Improving the Efficiency and Effectiveness of Genomic Science Translation: Workshop Summary

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Sarah H. Beachy, Samuel G. Johnson, Steve Olson, and Adam C. Berger, Rapporteurs; Roundtable on Translating Genomic-Based Research for Health; Board on Health Sciences Policy; Institute of Medicine

IMPROVING THE EFFICIENCY AND EFFECTIVENESS OF GENOMIC SCIENCE TRANSLATION

WORKSHOP SUMMARY

Sarah H. Beachy, Samuel G. Johnson, Steve Olson, and Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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Willing is not enough; we must do."
—Goethe

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

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The Roundtable expresses its gratitude to the expert speakers whose presentations helped outline the challenges to, as well as the opportunities for, improving genomic science translation. The Roundtable also thanks

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Abbreviations and Acronyms

AGRE	Autism Genetic Resource Exchange
ASD	autism spectrum disorder
CNTNAP2	contactin-associated protein-like 2
CRO	contract research organization
DMD	Duchenne muscular dystrophy
EMR	electronic medical record
FDA	U.S. Food and Drug Administration
GDP	gross domestic product
HHMI	Howard Hughes Medical Institute
MJFF	The Michael J. Fox Foundation for Parkinson's Research
NIH	National Institutes of Health
PPMD	Parent Project Muscular Dystrophy
RADD	Review of Approved Drugs for Duchenne

TACT	TREAT-NMD Advisory Committee for Therapeutics
TREAT-NMD	Translational Research in Europe–Assessment and Treatment of Neuromuscular Diseases
UCLA	University of California, Los Angeles

1

Introduction[1]

The process for translating basic science discoveries into clinical applications has historically involved a linear and lengthy progression from initial discovery to preclinical testing, regulatory evaluation and approval, and, finally, use in clinical practice. Despite significant advances in the understanding of human disease and clinical pharmacology, several stakeholders have recently expressed concern over the declining productivity of the translation of basic scientific discoveries into the practice of clinical medicine and the substantial cost of this process (Harrison et al., 2012). The low rate of translation from basic science to clinical application has been a source of frustration for many scientists, clinicians, investors, policy makers, and patients who hoped that investments in research would result in improved products and processes for patients (Mankoff et al., 2004). Although this is a general problem for scientific discoveries in the current translational pathway, these concerns also apply to genomic science. Specifically, some feel that the anticipated deliverables from the Human Genome Project have not yet materialized, and although understanding of human health and disease biology has increased, there has not been a

[1]The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

concomitant increase in the number of approved drugs for patients over the past 10 years.[2]

One of the major obstacles to translation is the lack of incorporation of ideas about clinical applications during the early stages of development of research projects. Not only is knowledge from outcomes and clinical or public health needs not routinely incorporated into the design of basic scientific research, but also the process of exchanging discoveries between basic and clinical scientists is not well defined. Improved communication to allow for clinical and patient needs to inform the priorities of basic science research can offer a clearer path toward improving clinical application. The realignment of academic incentives, the detection of innovative ways to fund translational research, and the generation or identification of alternative models that accurately reflect human biology or disease provide opportunities to work across sectors to advance the translation of genomic discoveries.

To foster collaboration and the exchange of ideas among stakeholders and to improve the utilization of genomic research for practical applications, the Roundtable on Translating Genomic-Based Research for Health hosted a workshop on December 3, 2012, in Irvine, California, to explore ways to improve the efficiency and effectiveness of the translation of genomic science to clinical practice. The workshop convened academic researchers, industry representatives, policy makers, and patient advocates to explore obstacles to the translation of research findings to clinical practice and to identify opportunities to support improvement of the early stages of the process for translation of genetic discoveries (see the workshop objectives in Box 1-1).[3]

WORKSHOP GOALS

Wylie Burke, Roundtable co-chair and professor and chair of the department of bioethics and humanities at the University of Washington, stated that although the Roundtable has spent a significant amount of time addressing issues in genomic medicine, such as the implementation of genome sequencing in the clinic and related regulatory and evidentiary

[2]In 2012, 39 new drugs were approved, which was a 16-year high. But as of October 8, 2013, the data suggest that there will be fewer new drug approvals in 2013 (at this point there were only 18: see *Summary of New Drug Approvals and Receipts, 1938 to the Present*, http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm and *New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products of 2013*, http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm [accessed October 8, 2013]).

[3]The workshop agenda, speaker biographical sketches, full statement of task, and registered attendees can be found in Appendixes A–D.

BOX 1-1
Workshop Objectives

- To examine how basic science can best be positioned to foster the successful translation of early genomic discoveries.
- To explore the challenges to and identify potential opportunities for improving the efficacy of the translation process.
- To define pathways for moving innovative basic science forward.

issues, the focus of the discussion at the workshop would be on the integration of progress in basic science research with the translational pathway for clinical implementation. Burke specifically noted that the challenges, barriers, and opportunities would be key interdisciplinary topics for conversation and that the successful integration of research discoveries and clinical medicine relies on the communication and expertise of a diverse group of stakeholders in the process.

The report that follows is a summary of the workshop and highlights the main discussion points that the workshop speakers and participants presented and considered. Chapter 2 introduces several of the broad issues associated with the process of the translation of research findings into improvements in health care. Chapter 3 focuses on how basic science research could be structured to promote translation. Chapter 4 examines the roles of industry and venture capital in the movement of discoveries along a translational pathway to the marketplace. Chapter 5 explores the role of advocacy groups in catalyzing translation, in part through the convening of the many stakeholders involved in the process. Finally, Chapter 6 provides additional discussions of data access, the management of the research enterprise, and the incentives that contribute to or hinder the translation of basic science research.

