives to treatments offered by traditional Western medicine. Sometimes this comes out of understandable desperation, but also it occurs because the system has failed them by denying an experimental therapy or by not proposing alternative options such as acupuncture and dietary therapies that may be part of the culture of medicine in countries other than the United States. This is not to encourage unproven treatments, but rather to encourage a more serious assessment of alternative treatments to determine what works and what doesn’t.

Amateur scientists in the “do-it-yourself” movement also have taken advantage of technologies and lab techniques that have become cheaper and easier to use to run experiments on genomics, synthetic life, and other cutting-edge fields in their own home labs. This fledgling movement has the potential to widen the possibilities for innovation, but also has attracted the attention of regulators and even agents of the Federal Bureau of Investigation, who worry about the misuse of these powerful technologies or the potential for accidents that would harm people or the environment.

Selected comment from the expert panel:

Arthur Caplan: “What evidence is there that having risk information about genes shapes or changes behavior?”

Eric Schadt: “Groups like PatientsLikeMe are allowing patients to get enabled to do their own thing without waiting for the ‘official word.’”

George Church. “We need grassroots educational efforts in genetics, like DIY-Bio and Bioweathermap.org.”

James Thomson. “Because of the Internet, individual patients can now often learn a great deal about their own condition, but the information is uneven and hard to evaluate for the nonprofessional. A central call to action, then, would be for the individual patient to take more control of their personal health, and to enable them to do so by giving them the computational tools to facilitate their use of advances in personalized medicine. However, the explosion of type 2 diabetes isn’t going to be cured by insights into people’s genomes, but by dietary changes (and not everyone that should get a colonoscopy gets one...), so personal responsibility is essential, and will become increasingly important the more personalized medicine actually can benefit the specific individual.”

Michael Roizen: “There are gaps in medicine embracing lifestyle treatments as treatments that reverse chronic disease.”

III. Narrowing the gap

"There are few people in the scientific community who are working to take the 20,000-foot view and to make sense of it all."

— Anthony Atala, MD

The need for linkage

On the eve of the second decade of the twenty-first century, innovators in the personalized health space have created hundreds of individual tests, protocols, algorithms, and points of knowledge that are in various stages of readiness, from on the cusp to several years away. As we have reported, this wealth of invention and discovery runs the gamut of molecular biology and biocomputation to neuroscience, regeneration, and nanotechnology. Many of the individual projects, however, are not moving along toward implementation as quickly as they might be, and most are being developed as stand-alone, independent projects, rather than as part of an overall plan to move toward a more holistic personalized health agenda.

> *"The transition from a paradigm in crisis to a new one… is a reconstruction of the field from new fundamentals, a reconstruction that changes some of the field's most elementary theoretical generalizations as well as many of its paradigm methods and applications."*
>
> — Thomas S. Kuhn, *The Structure of Scientific Revolutions*, 1962

For example, Bay Area-based Entelos, Inc., a biosimulation company that works with pharmaceutical companies to test drug candidates *in silico*, has developed an algorithm to assess a patient's heart attack risk. Called the Cardiovascular PhysioLab, this advanced computer model integrates numerous test results—genetic, family and health histories, CT and ultrasound scans, and a detailed metabolic chemical workup—and compares a patient to thousands of other people, real and virtual, who have been tracked over time to see how well a given profile of results predicts a heart attack in ten and twenty years. The program then finds a profile that closely matches the patient to provide him or her with a custom prediction.[96] The Entelos model runs hypothetical future scenarios for risk based on different health options for the individual. For instance, one subject profiled by the PhysioLab was given three distinct risk projections based on weight gain and taking statins. For this subject, even a minor annual weight gain of one pound a year after the age of forty gave him a risk factor for heart attack of 38 percent in ten years and 70 percent in twenty years—much higher than the average risk for a man over age forty. But if this same individual gained no weight, his risk of heart attack dropped to a mere 2 percent over the twenty-year span, a dramatic difference. (Note that these findings will be different for different people.) Taking statins reduced the subject's risk of heart attack to near zero percent over the same time span. This protocol, however—which Entelos would like to price at less than $1,000 for

individuals with a high risk for heart attack—is unavailable because of the high costs of clinical trials and the uncertainty of reimbursement for the test. Nor does the company have the resources to run comparative effective and cost-benefit studies that might prove—or disprove—that its test will save money and improve outcomes if expensive cardiac procedures are avoided.

Arguably, the challenges faced by Entelos and other stand-alone companies and projects have contributed to a collective slowing or stalling out of many potential breakthroughs. Imagine this situation as akin to a front line on a battlefield that has been racing forward across a broad stretch of territory. From an observation balloon 10,000 feet in the air, one can see the battalions and platoons sprawled out over valleys, hills, and fields, with each unit identified by its flags: the double helix flag of the geneticists, the image of a brain scan flapping in the wind to mark the neuroscientists, and the rest. The aim of this massive and expensive campaign is to capture the newly discovered land of personalized health. But the vast line of individual units (companies and labs) has slowed or stalled out for lack of a comprehensive battle plan as each one struggles alone to stay alive and to advance against an enemy that represents tradition, structural resistance, politics, and so forth. The situation becomes more complicated and in need of reform when one considers the need to better integrate the troops not only with each other—with other scientists and clinicians—but also with the other aspects of society that must be properly engaged to assure victory. But how?

> *"Drugs for AIDS were developed in 1.4 to 5.1 years, without any shortcuts (none have been removed due to unforeseen toxicity). We need to recreate the same sense of urgency and enable the FDA, NIH, and industry to work together as they did for HIV. Why is Alzheimer's or lung cancer any less of a national crisis than HIV was in the '80s?"*
>
> — Raymond Woosley, MD, PhD; CEO, Critical Path Institute

Create a new "science of integration"

The new health care regime promised by the science of personalized health cannot occur without a dedicated cadre of professionals trained in integration and in assessing and understanding the big picture in terms of individual scientific discoveries and protocols as they relate both to the whole and to a personal health profile for an individual patient.

"In order to accelerate science, we need to take a true multidisciplinary approach," said panelist Anthony Atala, "with a team of scientists who are the best in their respective fields working side by side. The approach requires both a change in the infrastructure and a change in attitude. The concept of 'I,' a single investigator, must become 'we,' a team working together to accelerate the science." Integrative learning programs have appeared in recent years in many universities, including several programs in integrative science, although much more is needed.[97]

Focus on the human organism

For integration to succeed, researchers and other specialists—and society at large—need to shift their collective mindset more toward the human body and a holistic model, rather than a focus on individual projects that at best are loosely connected, as the organizational template for health care.

> *"Why can't we continue to answer the underlying questions in biology while also addressing those questions critical to specific diseases? Why can't we do both?"*
>
> — David Baltimore, Nobel Laureate

"None of the discoveries on their own may have much value," said Eric Schadt, "but when combined, they may have high value." This holistic approach would encourage the funding and promulgation of projects based not just on their value as stand-alone efforts, but also on how they fit into broad goals aimed at understanding and treating diseases and entire systems—and in better integrating the needs of patients to stay healthy and well. Research and translational projects also should be linked with clinicians, ethicists, investors, regulators, and others at a very early stage in an integrative process.