2

Connecting Basic Research and Health Care Needs

Important Points Highlighted by Individual Speakers

- The costs of research and health care have increased considerably, but the falling price of genomic technology provides an opportunity to use genomics as a systems optimizer to reduce medical costs.
- The efficiency of scientific translation can be improved through the use of milestone and outcome-driven management approaches, along with scaling and logistical methods, to maintain a focus on research goals and shorten the time between discovery and development.
- The application of genomics in cancer can be used as a model to demonstrate how a stratified approach can categorize tumors and guide therapy choices.
- The success of personalized medicine relies on the collective efforts of clinicians, patients, and researchers to inform research inquiry and translation.
- Speed, flexibility, teamwork, skilled management, and powerful technologies will likely be the hallmarks of the success of research in the future.

Two speakers opened the workshop with broad overviews of the pathways from basic research to improvements in health care. Edison Liu,

president and chief executive officer of The Jackson Laboratory, explored ways of improving the efficiency of translation by taking advantage of scale and logistics and by using effective management to guide research on the basis of outcomes and milestone achievements. David Huntsman, associate professor of medicine at the University of British Columbia, used cancer as an example of the potential—and complexity—of personalized medicine.

IMPROVING TRANSLATION EFFICIENCY WITH A MISSION-ORIENTED MINDSET: MILESTONE- AND OUTCOME-FOCUSED RESEARCH

The costs of research and health care have risen, Liu said. Genomics, as a diagnostic tool, can be used as a systems optimizer, "where each diagnostic makes money by saving money for the system." Companies have begun to think about their business models in different ways to design cost-saving solutions to health problems. Veracyte, Liu explained, develops molecular tests to examine fine needle aspirates from thyroid nodules to determine the likelihood that a tissue is benign. As a business model, this results in minimization of the need for unnecessary surgery for a complete thyroidectomy, reducing direct medical costs by more than $120 million per year (Li et al., 2011). Big science should include more efficient research processes and cost-effective outcomes, as opposed to just focusing on profit-generating ones, Liu said.

"My central premise is that our academic biomedical research enterprise is inefficient relative to the technologies that we have available today. We need a new mindset, and that mindset may be characterized by mission-oriented research," Liu challenged. Mission-oriented research can be described as research driven by milestone accomplishments and focused on outcomes, he said. These goals can be accomplished by quality scientific managers who "execute with speed, flexibility . . . who can assemble functional teams quickly and disassemble them quickly . . . who can embrace powerful technologies and actually retire [out-of-date] technologies," Liu said.

Liu provided examples of organizations that are using this new mindset to work together as teams to achieve common goals. The Genome Institute of Singapore, which Liu helped develop, supports those with diverse skills to engage in collective decision making around the topics chosen for research through the development of integrated platforms. The Janelia Farm Research Campus in Virginia, which opened in 2006 and is supported by the Howard Hughes Medical Institute (HHMI), is an example of an effort to provide scientific focus for long-term grand challenges in an environment which offers opportunities for cross-discipline collaboration (Waldrop, 2011). Using Bell Laboratories and other successful research models, HHMI created the Janelia Farm to combine particular areas of

research focus with individuals with diverse skills and the freedom to pursue good ideas. The model provides researchers with a fixed time commitment for their work to reinvigorate the team and continually provide fresh ideas. As an example of how successful projects are managed at milestone-based organizations, Liu said that at the Defense Advanced Research Projects Agency, "project managers are empowered, are paid well, and have significant influence in how the component parts are run." He also cited the U.S. military's use of a 20-year scanning horizon as an example of the importance of giving strategic attention to an issue to make progress.

Employing Scaling and Logistics

The appropriate use of scaling and logistics can also improve the efficiency of the translational pathway, Liu said. He explained that the process of translating scientific discoveries to clinical practice can be accelerated by scaling. Genomic technologies were the first examples of what he referred to as a "mature research infrastructure," in which time-consuming technical and logistical tasks were replaced by automated or simplified ones so that more time could be spent on higher-order science. "We have never in this field seen this kind of efficiency in the tool sets that we have provided," said Liu. "This is a whole new mindset—which, by the way, engineers and physicists have [had] for the last 100 years: the ability to scale with orders of magnitude in terms of efficiency." For example, restriction nucleases are now readily available commercially and are inexpensive and ready to use, whereas 20 or 30 years ago, scientists needed to prepare their own. This has provided opportunities to expand science from production of a single item to production by use of the assembly line process, he said.

Logistics can also significantly shorten the length of time from discovery to clinical use of a drug because existing drugs may have uses for other indications. Many of the components in the translational pathway are already in existence, so once they are identified, it is just a matter of assembling the product. Liu used the analogy of computer parts being manufactured in different locations and then assembled together in one place to describe the increased efficiency that has started to occur in research. With improved technology and the appropriate use of scaling and logistics, a single investigator can conduct much of the work, Liu said.

In summary, Liu described that it took 41 years from the time of the genetic discovery in 1960 linking the Philadelphia chromosome as a marker for chronic myelogenous leukemia before imatinib (Gleevec) was developed and approved for patient use by the U.S. Food and Drug Administration (FDA) (Capdeville et al., 2002). In contrast, the more recent discovery of the kinase-activating gene fusion *EML-ALK* in a lung cancer patient resulted in the 2011 FDA approval of crizotinib (Xalkori), a process that

took just 4 years (Gandhi and Janne, 2012). The challenge now is to take advantage of a mature infrastructure and the increasing scale of the enterprise to advance the progress of basic scientific research, said Liu.