Another way to look at this comes from panelist Stephen P. Spielberg, who said that "the organization of health care delivery, and scientific discovery and development should be a 'team sport' focused on the human body, with individual brilliance and entrepreneurism nourished in the context of a system that supports collaboration, integration, and de-siloing."

Projects already under way

The idea of linkage is hardly a revolutionary concept in biomedicine, even if rebooting the current system toward a much stronger emphasis on integration would constitute a major shift in the current paradigm. Smart people have recognized the need to reform the biomedical enterprise and have initiated dozens of programs, proposals, and projects in the United States and abroad to encourage integration, translation, healthy wellness, and personalized health. As noted earlier, these changes in the United States include the roadmap initiatives at the NIH to study and encourage translational medicine[98] and interdisciplinary programs;[99] regulatory reform efforts at the FDA;[100] studies such as "A New Biology for the 21st Century" from the NAS;[101] and nonprofit efforts from the likes of FasterCures and PatientsLikeMe. Companies also are experimenting with creative ideas to speed up drug R&D.

One recent project that shares many of the goals and aims of this report is the P4 Medicine Institute (P4MI), cofounded by panelist Lee Hood, a pioneer in genetic sequencing and in personalized medicine. Taking the "four Ps" articulated by Hood—

predictive, preventive, personalized, and participatory—this new institute is setting out to accomplish the following:[102]

- Recruit academic research institutions and health systems as P4MI members.
- Work with private and public sectors to create the needed technical infrastructure.
- Integrate and support member programs by:
  - Coordinating knowledge and solution transfer between members;
  - Organizing joint responses; and
  - Supporting the analysis of societal issues and developing the necessary social infrastructure.
- Educate the policy, regulatory, and public spheres about value of P4 medicine.
- Advocate for public policies that will support/facilitate P4 medicine.

Another important initiative is the Personalized Genome Project (PGP), an initiative organized by a team led by Harvard geneticist George Church that is setting out to sequence 100,000 complete genomes.[103] The PGP places a strong emphasis on the personal participation of subjects, who must pass a rigorous test on their understanding of basic genetics, and about privacy and other ethical issues concerning DNA testing. This project is working to link up subjects with tools to interpret their results and integrate their DNA findings with other risk factors for traits and disease. Beyond genomics, the Church Lab at Harvard Medical School is a study in integrative science, with significant projects also under way in proteomics, epigenetics, microbiomics, and synthetic life.[104]

Also at Harvard is The Gene Partnership, spearheaded out of Children's Hospital Boston and Harvard Medical School.[105] The program's goal is to bring together clinical data, phenotypic data, genome sequencing, sensor data, and longitudinal monitoring, starting in Boston and then expanding globally. This initiative is meant to elucidate, with the correct powering, gene/gene and gene/environment interactions so we can begin to predict with high confidence who is at risk of disease presymptomatically, and what an individual should do to manage his or her health.

More ideas and initiatives are summarized in Appendix B. These projects are just the beginning, however, of what needs to be a much more extensive and comprehensive effort.

A proposal: The Personalized Health Project

The first step in accelerating a personalized health agenda is to establish a Personalized Health Project that will serve as a nonpartisan and neutral umbrella organization for existing efforts; continue to assess and analyze gaps and proposed solutions; and prepare and promote a detailed and comprehensive "blueprint for action."

Key priorities for change

The following is an outline of proposals and ideas that need to be further researched and detailed:

- Establish an inclusive and independent umbrella group that connects existing personalized health with translational initiatives and organizations, and encourages and facilitates a linkage of efforts.
- Engage important leaders from science, medicine, business, policy, government, patient advocacy, ethics, law, and the media in an advisory committee.
- Study and assess specific gaps between innovation and application, and assign task forces to address each substantial gap.
- Create a detailed and comprehensive plan for accelerating the shift to personalized health care, and create a blueprint for action for prioritizing and implementing specific initiatives in the public and the private sectors.
- Target, prioritize, and develop funding for the validation and application of new discoveries as part of the blueprint for action.
- Assess patient and consumer needs and help develop a framework for their participation in their own care.
- Rethink how physicians and biomedical scientists are educated to advance health and health care in an ever-more-complex and integrative milieu.

Conceptual framework

We propose the following goals to address the three major philosophical themes of the Personalized Health Project:

- *Balance an emphasis on both illness and healthy wellness*. Make the case that a health care system based as much on prediction, prevention, and personalized health as on illness is achievable, and can be accelerated by systematic planning and proper funding.
- *Shift from one-size-fits-all to personalized health care*. New discoveries are allowing a greater emphasis on the individual traits and needs of each patient, rather than trying to fit the patient into diagnoses and treatments based primarily on populations and averages.
- *Balancing reductionism with integration*. A balance between specialization and integration should be fostered among scientists and between scientists and other fields, including the clinic, commerce, policy, law, ethics, and the public.

The following general goals, ideas, and thoughts are contributed by the expert panel and from others, with the aim of pushing an aggressive agenda of personalized health and translational medicine:

Tradition and culture

- Encourage incentives for scientists, physicians, investors, and other key players in the life sciences to embrace predictive, preventive, and personalized health, and to reward the adoption of discoveries and protocols that support healthy wellness.
- Develop and fund the promotion of a new national policy that places a greater emphasis on integration in the life sciences.
- Build on the rising sensibility among many in the life sciences that a shift to personalized health is inevitable, and that new initiatives can accelerate its arrival.

Basic science

- Encourage structural changes to encourage collaboration and interdisciplinary projects within science, between scientists and clinicians, and between scientists and other related fields.
- Expand translational programs in the basic sciences and train scientists to specialize in the translation of discoveries by creating a system of funding, rewards, and incentives.

The Clinic

- Encourage a reboot of clinical medicine to better emphasize personalized health and healthy wellness; an understanding of alternative therapies; and patient involvement.
- Develop a larger cadre of physician-scientists trained to work with translational scientists to facilitate the incorporation of basic scientific discoveries into the clinic.
- Move to a more proactive model for introducing and implementing new discoveries and technologies into the clinic—one in which scientists and entrepreneurs work more closely with clinicians throughout the R&D process to enable a more aggressive adoption of innovation.
- Create a system to identify “best practices” and systematically identify successes (and failures) that can be accessed readily and shared across the biomedical landscape.
- Develop an ongoing system for validating predictive and diagnostic biomarkers, and for continually examining, monitoring, and adjusting these tests according to demonstrable results.

- Study how people react to predictive information and preventive strategies, and how and when behavior adjustments are made based on this information.

Technology

- Create a more effective system for researchers, physicians, entrepreneurs, industry, regulators, and others to work together in teams to develop and refine new innovations.
- Encourage the widespread use of digital and information technologies, and experimentation in how to best use mobile and cloud technologies and other cutting-edge innovations in IT.
- Engage policymakers in Congress, the administration and the U.S. Patent Office to settle patent and other legal uncertainties that are impacting investment in the development of new technologies that do not have a clear path to intellectual property.

Education and ethics

- Engage in a “Flexner II” review of medical education and medical schools to revamp them for an age of personalized health, a follow-up to the “Flexner I” report written in 1910 by the educator Alexander Flexner that a century ago led to substantial reforms in medical education.
- Reform medical education and scientific training to emphasize healthy wellness and a deeper understanding of the links between the new science and the clinic.
- Reorganize current academic institutions and their recognition and promotion systems to provide real opportunities for advancement for faculty engaged in novel, multidisciplinary approaches to discovery, development, and implementation.
    - Reengage medical education to focus on patient needs, and the “old-fashioned” ideas of physicians talking, listening, and partnering with patients.
    - Launch education and public relations programs to better inform the public and policymakers about predictive and preventive health, and about the benefits of taking personal responsibility for one’s health.
    - Support educational efforts to teach personalized health and the new biology in grades K through 12.
    - Create a strong program in ethics to study and take action on issues that include safety, privacy, discrimination, access, and coverage; and also less easily defined issues such as society-wide efforts to provide incentives for healthy wellness.

Funding

- Reassess federal funding priorities and increase spending for programs in translational medicine, integrative programs, and personalized health.
- Provide greater resources for both low-tech and high-tech preventive solutions.
- Create methods to assess the true cost benefit of personalized health and healthy wellness.
- Assure funding sources from the NIH to drive “gap closers.”

Commerce

- Provide incentives for entrepreneurial and commercial efforts to develop new products and protocols based on the science of personalized health and healthy wellness.
- Create groupings of small-scale companies and efforts around specific diseases that can acquire funding together and work toward collective goals where each is a part of a whole.
- Modify the biotechnology investment model based on the IT industry to take into account the high failure rate of drug discovery, long development time, and high costs.
- Study and emulate success stories, such as the rapid development of AIDS treatments in the past twenty years.
- Develop creative efforts to fund and encourage early stage discoveries and innovations in a style similar to DARPA.

Reimbursement

- Reorganize payment systems and strategies in the private and public sectors to better emphasize predictive and preventive health.
- Broaden the CMS code system to embrace predictive and preventive measures and other personalized health categories, and eliminate the rigidity of codes to allow more flexibility in diagnosis and treatment.

Regulatory and legal

- Support the current FDA initiative to establish a new “regulatory science” in universities, and expand this approach to include an emphasis on integration among regulators, scientists, clinicians, industry, and other governmental agencies.
- Pool reform ideas developed by numerous organizations that call for an increased use of new science and technology to be faster, more proactive, and more flexible with companies developing new biomedical products.

- Launch a campaign to educate and work with Congress to adopt a more aggressive personalized health agenda.
- Develop creative solutions for establishing IP beyond traditional patents for genetics and molecular markers, and for other personalized health technologies.

Communication and the media

- Develop effective and independent training programs for science writers and journalists, and educational pathways for students trained in science to become science writers.
- Encourage the open source model in publishing scientific discoveries and in sharing scientific data.

Patients and consumers

- Encourage and enable the rise of the patient-consumer who is armed with validated information on predictive and preventive tests, protocols, and lifestyle options such as nutrition, diet, and exercise.
- Promote the greater funding and participation of patient advocacy groups to exert pressure on government and the biomedical enterprise to shift to a more aggressive translational model and a more timely adoption of personalized health discoveries and technologies.
- Work to shrink the “partnership gap” between patients and physicians, and encourage studies that will validate the importance of partnership in outcomes.

The Fund for Human Integration

Given the difficulties in financing and scaling personalized health products and protocols, it might make sense to seek out and develop alternative business models and systems for funding and prioritizing early stage efforts. We have mentioned the idea of creating a DARPA for biotechnology. This was done on a limited scale in 2006 when Congress created the Biomedical Advanced Research and Development Authority (BARDA) to fund the early stage development of drugs and vaccines against pandemics, whether they are naturally occurring, accidental, or intentional.[106] DARPA itself has begun funding some life science projects in recent years, providing researchers with a small amount of funding to test new ideas for a limited period of time.[107]

Another idea is to create a venture-style fund, with contributions made by the private equity market and the federal government, that is specifically tied to the priorities established in a detailed PHP blueprint. This fund would group individual discoveries and innovations by disease and other broad-based criteria that would allow the projects

to move forward in tandem as part of a coordinated effort rather than as a series of one-offs. For instance, Entelos might acquire an investment from this fund as part of a group of projects that complement each other and together offer a more viable path toward commercialization and profitability than would the company acting alone. Contributors to the fund would share proceeds in successful ventures. Panelist and neuroscience entrepreneur Zack Lynch described a version of this idea, calling for "a trans-NIH molecular biology/industry initiative with large-scale funding to promote the acceleration of new findings directly into translational projects within small and large companies. This would require a staff to seek out new technologies, devise strategies for using these technologies within existing company strategies, and then getting funding for companies."

Emphasis on global health

A transition of society to a personalized health system will require a substantial up-front investment. Early stage translational products also will be expensive at first. However, as these protocols become more commonplace and the technologies less expensive in the developed world, efforts should be made to develop personalized health initiatives aimed at the diseases and special concerns of the developing world. A major push should be to develop inexpensive diagnostic and predictive tests that can identify at-risk subgroups and individuals so that treatments and global health initiatives can be better targeted. An example is the effort being made by pharmaceutical companies and researchers to better identify specific mutations in HIV that might one day allow physicians to better target antiretrovirals according to a patient's specific infection.[108]

The new "Age of Personalized Health"

A true age of personalized health will not mean an end to illness and death. Nor can anyone predict when health care will make a true paradigm shift to emphasize healthy wellness, prediction, prevention, and individualized care and treatment—or the true impact of this new era on health and on costs. This study has offered a brief outline of some of the trends, issues, challenges, and opportunities made possible by the recent breakthroughs in science and technology—and some of the gaps in implementing them. The proposed solutions and action plan presented also are in outline form, and await a more detailed treatment.

Appendix A

The Personalized Health Manifesto

An old-fashioned call to arms and action plan for a new age of health care

by David Ewing Duncan
Director, The Center for Life Science Policy, UC Berkeley

This document was prepared in Autumn 2010 with the participation of thirty-five life science leaders representing science, medicine, business, government, patients, law, and the media (a complete list of participants appears at the end).

American society is on the cusp of a vital new era of health care, one in which medicine will shift from primarily addressing illness to a greater emphasis on prediction and prevention, and on individualized care. This historic transformation comes from a deepening understanding of biology, the emergence of new technologies, and a rising demand by individuals to understand and take charge of their own health. Yet a widening gap exists in integrating and implementing this promising new epoch of personalized health.

Resistance comes from traditions and attitudes that emerged during an age when medicine was limited primarily to diagnosing and treating disease, and by the prevailing use of drugs and protocols targeted more for populations and averages than for individuals. Even today, the biomedical enterprise overwhelmingly focuses on developing and paying for costly drugs, procedures, and devices that will be deployed after a person gets sick, with too little consideration for their personal physiology and circumstances.

This dominance is now being challenged. Discoveries in genomics, proteomics, environmental toxicology, microbiology, biocomputing, and many other fields are poised to provide unheard-of insight into a person's future health risks, and also to offer individualized options for improving health and wellness, and for managing disease.