GENOMICS AND PERSONALIZED CANCER TREATMENT

Only some of what is called "basic research" is truly that, meaning that it is an interesting story but does not relate to a translational pathway, Huntsman said. True translational medicine requires that specific clinical questions and translational pathways be identified, but the current health care system is not prepared for the translational initiatives that Liu mentioned earlier, Huntsman said. "Once you start mentioning a disease and you have a focus on the disease . . . at that point the health care needs you are trying to address would have to be defined and a translational pathway predetermined." However, Huntsman cautioned that the power of collective research efforts can sometimes be weakened when those conducting basic scientific research are forced to decide up front how their research will be clinically relevant, said Huntsman.

In referring to the health care system in British Columbia, Huntsman pointed out that the structure focuses on answering questions of cost-effectiveness, treatment effectiveness, and the quality of the patient and clinician experience. Without collective efforts, the delivery of equitable personalized health care in this system will be a challenge, which is a reason why cancer makes a good model for personalized medicine, as it is a disease consisting of the interplay between two genomes—that of the host and that of the tumor, Huntsman noted.

Cancer can be considered three different diseases because of its characteristics: some cancers involve many different events such that thousands of cases may need to be examined to understand the drivers involved; other cancers are more monomorphic and have single mutations driving the disease; and finally, some cancers are in between these two states and contain multiple mutated pathways, Huntsman explained. These different disease pathways necessitate the use of different approaches to translate related discoveries in basic science into the clinic. A given type of cancer may have several different subtypes for which driver pathways, prognoses, and potential treatments are distinct. These attributes of disease emphasize the importance of defining the questions to be answered when a translational research program is devised.

Cancer: A Model for a Stratified Approach

A major goal of the translation process in cancer is to move from generic management, which does not account for tumor heterogeneity,

toward more individualized or stratified cancer treatments. Successes have been achieved to date, but many of the available approaches are still too crude for use in practice. Cancer stratification can be defined by molecular features, but a critical question is how to group tumors for treatment. One approach to address this issue would be to categorize tumors into "finer and finer groups," Huntsman said. He gave the example of a mucinous carcinoma of the ovary, which represents about 4 percent of ovarian tumors, but close to 20 percent of mucinous carcinomas have a *HER2* gene amplification, for which a targeted therapy, trastuzumab, exists (Anglesio et al., 2013; McAlpine et al., 2009).

The challenge with finely stratified disease is that it makes it difficult to get enough patients to conduct clinical trials of treatments, Huntsman stated. A potential way to identify larger numbers of patients to facilitate clinical trials may be through social networking, but this has not yet been proven, Huntsman said.

Another approach used to categorize tumors, Huntsman explained, is to stratify cancer by molecular features that are shared among particular types of cancer (NRC, 2011). This stratification approach would enable the construction of a "molecular taxonomy of cancers that moves beyond subtype," but it does not take into account three key features of cancer: heterogeneity within tumors, the activation status of mutations, and cell context, Huntsman said.

Genomic heterogeneity is particularly worrisome, Huntsman said. A one-time single sampling of a cancer may not reveal the biomarkers needed to determine treatment because the molecular signature of the tumor may change over time. A mutation critical in the early development of cancer may no longer be active, or mutations that are invariably active in one cancer type may no longer be active in another. One way to identify active mutations is to use existing bioinformatics tools to understand how mutations disrupt networks and then create lists of common and active mutations. Cell context is also important: a melanoma and a colon tumor with the same mutation may not have the same response to one targeted therapy. "We can't just blindly move ahead with treating mutations and not cancer," Huntsman said. Importantly, the system is lacking appropriate models that accurately reflect disease. For example, cell lines need to be carefully chosen for use in experiments to validate findings in a disease context that makes the most sense.

Many of the same questions surround the treatment of relapsed disease, Huntsman said. Treatment decisions need to be revisited over time as tumors change. Average samplings over time to detect circulating tumor mutations that are free in the plasma may be one way to approach this.

Today, there are often too many data for effective on-the-fly integration in the clinic, but better integration will be possible as genomics and

bioinformatics become common decision support tools. In particular, care communities could reformulate themselves around high-content medicine and an informatics backbone. Those that do so, especially in general practice, will embrace a future that will encourage others to do the same, Huntsman said. He said that he looks forward to a time when instead of working as a pathologist and diagnostician he will work on an integrated team with other diagnostic specialists, including informaticians, to collaboratively interpret data and make decisions.

IMPLEMENTING CHANGE FOR THE FUTURE

Liu made several projections for the future of genomic medicine. The genomes of all children with developmental disorders will be sequenced, he said, and all cancers will be sequenced. Medical analytics in a secure environment with honest brokers will be important not only to drive efficiency but also as a revenue generator for biotechnology companies. Such efforts will improve the effectiveness of delivery of health care by creating better outcomes at reduced costs. Progress will be iterative, he said, with each step forward built on the basis of experience and new knowledge.

The most impactful space to begin making changes that would improve the translational pathway would be in general practitioners' offices, Huntsman suggested. In this way, the focus would be on the patient–caregiver interaction, and this interaction would have more of an impact on improving patient care decisions than a meeting with a specialist for treatment of, for example, an advanced-stage cancer would. Academic clinicians would be an important group to ask which challenges within the translational pathway are crucial to work on.

Liu and Huntsman both addressed where the research and clinical care communities could begin to implement systemwide changes that would have significant impacts on the translation of basic genome science into the clinic. Liu noted that hospital systems would be a good starting point, because the inefficiency of translation could be considered an issue of competitiveness in a challenging economy and innovation could be used as a cost-lowering tool. The important stakeholders for discussions of this would be the health insurers and the genomics scientists. Liu said that having access to the wealth of data from insurers on survival data from patients with subsets of cancer, for example, would be very helpful. The Jackson Laboratory, he explained, is working with Aetna to develop a model of outcomes and cost reduction for its 1,400 employees. Huntsman mentioned the importance of working with the community in new ways to improve the health of medically underserved populations. He discussed that the Ministry of Health in Canada is interested in the health of the country's First Nation populations, whose health lags behind that of the majority population.

Time, cost, and information deficits will continue to be challenges to establishment of an improved pathway of translation. Data sharing would alleviate some of these constraints, said William Rutter, chair and founder of Synergenics and session moderator. The President's Council of Advisors on Science and Technology *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation* would help provide a strategy for the coupling of transparency in data sharing with regulatory approval (PCAST, 2012). "Both speakers have articulated a need for systematic change, systemic reform [of the translational research pathway]. . . . [The] confluence of information provides the basis for change, and the cost issues demand it," Rutter summarized.

3

Moving Basic Science Forward

Important Points Highlighted by Individual Speakers

- Online resources, including data, research services, and biological specimen repositories, provide a wealth of largely untapped existing information that is publicly available and that could be used to accelerate discovery and development.
- Provision of incentives for sharing of all publicly funded data could maximize the full potential of existing data.
- Open data sharing needs to be enforced by funding agencies and scientific journals for meaningful change to occur.
- Alignment of research goals with academic incentives is needed to foster cross-discipline collaboration, training, and innovation and to provide a focus on outcomes that bring value to society.
- The use of a systems biology approach to study complex diseases would allow the integration of multiple levels of genetic and phenotypic data and more rapid and extensive hypothesis testing.

An effective way to move the translation of genomic science forward is to change the culture through the more complete integration of systems biology approaches and open sharing of data and resources. Atul Butte, chief of the Division of Systems Medicine at the Center for Pediatric Bioinformatics of Stanford University, described the wealth of tools that are

already available online and the ways in which those tools are changing the conduct of research and the training of researchers. Daniel Geschwind, Gordon and Virginia MacDonald Distinguished Chair in Human Genetics and professor of neurology and psychiatry at the University of California, Los Angeles (UCLA), School of Medicine, used autism research as an example of the potential of the systems biology approach to be used to study a complex issue in neuroscience in which the use of cross-disciplinary tools could yield more rapid progress.

DISCOVERING NEW DRUGS AND DIAGNOSTICS FROM 300 BILLION POINTS OF DATA

As an example of the power of modern technologies, Butte showed the audience an Affymetrix gene chip, an example of technology the size of a thumbnail that can quantitate the expression of every gene in the genome. This invention, which has been around for 15 years, is now commonly used by laboratories at universities and academic medical centers, and such chips have become commodity items in academic research.

In August 2012, more than 1 million gene expression datasets were available to the public, and that number is rapidly increasing (Baker, 2012). Since the early 2000s, journals have been requiring that the data from gene expression studies that they publish be deposited into publicly accessible international repositories for others to use, "and to me that is the most enabling thing in the world," said Butte.

Making Data and Resources Available

Anyone can now download microarray datasets and conduct original research by using the contents. "A high school kid can do this," Butte said. Researchers can now have access to 20,000, 30,000, or 40,000 samples of any cancer or any disease that they want. This collection of open data contains more breast cancer samples, for example, than any breast cancer researcher will ever have in his or her lab, Butte said.

Furthermore, the number of available datasets is continually expanding, encompassing not just basic research data but clinical data and data of direct relevance to industry. "It's just sitting there waiting for people to exploit it," he said. For example, the Framingham Heart Study, a longitudinal study started in 1948 by the National Heart, Lung, and Blood Institute and Boston University, has collected thousands of genotypes and years of clinical and research data that are openly available for downloading. ImmPort is another resource that contains an archive of genomic, proteomic, and immunological data from research supported by the Division of Allergy, Immunology, and Transplantation of the National Institute of Allergy and Infectious Diseases.

In addition to datasets available on the Internet, Butte discussed other resources. For example, contract research organizations (CROs) provide a variety of both basic and clinical research services. As one example, Butte described a website called AssayDepot.com, which bills itself as the "marketplace for pharmaceutical research services" by providing drug testing in a wide variety of mouse models. For $9,000, a CRO accessed through AssayDepot can run a test of a diabetes drug for 28 days in 16 mice from The Jackson Laboratory, divided into treatment cohorts. The CRO will also perform fasting blood sugar, insulin tolerance, and glucose tolerance tests in a blinded format. Butte acknowledged that researchers have concerns over assuring the quality from experiments purchased from these organizations. He said that because companies all over the world are providing such services, results can be independently verified in replicate experiments ordered from independent labs. Running the actual validation experiment is "not a rate-limiting step anymore," Butte explains, but is only a matter of funding to complete these experiments. For example, instead of researchers arranging for the transfer of mice from one institution to another and then waiting for the mice to breed, "why not just pay [the original lab] to do the experiment because they have the mice already?" Furthermore, Butte said that private companies can often send researchers biological specimens much faster than academic institutions can prepare them for study; he regularly orders tissue and sera samples from privately run banks. It is not just about making the data available, but it is also the resources, he said.

Burke inquired about validation problems that may arise when using an outsourcing model for experiments. Butte acknowledged that there is no one lab that will have the expertise in using every mouse model but that these organizations will have experience with the more common experiments and techniques. If a specialized technique is needed, that is when it may be more appropriate to collaborate with other academic labs to complete the experiments, he said.