Significant impediments and gaps remain, however, in applying this "new science"—not only in the clinic, but also in funding, infrastructure, regulation, law, business, education, and communication. Some of these gaps are unavoidable and naturally occur with any new discovery, while others are avoidable and potentially fixable.

A major hurdle is the unintended consequence of a system that has devoted considerable time and resources to basic research, and on creating an ever-more-specialized phalanx of experts delving into the mechanisms of life. Over the years, this reductionist enterprise has produced critical insights that have made an age of personalized health possible. But it also has encouraged a parsing of knowledge and a

silo effect that has made it difficult to capitalize on vast new stores of knowledge about human biology.

The time has come for an intensive focus on integration, the crucial complement to reductionism. Basic research and specialization remain crucial to the biomedical enterprise, but a reordering of priorities is required to stress the application and translation of what has been learned to improve health and reduce health care costs.

Integration requires, first, a new urgency for scientists to work together to focus on the whole human organism; and, second, for society to absorb and implement scientific discoveries in the realms of clinical medicine, law, government, education, and commerce with greater creativity and resolve. To realize this vision will require coordination, funding, and a mandate for bold action.

To launch a new era of personalized health does not require a radical new blueprint for change. Rather, it can utilize an existing body of suggested proposals, reforms, and plans already put forth by individuals and organizations inside and outside of government. Some of these ideas have been tentatively initiated, but they require significantly more funding and support.

To accelerate a transformation to personalized health, we, the undersigned, call on the life science community, policymakers, patients, and society to take the following actions:

First, to acknowledge that:

- New scientific discoveries are on the cusp of enabling a shift from health care based on illness to one equally centered on prediction, prevention, and personalized health.
- A balance between specialization and integration needs to be restored, with an emphasis on the whole human organism as much as its parts, and as much on individual patients as populations.
- Gaps exist that exacerbate the normal lag between discovery and application, both inside and outside the scientific community.
- Shifting to a health care system based as much on healthy wellness as illness is achievable, and can be accelerated by systematic planning and proper funding.

Second, to advocate the following:

- A Personalized Health Project that will:
  - recruit key leaders from science, medicine, business, policy, government, patient advocacy, ethics, law, and the media;

- study and assess specific “gaps” between innovation and application, and assign task forces to address each substantial gap;
- create a blueprint for implementing specific initiatives and enhancing existing projects in the public and private sectors to support predictive and preventive health care; and
- target, prioritize, and develop funding streams for the validation and application of new discoveries based on integrating individual discoveries and projects into a holistic model based on the needs of individuals and populations.

Third, to offer support for reforms in:

Education

- Establish a new academic discipline focusing on the science of integration, including educational programs, funding, and journals.
- Modify medical education and scientific training to emphasize wellness, predictive and preventive medicine, and a deeper understanding of the links between the new science and the clinic.
- Provide incentives for medical trainees to pursue primary care and integrative fields such as medical genetics.
- Organize an awareness campaign on the need to integrate fields within the life sciences and between the life sciences and society.

Policy

- Refocus regulation and oversight to better utilize science and technology to streamline the drug and diagnostic approval process.
- Embrace a new model based on predictive and preventive medicine and personalized treatments.
- Develop standard data elements for this new and emerging field.
- Remove barriers to the flow of scientific information by adopting open source models for publishing studies and organizing databases.
- Support improvements in information technology to better integrate data and to develop effective predictive models for populations and individuals.
- Create methods and programs to assess the true cost benefit of personalized health science and protocols.

Patient Participation

- Encourage and enable the rise of the patient-consumer in health care.
- Arm people with validated information on predictive and preventive tests, protocols, and lifestyle options such as nutrition, diet, and exercise.

Business

- Encourage entrepreneurs, investors, and commercial efforts to develop new products and protocols based on the science of personalized health.
- Create a Human Integration Fund: a hybrid of public and private money dedicated to investing not in individual efforts, but in groupings of efforts that jointly target a disease or system, or the human body.

Reimbursement

- Establish a reimbursement process that pays for and encourages predictive tests, prevention, healthy wellness, and targeted treatments.

Ethics and Global Health

- Study the impact and the ethics of personalized health initiatives to ensure their adoption is safe and effective, and that privacy, personal choice, and access are protected.
- Work to develop predictive and preventive strategies that are suitable for both the developed and developing world, and work to develop funding and initiatives for global personalized health.

End of Life

- Acknowledge that illness and death remain a part of life, continue a dedicated focus on personalized medicine to better customize treatment options, and encourage the use of palliative care where indicated.

Shifting to a health care paradigm that embraces healthy wellness and personalized health is a formidable challenge that will take many years. Yet we believe this transformation can be accelerated with a thoughtful and comprehensive plan to advance the science and practice of personalized health, and that no time is better than now to launch this effort.

Expert panel

The following individuals participated in the development of the Personalized Health Manifesto and have endorsed it; neither they nor anyone else has had any editorial influence over this document:

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Frank L. Douglas, MD, PhD, president and CEO, Austen BioInnovation Institute of Akron, Ohio; founder and first executive director of the MIT Center for Biomedical Innovation, Massachusetts Institute of Technology; former chief scientific officer, Aventis
Frederick Frank, MBA, life sciences investment banker; vice chairman, Peter J. Solomon Company; former vice chairman, Lehman Brothers
George Church, PhD, molecular biologist, professor of genetics, and director, Center for Computational Genetics, Harvard Medical School
George Poste, PhD, researcher, policy analyst, and former pharmaceutical executive; chief scientist, Complex Adaptive Systems Initiative; professor of Health Innovation, Arizona State University; former president, R&D, of SmithKline Beecham
Greg Simon, JD, senior vice president for Worldwide Policy, Pfizer; former president, Faster Cures; former chief domestic policy advisor to Vice President Al Gore
Gregory Stock, PhD, MBA, founding CEO, Signum Biosciences; founding director, Program on Medicine, Technology and Society, University of California at Los Angeles School of Medicine
Hank Greely, JD, professor of Law, Stanford University; director, Center for Law and the Biosciences
James Heywood, co-founder and chairman, PatientsLikeMe

James Thomson, VMD, PhD, stem cell scientist; director of Regenerative Biology, The Morgridge Institute for Research, University of Wisconsin School of Medicine and Public Health
Joshua Adler, MD, physician, chief medical officer, University of California at San Francisco Medical Center
Lee Hood, MD, PhD, molecular biologist and bioinformaticist; founder and director, Institute for Systems Biology
Linda K. Molnar, PhD, entrepreneur, personalized medicine and nanotechnology expert; founding principal, LKM Strategic Consulting
Margaret Anderson, executive director, FasterCures
Martyn Smith, PhD, professor of toxicology, School of Public Health, Division of Environmental Health Sciences, University of California at Berkeley
Michael Roizen, MD, preventive medicine; director, Wellness Institute, Cleveland Clinic
Misha Angrist, PhD, assistant professor, Duke University Institute for Genome Sciences & Policy
Nathaniel David, PhD, entrepreneur and venture capitalist; venture partner, Arch Venture Partners
Paul Billings, MD, PhD, clinical geneticist; chief medical officer, Life Technologies
Ray Woosley, MD, PhD, president and CEO, Critical Path Institute
Safi Bahcall, PhD, entrepreneur; CEO, Synta Pharmaceuticals Corp.
Stephen Friend, MD, PhD, president, CEO, co-founder, Sage Bionetworks; former senior vice president and franchise head for Oncology Research, Merck
Stephen P. Spielberg, MD, PhD, pediatrician; director, Center for Personalized Medicine and Therapeutic Innovation, Children's Mercy Hospital, Kansas City, Mo; former dean, Dartmouth Medical School
Steve Wiggins, venture capitalist and former health insurance executive; managing director of Essex Woodlands Health Ventures; founder and former CEO, Oxford Health Plans
Zack Lynch, executive director, Neurotechnology Industry Organization