Biomedical research has been slow to take advantage of the services available today, but that is changing, said Butte. Today, the production of clinical and molecular data, the application of statistical and computational methods, and the validation of a drug or biomarkers are all commodity services. "I'm just waiting for the next Genentech to start in a garage, [or] the next Merck or Pfizer to start in a dorm room," Butte said, because with a credit card you have 1 million microarrays and every possible mouse model in your garage today.

Cross-Disciplinary Collaborations

The only item that cannot be outsourced, said Butte, is a good question, and formulation of these questions requires an understanding of unmet

medical needs. In this regard, it is crucial to encourage collaborations among groups that would not otherwise be connected. Computational experts as well as clinicians and patients, for example, are all needed to devise an appropriate approach to solving specific problems. Effective cross-disciplinary conversations could be incentivized through late-stage training grants, Butte said.

Accelerating Drug Development with Available Tools

To demonstrate the point that new discoveries can be made with existing, publicly available data and resources that are ready to go, Butte described projects that he and his colleagues have been pursuing in their laboratory at Stanford. The first one involves type 2 diabetes, which affects between 90 and 95 percent of the almost 19 million people diagnosed with diabetes in the United States; the estimated total medical costs for those with diabetes in the United States is $174 billion (CDC, 2011). Although many drugs are available to improve insulin response and regulation, more effective drugs are needed, said Butte.

In their study of diabetes, Butte and his colleagues identified the top differentially expressed genes that are associated with diabetes by comparing genome-wide association studies from 130 publicly available independent experiments (Kodama et al., 2012). For example, after comparison of the expression of RNA in tissue from nondiabetic and diabetic patients through the use of existing, available data, the expression of a cell surface inflammatory receptor, *CD44*, was found to be differentially expressed more than any other gene in these types of experiments. Butte's group then examined *CD44* expression levels in healthy wild-type mice of the C57BL/6J strain, which are known to become obese and develop insulin resistance when fed high-fat diets. Butte's group found that *CD44* expression levels were increased in the group of mice fed a high-fat diet (obese) compared with the levels in the group fed a normal-fat diet. Specifically, *CD44* expression was increased in the inflammatory infiltrate in the adipose tissue of the obese mice. Next, Butte and his colleagues obtained a commercially available mouse strain in which the *CD44* gene was deleted ($CD44^{-/-}$ mice). This strain was developed more than a decade ago but had not yet been tested for glucose levels, he said. Experiments determined that $CD44^{-/-}$ mice had greater sensitivity to insulin than wild-type mice and did not die from diabetes. Use of commercially available CD44-blocking antibodies by Butte and his team in wild-type mice fed a high-fat diet (obese) lowered their blood sugar levels.

The CD44 protein makes an attractive therapeutic target because it is abundant in adipose tissue, which is readily available for study. Furthermore, CD44 can be cleaved from the cell surface and shed into blood in its

soluble form, making it easy to measure. Identification of a new therapeutic target for type 2 diabetes "took us about 18 months of work, starting from the same data any high school kid can get today," said Butte. "All those [data] are sitting there. Everyone devalues them. Because they're on the Internet, that must mean they're not valuable. But it's all of our excellent peer investigators putting [those] data out there."

The development of drugs by these new approaches can be much faster than traditional approaches. For example, Butte described a drug that can "melt away" lung cancer tumors that went from computational prediction to use in humans in just 15 months. "I'm a huge optimist that we can do this, but it means [developing] a new set of skills [and] not just finding people who can generate more and more data to get higher and higher resolution but . . . [taking] advantage of the data we've been so great at generating." This approach could be very widely applied, Butte remarked. "I'm giving my secrets away here. I want more people to be able to do this. This is how to scale, so you get more people interested."

Butte imparted several lessons from his drug discovery strategy. First, he indicated that public molecular data have incredible utility. For this reason, all data from publicly funded research should eventually become publicly available and secondary uses of the data and the development of computational approaches need to be encouraged and funded. Second, enough high-quality data that can have a major impact on medicine already exist. He suggested that the data do not need to be perfect because a requirement for perfection can slow the deposition of data.

Butte also pointed out that funding may need to be provided explicitly for the generation and public release of data; along with funding for mice and equipment, specific funding should be designated for data sharing. "We should have a [budget line item] there for data sharing; make sure it's funded, so that there are no excuses. You can't say you didn't get enough money to put [those data] out there in the repositories," Butte said. Fund the sharing of those data, he indicated.

He also mentioned that the infrastructure for data reuse needs to be not just developed but also used so that others can learn how the data can be put to good use. Furthermore, Butte said, "sticks seem to work better than carrots" for catalyzing change; funders and journals need to enforce data sharing to change the culture of the research enterprise.

Lastly, Butte emphasized the importance of training of students of all ages since researchers and clinicians are all lifelong students. He indicated that training is the best way for scaling to have an impact. To emphasize this point, he described a program at Stanford University called SPARK that helps academicians move research innovations from the bench to the bedside by educating faculty members, postdoctoral fellows, and graduate students about the translational research process so that the development

of promising discoveries becomes second nature. Student involvement in innovation and entrepreneurship is the best way to scale up innovations, said Butte. "You want this to change the world? . . . You've got to get more of the younger folks involved."

LESSONS FOR TRANSLATION FROM AUTISM RESEARCH

The process of translation from discovery to therapeutics often occurs along a linear path in multiple laboratories, with relatively weak connections existing among institutions. A better approach, said Geschwind, would be to incorporate a multidisciplinary systems biology approach in which different activities can inform each other. Multiple levels of genetic and phenotypic data could be integrated to yield more rapid and extensive progress.

Using autism as an example, Geschwind illustrated this integrated approach. Autism spectrum disorder (ASD) is a complex neuropsychiatric condition that includes overlapping phenotypes, including social communication deficits, language deficits, restrictive or repetitive behaviors, anxiety or attention deficit-hyperactivity disorder, and other medical comorbidities. In some cases it is caused by rare single nucleotide variants or copy number variations. In other cases, a mixture of common and rare genetic variants with different effect sizes seems to be involved. "Genetic variants accounting for 20 percent of ASD risk have been identified, and most of these are de novo genetic variants," Geschwind said (Abrahams and Geschwind, 2008). Environmental factors are likely to be involved as well, though the influence of these factors is largely unknown. Genetic variants have been studied in the human brain and in animal models to understand dysfunction at the level of brain circuits, synapses, cells, and behaviors; and several new pharmacological treatments are in early trials. "It's a classically complex genetic problem," said Geschwind.

In the late 1990s, Geschwind helped set up the Autism Genetic Resource Exchange (AGRE), which now includes more than 10,000 DNA samples and data from more than 1,500 families, including clinical data that have been extensively validated, which ensures that the data are of high quality. AGRE is an open resource shared with the scientific community, and the exchange has greatly accelerated the pace of sample collection and research, contributing to more than 200 publications since 2001. "Many of the major findings aren't from my lab," said Geschwind. "They're from people who had different ideas than we did, and they . . . were better than our ideas."

The quality of the data is an important consideration, according to Geschwind. The data in databases need to be validated to be used with confidence. Also, bigger is not necessarily better. "There has to be some thought put into what's going to be in the data."

The data from AGRE have helped reveal an autism locus on almost every human chromosome, demonstrating the heterogeneity of this syndrome (Abrahams and Geschwind, 2008). Exome sequencing studies using the Simons Simplex Collection of data for families with one autistic child and unaffected parents and siblings have also revealed many hundreds of de novo mutations that contribute to autism with various effect sizes (Iossifov et al., 2012; O'Roak et al., 2012; Sanders et al., 2012). No single mutation accounts for more than 1 percent of cases, and many mutations have reduced penetrance. In addition, most of the mutations with large effect sizes are associated with other things as well, such as schizophrenia, intellectual disability, developmental delay, or learning disability. These results should not be surprising, Geschwind said, but they emphasize the fact that diagnostic categories are not very helpful in identifying genes involved in ASD.

Stratification of Disease by Genotype

The association of genetic factors with specific, measurable components of each disease, such as language and social behavior, called "endophenotypes," will be stronger than the clinical diagnosis alone. To be most useful for genetic analysis, endophenotypes should be associated with the disease, heritable, relatively stable, identified in first-degree relatives more than the general population, and quantifiable. For example, a gene might be involved in social cognition, working memory, or implicit learning, "psychological constructs that are much more elemental than the broad diagnostic category of autism," Geschwind said.

In neuroscience, functional imaging can be used to study the genetic variant as a biomarker or endophenotype related to the disorder because variants are not disease specific. In this way, personalized medicine can reduce heterogeneity by stratifying disease by genotype, said Geschwind, though so far this has not been a focus of translational research.

Geschwind described a mouse model of autism as an example of such research. Studies of the complex social behavior of mice in the mid-2000s discovered that mice communicate with ultrasonic vocalizations (Holy and Guo, 2005). This information was used to study mice with a knockout of the gene, contactin-associated protein-like 2 (*CNTNAP2*), which is associated with an increased risk of ASD in humans; *CNTNAP2* mutations are associated with autism in roughly 70 percent of patients with this variant. These patients also have reduced communication, reduced sociability, increased repetitive behaviors, and increased hyperactivity. Furthermore, mice treated with oxytocin as a prosocial promoter therapy showed fewer effects, suggesting that the mouse model has predictive value and can be studied further to understand the mechanism of action of the drug and as a screening tool for other potential therapies, Geschwind said.

Key Approaches for Studies in Neuroscience

Network biology can provide an integrated view of the core drivers of ASD, Geschwind said. The functional relationships of several thousand genes can be reduced to groups of coexpressed gene modules that correspond to key elements of biological function. Within modules, the most central "hub" genes can be identified, and the network structure serves as the basis for making experimental predictions, testing causal and regulatory relationships, and integrating large sets of data with other sets of data.

An understanding of the multiple levels of disease-associated dysfunction that lead to abnormal behavior and cognition calls for systems biology approaches that are multidisciplinary and collaborative and that allow more rapid hypothesis testing, Geschwind said. A fundamental question is whether a therapy developed for one form of autism is relevant for another. "Are we talking about a thousand different drugs that we need, or can we coalesce this into 10 or 20 different pathways?" More genetic information will be needed to answer such questions, he said.

Because patients with brain disease cannot contribute tissue for diagnosis or research, live imaging studies and mouse studies can provide mechanistic insights, but these insights typically do not extend to the development of drugs. These limitations are why human-induced pluripotent stem cell–derived neurons may provide a way to study developmental function and may guide studies in mice for the development of therapies, said Geschwind.

Electronic Medical Record–Based Genomics

Genetic and phenotypic heterogeneity requires large numbers of samples to be examined to pinpoint the genetic variation. Etiological overlap means that studies will need to extend across disorders and measure appropriate phenotypes, which will be greatly furthered by the use of electronic medical records (EMRs) for storing data that could be used for research. "I think the future is in EMR-based genetics," Geschwind said. UCLA already does exome sequencing as a clinical test, and soon it will do genomic sequencing on many of its patients and certainly those patients in neurology. The data will be put into EMRs, and if the data are good enough, they can be used for research. "We'll have the millions of people that we need instead of the 10,000 [whose genomes] I can sequence in my lab or with a group of labs."