Appendix B

Selected personalized health projects already under way

Numerous projects and initiatives are under way to address the gap between innovation and application, and to support an enhanced emphasis on integration and personalized health. Many of the suggested initiatives in the report and in the Personalized Health Manifesto already have been the topic of proposed reforms; some already have been implemented, usually in small initiatives with limited budgets. A few are more large-scale. When viewed collectively, this creative effort offers an early stage platform on which a more aggressive effort can build. Below are some examples of programs; this list is not comprehensive.

The authors of this study would welcome suggestions of additional programs to include. Please contact us at david@davidewingduncan.com.

Federal government initiatives

The Department of Health and Human Services (HHS) includes the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Centers for Disease Control (CDC). Other government agencies supporting translational life sciences programs include the National Science Foundation (NSF) and DARPA. Snapshots of some specific federally funded programs are given below.

The Department of Health and Human Services

Small business tax credits. In the summer of 2010, Congress authorized a $1 billion small business tax credit through the HHS to encourage the development of new therapies. Under the Act, the government makes a Qualifying Therapeutic Discovery Project Credit available to companies with 250 or fewer employees. The purpose behind the credit is to encourage the research and development of new therapies in the pharmaceutical and medical device industries. The tax credit further emphasizes projects designed to treat or prevent diseases through conducting pre-clinical or clinical studies and research protocols that meet the following criteria:

1. Projects that intend to diagnose diseases or conditions, or to develop diagnostic procedures to assist doctors and patients in making therapy decisions; and
2. Projects with the purpose of creating or developing a product or technology to further the delivery of therapeutics.

Additional criteria include the potential to produce new therapies, address unmet medical needs, reduce the long-term growth of health care costs, and advance the goal of curing cancer within the next thirty years. Projects that can generate jobs and boost competitiveness in the life sciences sector likely will be able to secure financing through this program.

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). The SACGHS's purpose had been to advise the secretary of Health and Human Services on issues relating to the use and potential misuse of genetic technologies. From its website: "The SACGHS recognizes that there are medical, ethical, legal, and societal implications surrounding advances in our knowledge of biology, genomics, and human genetics, and their integration into clinical and public health practice must be done with great care. Study topics include many areas relevant to personalized health, such as the following: clinical utility and comparable effectiveness of genetic testing information, coverage and reimbursement of genetic technologies, genomic data sharing, and genetics education for health care professionals." The SACGHS was disbanded in the fall of 2010.

Website: http://oba.od.nih.gov/SACGHS/sacghs_home.html

Food and Drug Administration

Publication, "Advancing Regulatory Science for Public Health," Office of the Chief Scientist, U.S. Food and Drug Administration, October 2010. From the overview: "Recent breakthroughs in science and technology—ranging from sequencing of the human genome to advances in the application of nanotechnology to new medical products—have the potential to transform our ability to prevent, diagnose, and treat disease. These developments will result in moving treatment strategies toward approaches that are tailored or personalized to individual patients, thus maximizing the benefit of treatments while decreasing their safety risks. Similarly, advances in research and information technologies are enabling us to more efficiently identify microbial pathogens, track food contamination outbreaks, and determine where foods and other FDA-regulated products are produced or manufactured, how they are transported, where they go, and who uses them. These tools also can play an important role in preventive health by enabling more comprehensive immunization strategies, especially in the face of emerging pandemics. For these advances to reach their full potential, the Food and Drug Administration (FDA) must play an increasingly integral role as an agency not just dedicated to ensuring safe and effective products, but also to promote public health and participate more actively in the scientific research enterprise directed toward new treatments and interventions. We must also modernize our evaluation and approval processes to ensure that innovative products reach the patients who need them, when they need them.

"These new scientific tools, technologies, and approaches form the bridge to critical twenty-first century advances in public health. They form what we call *regulatory*

science: the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. This document outlines a broad vision for advancing regulatory science and unleashing its potential to improve public health. It discusses the role of the FDA, working with partners, to strengthen the field, both within the agency and throughout the nation."

NIH and FDA joint program to streamline the regulatory process. In February 2010, the FDA and the NIH unveiled an initiative designed to accelerate the process from scientific breakthrough to the availability of new, innovative medical therapies for patients. The initiative involves two interrelated scientific disciplines: translational science, the shaping of basic scientific discoveries into treatments; and regulatory science, the development and use of new tools, standards, and approaches to more efficiently develop products and more effectively evaluate product safety, efficacy, and quality. Both disciplines are needed to turn biomedical discoveries into products that benefit people.

As part of the effort, the agencies will establish the joint NIH-FDA Leadership

Council to spearhead collaborative work on important public health issues. The Joint Leadership Council will work together to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. As part of the initiative, the NIH and the FDA issued a joint Request for Applications, making $6.75 million dollars available over three years for work in regulatory science.

Website:
http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm

Bioinformatics Tools. From the FDA website: "The National Center for Toxicological Research conducts research in bioinformatics and chemoinformatics, and develops and coordinates bioinformatics capabilities within NCTR, across FDA Centers, and in the larger toxicology community. Bioinformatic tools created at NCTR with the goal to develop methods for the analysis and integration of omics (genomics, transcriptomics, proteomics, and metabolomics) datasets include:"

ArrayTrack™: DNA microarray data management, mining, analysis, and interpretation software
Decision Forest: Novel pattern-recognition method for analysis of data from microarray experiments, proteomics research, and predictive toxicology
Endocrine Disruptor Knowledge Base (EDKB): Scientific resources to predict estrogen and androgen activity
Liver Toxicity Knowledge Base (LTKB): Project to study drug-induced liver injury
MicroArray Quality Control (MAQC): Project to develop microarray quality control metrics and thresholds
MolD2: Software that generates molecular descriptors from two-dimensional

structures
SNPTrack: Integrated solution for the management, analysis, and interpretation of genetic association study data

Interdisciplinary Pharmacogenomics Review Group (IPRG). From the IPRG website: "The mission of the Interdisciplinary Pharmacogenomics Review Group is to establish a scientific and regulatory framework for reviewing genomic data. The IPRG is an Agency-wide review group, whose members include individuals from CDER, CBER, CDRH, NCTR, OCP, and CVM. The IPRG is the primary review body for Voluntary Exploratory Data Submissions (VXDS) [formerly Voluntary Genomic Data Submissions (VGDS)]. Upon request, the IPRG also consults with FDA review staff on the review of required submissions, e.g., IND, NDA, BLA or IDE, containing genomic data."