CHANGING THE RESEARCH CULTURE

Both speakers commented on the need for a culture change in the biomedical research field for the field to move forward with the successful

translation of basic science. In addition to increases in communication and collaboration across silos, Geschwind noted that the creation of different types of incentives for achieving goals that are focused on understanding disease is also needed to make progress. At present, a main goal of a researcher is to achieve academic tenure by publishing papers, but this is not the appropriate reward-based system needed to improve the translation of scientific discoveries to the clinic. "If your goal is to solve disease, those are the wrong incentives—papers don't solve diseases."

Furthermore, competitive academic institutions provide few incentives to collaborate because of the competitive nature of achieving a tenured position. He pointed out that clear, socially responsible goals would help align incentives. A workshop participant commented that the current tenured generation of scientists can be empowered to set different incentives but will need to accept the fact that these incentives are different from those that they were accustomed to in the past.

Butte mentioned that a career in the biomedical sciences may attract future generations of scientists if potential scientists see that the establishment is changing to become more collaborative, innovative, and open to change. Members of the younger generation are likely to choose a career path that they perceive to be more entrepreneurial. If scientists work together to embrace innovation, that might change the perception of the field. "To get to big science, we're going to need team science," he said.

4

Industry and Venture Capital

Important Points Highlighted by Individual Speakers

- The creation of more certainty and predictability within the translational research pathway would make investment in this sector more desirable.
- Adjustment of the health care ecosystem to account for advances in technological innovations could improve the translational pathway through reductions in bottlenecks to product development in the later stages of the process.
- Obstacles to translation could be reduced by leveraging of new technologies, opportunities afforded by globalization, regulatory reform, and alternative research models.
- A successful business model for the translation of the findings of basic research to personalized medicine requires that patients be put first through the creation of well-designed clinical questions and the generation of sound clinical data for clinicians and payers.
- A shift in investments from pharmaceutical development to preventive diagnostics would result in a more efficient drug development process because it would provide cost-saving measures for care and new knowledge about disease.
- Patients who own and control their genomic data will benefit from data sharing, lessening the need for sharing of enforcement strategies.

The successful translation of biological discoveries into commercial applications depends on a partnership with industry. Geoffrey Duyk, partner and managing director of TPG Biotech, explained why venture capitalists have been reducing their investments in biomedical companies that are developing products for which the risk is uncertain. He also outlined opportunities for overcoming barriers to the commercialization of research discoveries. Randy Scott, chair and chief executive officer of InVitae, described innovative business models that provide new ways to translate discoveries in basic science to personalized medicine.

THE HIGH COST OF UNCERTAINTY FOR VENTURE CAPITAL

Over the past decade, venture capital has been the "worst returning subsection within private equity," said Duyk. One of the reasons for its poor performance may be that the development of a new product costs more and takes longer than it did in the past. As a result, even if the product is successful, the return on investment is less than it was a decade ago. "It's no surprise that capital is leaving the market," Duyk said.

Duyk and other investors have been rethinking how they invest money in health care. Spending on health care as a percentage of the gross domestic product (GDP) is much higher for the United States than for any other industrialized country, yet health outcomes in the United States are in many ways worse (see Figure 4-1). Improvement of the cost-effectiveness of the system therefore provides a potential opportunity. Duyk mentioned the inefficiencies in the health care system, including the problem of the nonalignment of incentives in medicine, in which treatment of a patient for diabetes prevention today will not produce its full return to the health care system for decades. "This is an area where there needs to be scholarship. . . . We have to figure out an economic model to align incentives so you can deal with preventive care," Duyk said.

Many obstacles to bringing a product to market exist, and most of those obstacles are not technological, Duyk said. "I worry less about technological problems because I have more confidence in the ability of the system to solve them. I worry more about the [uncertainty from] the regulators, the public and financial markets, and the reimbursement," Duyk said. Duyk also recounted the central problem that others mentioned earlier in the workshop, that the translational pathway has challenges because "the early stages of research have become faster, better, and cheaper, but everything else downstream has not really caught up . . . and unless we make concomitant investments in these areas, what we're doing is accelerating ourselves to a bottleneck," said Duyk. These uncertainties have "a huge impact on the cost of doing business," he said. If preclinical processes were more predictable, drugs could fail faster and with fewer costs. This

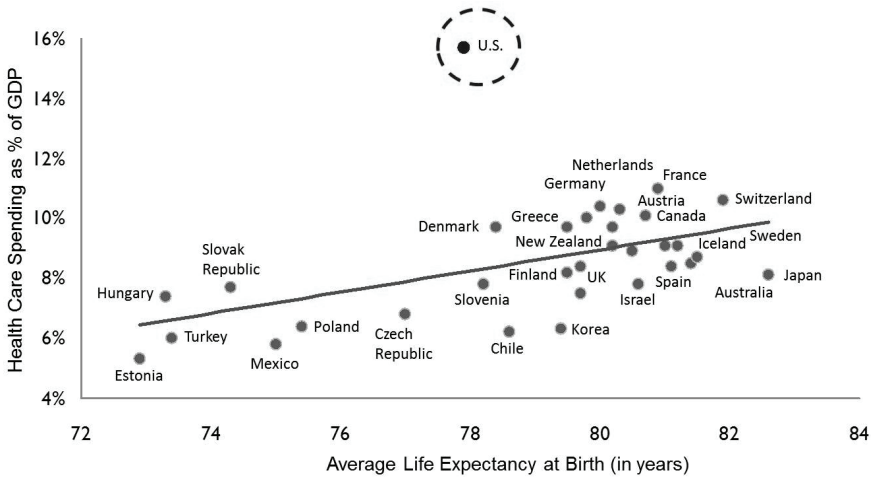

FIGURE 4-1 Health care spending as a percent of GDP by country.
SOURCE: Data from the Organisation for Economic Co-operation and Development, 2007 (http://www.oecd.org/els/health-systems/oecdhealthdata2013-frequentlyrequesteddata.htm [accessed October 3, 2013]).

predictability would then propagate through the rest of the system, bringing greater clarity to regulation, reimbursement, and health care delivery.