Website: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics

For a complete list of FDA initiatives: www.fda.gov

National Institutes of Health

Clinical and Translational Science Awards (CTSAs). As part of the NIH Roadmap for Medical Research, the National Center for Research Resources (NCRR), a part of the NIH, launched the Clinical and Translational Science Awards program in 2006 with twelve centers in order to create a definable academic home for clinical and translational research. CTSA institutions work to transform the local, regional, and national environment to increase the efficiency and speed of clinical and translational research across the country. Now in its fourth year, the consortium added nine additional institutions, bringing the total number of CTSAs to fifty-five medical research institutions located throughout the nation. When fully implemented by 2012, about sixty institutions will be linked together to energize the discipline of clinical and translational science.[1]

Website: http://nihroadmap.nih.gov/ctsa/

The Encyclopedia of DNA Elements (ENCODE) Project. Launched by National Human Genome Research Institute (NHGRI) in 2004, ENCODE is a consortium that seeks to identify functional elements in the human genome. To aid in the integration and comparison of data produced using different technologies and platforms, the ENCODE Consortium has designated cell types that will be used by all investigators. These common cell types include both cell lines and primary cell types, and plans are being made to explore the use of primary tissues and embryonic stem cells. Cell

[1] As this study was being completed, the NIH announced plans to form a The National Center for Advancing Translational Sciences (NCATS). Details were not yet available.

types were selected largely for practical reasons, including their wide availability, the ability to grow them easily, and their capacity to produce sufficient numbers of cells for use in all technologies being used by ENCODE investigators.

Website: http://www.genome.gov/26524238

Pharmacogenomics Research Network (PGRN). Launched in 2000 by the National Institute of General Medical Sciences (NIGMS), the PGRN's aim is to "lead discovery and advance translation in genomics in order to enable safer and more effective drug therapies," according to its website. "In that time, the PGRN, a nationwide collaborative, has grown to encompass fourteen scientific research projects and seven network resources. The PGRN aims to turn discovery of novel insights into mechanisms relating genomic variation to differences in drug responses, to demonstrate the use and utility of genomic information to improve outcomes for drug therapies, and to incorporate genomic data into routine clinical practice in order to predict and personalize medicine. Scientific accomplishments include the finding that the CYP2C19 gene variant, carried by about a third of the population, plays a major role in this group's response to an anti-clotting medicine, clopidogrel (Plavix). (Shuldiner group: August 26, 2009 *JAMA* 302(8):849–857) and a new method to help doctors determine a patient's optimal dose of the blood thinner, warfarin. The method was devised using data from thousands of genetically and geographically diverse patients. (Altman, Johnson, McLeod, and Roden groups: Feb. 19, 2009 *NEJM* 360:753–764)."

Website: http://www.nigms.nih.gov/Initiatives/PGRN

The Genes, Environment, and Health Initiative (GEI). The GEI was established in 2006 to support research that the organization's website says will lead to "the understanding of genetic contributions and gene-environment interactions in common disease. GEI is planned and led by an NIH-wide Coordinating Committee, administratively led by the National Human Genome Research Institute and the National Institute of Environmental Health Sciences (NIEHS)."

Website: http://www.genome.gov

For a complete list of NIH initiatives: www.nih.gov

National Cancer Institute

The Cancer Genome Atlas (TCGA). Launched in 2005, the TCGA is a three-year, $100 million pilot project. The Atlas's aim, according to its website, is a "comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The overarching goal of The Cancer Genome Atlas (TCGA) is to improve our ability to diagnose, treat, and prevent cancer … A related program, the International Cancer Genome Consortium (ICGC),

was formed in 2008. The ICGC is coordinating project efforts to sequence 500 tumors from each of fifty cancers. Together, these projects will cost in the order of US$1 billion. Eleven countries have already signed on to cover more than twenty cancers. The Cancer Genome Project has churned out more than 100 partial genomes and roughly fifteen whole genomes in various stages of completion, and intends to tackle 2,000–3,000 more over the next five–seven years."

Website: http://cancergenome.nih.gov/

NCI Alliance for Nanotechnology in Cancer. Launched in 2005, this $144.5 million project is a translational program engaged in efforts to harness the power of nanotechnology to radically change the way we diagnose, treat, and prevent cancer. It is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of nanotechnology's best capabilities to cancer. A major NCI goal is to integrate research infrastructures and catalyze cross-disciplinary collaborations to take on large problems in human cancer research and technology development that cannot be addressed by individual investigators. The Alliance for Nanotechnology in Cancer will integrate the capacities of centers, partnerships, and consortia to increase the pace of technology development and clinical application in the fight against cancer.

Website: http://nano.cancer.gov/

Clinical Proteomic Technologies for Cancer (CPTC). Launched in 2006, this initiative seeks to foster the building of an integrated foundation of proteomic technologies, data, reagents, reference materials, and analysis systems to systematically advance the application of protein science to accelerate discovery and clinical research in cancer. This initiative is a highly collaborative effort, made up of scientists from nearly fifty federal, academic, and private-sector organizations who are working together to make clinical proteomics a reality—far too great an endeavor for a single institution.

Website: http://proteomics.cancer.gov/

The Office of Biorepositories and Biospecimens Research (OBBR). Launched in 2006, this project ensures that human specimens available for cancer research are of the highest quality. Key to that mission, the OBBR is responsible for developing a common biorepository infrastructure that promotes resource sharing and team science in order to facilitate multi-institutional, high-throughput genomic and proteomic studies.

Website: http://biospecimens.cancer.gov/

The Translational Research Working Group (TRWG). Established in the summer of 2005, the TRWG, according to its website, works with the cancer research community "to develop recommendations about how the National Cancer Institute

can best organize its investment to further 'translational research.' Over the span of two years, the TRWG reviewed NCI's current intramural and extramural translational research portfolio (within the scope of the TRWG mission), facilitated broad community input, invited public comment, and recommended ways to improve and integrate efforts. The ultimate goal was to accelerate progress toward improving the health of the nation and cancer patient outcomes. The NCI is committed to translational research and has begun implementation of the strategy developed by the TRWG."

Website: http://www.cancer.gov/trwg

For a complete list of NCI initiatives: www.cancer.gov

Department of Defense

The Defense Advanced Research Projects Agency. DARPA supports efforts in the life sciences primarily through the Defense Sciences Office (DSO). DSO manages a growing portfolio of programs in human combat performance, tactical and restorative biomedical technologies, and biologically inspired platforms and systems. These "thrust areas" have emerged out of a basic research program designed to understand fundamental processes in biology through promoting interactions among the most creative thinkers in biology with leaders in disparate fields such as physics, mathematics, and engineering. DARPA further seeks to support technology development that focuses on the translation of fundamental science into businesses and products with both civilian and noncivilian applications. Areas of interest include such topics as: sequencing (biological threats), point-of-care diagnostics, sensors, robotics, and wireless medical devices.

Website: http://www.darpa.mil/dso/thrusts/bio/index.htm

Department of Energy

The Department of Energy (DOE), through its Office of Biological and Environmental Research (BER), funds research programs and develops scientific tools to determine protein structures and genomic DNA sequences, and also funds efforts to understand the structure, function, and regulation of multiprotein complexes from energy-relevant organisms.

Website: http://www.sc.doe.gov/ober/bssd_top.html

National Science Foundation

Biomedical Engineering Program. NSF's life science funding focuses primarily on efforts to integrate engineering and the life sciences to solve biomedical challenges in both the long term and the short term. NSF seeks to provide opportunities to develop novel ideas into discovery-level and transformative projects at the interface of engineering and medicine. NSF also supports a wide variety of medical

applications of nanotechnology, such as targeted nanoparticles, which can have implications for personalized medicine.

Website: http://www.nsf.gov/

Acceleration Innovation Research (AIR). This program encourages the translation of NSF researchers' fundamental and technologically promising discoveries and draws on the entrepreneurial spirit of NSF researchers and students. AIR also fosters connections between existing NSF innovation research alliances—for instance, the Engineering Research Centers (ERC), the Industry & University Cooperative Research Centers (I/UCRC), Partnerships for Innovation (PFI),and other institutions—whose complementary focus will spur the development of discoveries into innovative technologies through collaboration.

Website: http://www.nsf.gov/bfa/dias/policy/dmp.jsp

National Academies of Science

Publication: "A New Biology for the 21st Century," published by the National Academies of Science, 2009.. From the website: "Now more than ever, biology has the potential to contribute practical solutions to many of the major challenges confronting the United States and the world. *A New Biology for the 21st Century* recommends that a 'new biology' approach—one that depends on greater integration within biology, and closer collaboration with physical, computational, and earth scientists, mathematicians, and engineers—be used to find solutions to four key societal needs: sustainable food production, ecosystem restoration, optimized biofuel production, and improvement in human health. The approach calls for a coordinated effort to leverage resources across the federal, private, and academic sectors to help meet challenges and improve the return on life science research in general."

Website: http://www.nap.edu/catalog.php?record_id=12764#toc

Foundation, nonprofit, open source, and patient-centered initiatives

In recent years, disease-specific foundations and nonprofit institutions have stepped into the translational and personalized health research space. The creation of these organizations is, in part, a reaction to the gap between fundamental research and applications, and a perceived need to speed up new developments in diagnostics and therapeutics to patients—particularly for rare and often-fatal diseases. Many of these organizations have established partnerships and collaborations with universities, institutes, nonprofits, private companies, and programs within the federal government. A few examples are listed below.

The P4 Institute. Taking the "4 Ps" articulated by Hood—predictive, preventive, personalized, and participatory—this new institute is setting out to accomplish the following:[109]

- Recruit academic research institutions and health systems as P4MI members.
- Work with the private and public sectors to create the needed technical infrastructure.
- Integrate and support member programs by:
  - coordinating knowledge and solution transfer between members;
  - organizing joint responses; and
  - supporting the analysis of societal issues and developing the necessary social infrastructure.
- Educate the policy, regulatory, and public spheres about the value of P4 medicine.
- Advocate for public policies that will support/facilitate P4 medicine.

Website: http://p4mi.org/

Personalized Genome Project (PGP). This initiative, organized by a team led by Harvard geneticist George Church, is setting out to sequence 100,000 complete genomes.[110] The PGP places a strong emphasis on the personal participation of subjects, who must pass a rigorous test on their understanding of basic genetics, and about privacy and other ethical issues concerning DNA testing. This project is working to link up subjects with tools to interpret their results and integrate their DNA findings with other risk factors for traits and disease. Beyond genomics, the Church Lab at Harvard Medical School is a study in integrative science, with significant projects also under way in proteomics, epigenetics, microbiomics, and synthetic life.[111]

Website: http://www.personalgenomes.org

The Gene Partnership. Spearheaded out of Children's Hospital Boston and Harvard Medical School,[112] the goal is to bring together clinical data, phenotypic data, genome sequencing, sensor data, and longitudinal monitoring, starting in Boston and then expanding globally. This initiative is meant to elucidate, with the correct powering, gene-gene and gene-environment interactions so we can begin to predict with high confidence who is at risk of disease presymptomatically, and what an individual should do to manage his or her health.

Website: http://www.genepartnership.org

The Redstone Acceleration and Innovation Network (TRAIN). This group of unique nonprofit foundations, which includes organizations such as the Cystic Fibrosis Foundation, the Michael J. Fox Foundation for Parkinson's Research, and the Multiple Myeloma Research Foundation, funds and conducts medical research

across a spectrum of diseases, from breast cancer to Parkinson's disease. TRAIN has come together under the auspices of FasterCures to help its members more easily and effectively support each other's efforts to produce better and faster results, and to bring their sense of urgency about conducting bench-to-bedside translational research to the medical research community as well as the public at large. Building collaborations is central to the philosophy of the TRAIN research organizations—among researchers of different disciplines, among institutions, and among sectors. Most of these organizations have created formal consortia of medical research centers to team on disease research and share information. Increasingly, they are collaborating with the pharmaceutical and biotechnology industries to advance clinical trials and drug development. The existence of these academic research consortia often are a motivator for industry to develop drugs, since the networks are available to help quickly advance clinical development of promising compounds.

Website: http://www.fastercures.org/train

Accelerated Brain Cancer Cure. This group believes in a focused, aggressive, entrepreneurial model for delivering results to patients. Its approach is to fund novel translational research aimed at finding the fastest possible route to a cure. It partners with early stage biotechnology companies and large pharmaceutical companies to move treatments as fast as possible from basic discovery to the clinic.

Website: http://abc2.org/our-approach

The Personalized Medicine Coalition. The PMC was launched in 2004 to educate the public and policymakers, and to promote new ways of thinking about health care. Its aim is to provide support for the realization of personalized medicine. Today, it comprises a vast network of more than 200 organizations spanning the spectrum of academic, industry, patient, provider, and payer communities.

Website: http://www.personalizedmedicinecoalition.org

Critical Path Institute. C-Path was established in 2005 as an independent, nonprofit organization whose mission is to serve as the impartial facilitator of collaborative efforts among scientists from government, academia, patient advocacy organizations, and the private sector to support the FDA's regulatory science initiatives. This involves creating faster, safer, and smarter pathways for innovative new drugs, diagnostics, and devices that will significantly improve public health.

Website: www.c-path.org

PatientsLikeMe. Founded in 2004 by three MIT engineers whose collective experience ranges from running the world's only nonprofit biotechnology laboratory to large-scale online commerce applications, PatientsLikeMe is a privately funded company that uses online tools to help patients manage their own diseases. The

organization has created a community of patients, doctors, and organizations that informs and empowers individuals.

Website: http://www.patientslikeme.com

Regenerative Medicine Foundation. The Regenerative Medicine Foundation was created in 2005 to enable the advancement of new treatments and therapies based on regenerative medicine and, ultimately, to realize the goals of personalized medicine. Through educational programs, translational conferences, and public policy initiatives, the foundation advocates for increased medical research, promotes the training and education of scientists, and facilitates the translation of therapies to patients.

Website: http://www.regenerativemedicinefoundation.org/home.php

Sage Bionetworks. From Sage's website: **"**Sage Bionetworks is a nonprofit medical research organization established in 2009 to develop a new paradigm for addressing the complexity of human biological information and the treatment of disease. Sage and its academic and commercial partners employ multiple comprehensive molecular and clinical datasets to create validated disease models that improve the speed and efficiency of therapeutic drug development. Sage's vision is to create an open-access, integrative bionetwork evolved by contributor scientists working to eliminate human disease."

Website: http://www.sagebase.org

Academic programs in integrative and translational medicine

Institute for Translational Medicine and Therapeutics. From the institute's website: "The Institute for Translational Medicine and Therapeutics (ITMAT) supports research at the interface of basic and clinical research focusing on developing new and safer therapeutics. ITMAT includes faculty, basic research space, and the Clinical and Translational Research Center (CTRC), which derives from the integration of the former General Clinical Research Center of both Penn and the Children's Hospital of Philadelphia. ITMAT also offers research cores, educational programs (including a master's in translational research), and research centers. These are designed to facilitate training and research from proof of concept in cellular and animal model systems across the translational divide to proof of concept and dose selection in humans."

Website: www.itmat.upenn.edu/index.shtml

SPARK. SPARK is a translational program at Stanford School of Medicine. From the SPARK website: "SPARK provides the infrastructure to bring investigators involved in translational research together to generate new drugs and treatments. It provides a

structured focus for these activities, accelerating the testing of potential benefits derived from scientific discovery. It also helps streamline communication between academia and industry, clarifying the language and assumptions of these sometimes-disparate groups. The program also promotes new ways of thinking about how research can be applied to workable solutions. Its broad base of participants allows new and unique perspectives on projects that may have lost momentum on their original premise. SPARK can help identify failures that may show potential in seemingly unrelated applications, allowing other participants to pick up the pieces of another project."

Website: http://sparkmed.stanford.edu

The "Anti-Medical School "graduate seminar at the University of California at Berkeley. From the seminar's website: "Medical schools teach what is known in medicine, explains BioE associate professor Steve Conolly, who helped bring the course here from the University of California-San Francisco. Anti-Medical School explores what is unknown and unsolved in medicine, and that's what the course's seventy students, mainly first- and second-year bioengineering graduate students, found compelling."

Website: http://innovations.coe.berkeley.edu/vol4-issue1-feb10/anti-medical-school

The Translational Genomics Research Institute. TGen is based in Phoenix, Arizona. From the TGen website: "Working with collaborators in the scientific and medical communities, TGen believes it can make a substantial contribution to the efficiency and effectiveness of the translational process. TGen's vision is of a world where an understanding of genomic variation can be rapidly translated to the diagnosis and treatment of disease in a manner tailored to individual patients. TGen is dedicated to the next revolution in health care. With the patient at its helm, TGen is guided by three core principles: *integrate, translate, and accelerate*."

Website: http://www.tgen.org/

The Scripps Translational Science Institute. From the STSI website: "The Scripps Translational Science Institute (STSI) aims to replace the *status-quo* of one-size-fits-all-medicine with individualized health care that is based on the known genetic factors influencing health and disease and that takes advantage of advances in digital technology for real-time health monitoring… STSI has created major programs in both research and education-training that bridge science with medicine, and academia with industry."

Website: http://www.stsiweb.org/

The Wyss Institute for Biologically Inspired Engineering. From the Institute's website: "The Wyss Institute aims to discover the engineering principles that nature uses to build living things, and harnesses these insights to create biologically inspired materials and devices that will revolutionize health care and create a more sustainable world. In medicine, the Institute is developing innovative materials, devices, and disease

reprogramming technologies that emulate how living tissues and organs self-organize and naturally regulate themselves. Understanding of how living systems build, recycle, and control is also guiding efforts focused on development of entirely new approaches for constructing buildings, converting energy, controlling manufacturing, and improving our environment."

Website: http://wyss.harvard.edu/

The Harvard Clinical and Translational Science Center (Harvard Catalyst). From the center's website: "Harvard Catalyst | The Harvard Clinical and Translational Science Center is dedicated to improving human health by enabling collaboration and providing tools, training, and technologies to clinical and translational investigators. Founded in May 2008, Harvard Catalyst is a shared enterprise of Harvard University, its ten schools and its eighteen Academic Health Care Centers (AHC), as well as the Boston College School of Nursing, MIT, Harvard Pilgrim Health Care, and numerous community partners."

Website: http://catalyst.harvard.edu/about.html

Appendix C

Project questionnaire

The Personalized Health Project questionnaire was sent out to thirty-eight experts and leaders in life sciences; thirty-four answered its eight questions. Below is the survey text as it appeared when it was sent to participants.

Dear Personalized Health Project Panelist:

Please read the following summary of the project:

“Recent advances in molecular biology and the life sciences hold great promise not only for improving the health of individuals, but also to shift medicine and society from primarily treating illness to an emphasis on prediction, early diagnosis, prevention, and personalized treatments. Applying these discoveries, however, has been slow. We will first describe some key elements of the recent scientific breakthroughs in genomics, proteomics, epigenomics, neuroscience, environmental influences, and complex biology, and then identify and assess key obstacles to application and integration. This includes what we believe is a systemic failure to communicate and coordinate new innovations and concepts across multiple disciplines and institutions throughout society—science, medicine, industry, finance, patient advocacy groups, government, politics, ethics, law, and the media. We plan to interview and engage leaders in each of these fields to join us in assessing the perceived “gap” between discovery and application, and also in writing a “call to action” containing specific steps to close the gap, and to speed up the acceptance and implementation of personalized health and medicine.”

Questions (please answer at any length):

1. Do you perceive that a gap exists between recent scientific discoveries in molecular biology and their application in the clinic and for patients?

If no, please explain—and then you’re finished.

If yes, please continue with the questions below.

2. Is this gap unavoidable (that is, a product of the natural lag that occurs between discovery and application), or do you believe that the gap is avoidable (caused by factors that could be corrected with more resources, a change in infrastructure, or attitudes)?

3. What are the top three causes of this gap?

4. Do you have ideas for solutions to address these causes and to bridge the gap?

5. Are you familiar with studies, articles, or commentaries that address the notion of a gap, its causes, and possible solutions? Would you mind providing links or contact information?

6. The authors of this study would like to present three brief case studies that illustrate the detrimental impact of a gap in slowing or hindering the application of new scientific discoveries—do you know about a case study to propose?

7. Likewise, the authors want to present three case studies where innovative ideas have bridged the gap and illustrate how efforts to overcome barriers have worked. Do you know about a case study illustrating a success in closing the gap?

8. Finally, this paper will end with a manifesto calling for action to be taken to bridge gaps and to remove barriers to the adoption of new scientific discoveries. What are the top three action items you would like to see happen? (Feel free to repeat comments already made).

NOTES

[1] Committee on a New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution, National Research Council of the National Academies, *A New Biology for the 21st Century* (Washington, D.C.: The National Academies Press, 2009).
[2] See Appendix C for the expert panel's answers to an eight-question survey, including a question about whether the current gap between discovery and application is "natural" or "artificial."
[3] Research America, "2008 Investment in U.S. Health Research," http://www.researchamerica.org/uploads/healthdollar08.pdf.
[4] Kevin Davies, "Illumina's HiSeq 2000 Hits $10,000 Genome Mark," *Bio-IT World Magazine* (March/April 2010).
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