Duyk demonstrated the impact that uncertainty can have on investment by explaining a scenario from the work of Gneezy and colleagues (Gneezy et al., 2006). The average price that someone would pay to purchase a $50 gift certificate from a friend is $26. Similarly, someone would pay $45 for a $100 gift certificate, or about 50 percent of the original purchase price, Duyk noted. However, when uncertainty is introduced into the circumstance and the buyer knows only that the gift certificate is worth either $50 or $100 but not which amount specifically, he or she is willing to wager only $16. In this case, the risk is overvalued, resulting in an undervalued product. "Anything we can do to create certainty and predictability in translational research has enormous economic impact, [so] I wouldn't underestimate [value] in the system," Duyk said.

To improve the translational pathway, the entire translational research ecosystem needs to be considered, he said, explaining that all the parts need to be taken into account, just like a car needs to be cared for: it needs fuel, tires, and insurance so that it functions properly. The challenge is that the entire ecosystem needs to change around new technologies, such as genomics. "Sometimes, the technologies induce the change. Other times, you, as an innovator, have to figure out how . . . to allow change to occur."

However, changing the ecosystem in health care is a significant hurdle because health care is a big business and many external forces affect the system by creating costs and obstacles to progress, Duyk said. The health care system is highly regulated, structured, and paternalistic, which has an enormous impact on making investment decisions. Health care is enabled by technology, but the technology is associated with high cost and risk. The status quo is not sustainable, and fundamental change may require structural change, he said.

Suggestions for Changing the Current Dynamics

Duyk described a range of opportunities that would begin to change the health care ecosystem to adjust for new technologies. Today, the areas in medicine that are some of the most innovative are those in which consumers provide most of the capital, such as laser vision correction surgery, cosmetic surgery, and in vitro fertilization. In the past, most economic decisions were made by physicians, whereas today most decisions may be influenced by reimbursement policies. Duyk suggested that in the future, more decisions and more capital will be derived from the consumer, and as more opportunities arise to empower patients as consumers, patients will expect more data and more transparency when they are responsible for more of the costs, said Duyk. This consumer demand can "force change and give you a place of market entry," he said.

Mobile communications and cloud computing are other areas in which a market trend presents an opportunity for innovations in health care. Interconnected devices are creating vast stores of information about individuals, and new devices could monitor a wide range of health-related indicators and relay information to consumers, said Duyk.

The way in which people are thinking about privacy concerns and patient data is also changing. Privacy is a major issue, Duyk acknowledged; however, younger and older generations seem to have different perspectives about privacy concerns. Once a consumer can acquire his or her DNA sequence for a few hundred dollars, the dynamic between the holder of that information and the potential uses of that information will fundamentally change. More research is needed to address privacy issues, but "if we don't adjust the system to reflect new norms of privacy, then the system will adjust," Duyk said.

Globalization represents another opportunity to explore different types of health care systems, said Duyk, because the demand from emerging markets drives the growth of industry. Although the U.S. health care system is well established and the costs of making changes to this system are high, new types of health care solutions will be appealing in countries where the

GDP is rising rapidly. This trend is already occurring as demands from growing global markets have driven the development of the pharmaceutical industry. Duyk indicated that knowledge-based health care systems, such as those in the United States, are less scalable, but rule-based or evidence-based systems are more conducive to scaling, as exemplified by the cost-effectiveness of AIDS treatment in Africa.

Already, drug development increasingly occurs outside of the United States where regulatory agencies are more cooperative and collaborative, such as the biosimilars market, said Duyk. Other countries are improving their regulatory systems, and some drugs are now being approved elsewhere as a result. Investments need to be made in FDA, which is "underfunded and understaffed," Duyk said. Rethinking a regulatory agency from the ground up is very difficult, he admitted, but time and effort need to be devoted to the task. One approach may be to restructure one of the divisions of FDA and use that as an example to spread reform through the rest of the agency. A workshop participant pointed out that FDA is preparing to handle genomics data and noted that similar regulatory systems around the world are not structured in the same way. Because genomic data are imperfect, for example, an error rate of even only 0.001 percent yields 3 million errors per haploid genome sequence, so the validation and qualification of the information are important.

Alternative research models and centers are also needed, said Duyk. "I honestly think we're not going to fix translational research in the halls of a traditional university," he said. Models such as the Massachusetts Institute of Technology Media Lab of the Center for Bits and Atoms, and the Santa Fe Institute demonstrate how to create different environments in which translational research can thrive.

Crowd sourcing also makes it possible to tap into the power of communities. "There are a lot of very smart people out there. If you give them access to data, they are going to figure things out." Duyk went on to highlight a crowd-sourcing example from a game called Foldit, which originated at the University of Washington in Seattle. Essentially, a protein-folding problem was fashioned into a game whereby, while a person was playing it, competitive solutions for protein folding were simultaneously developed. "So what I would advocate is thinking about these out-of-the-box . . . ways of approaching education," Duyk said. Students want to work on bioinformatics problems, Duyk insisted, but they are not aware of the problems that exist or of the rewards to be gained by solving those problems. "I don't think that there is a deficit [of] people who want to work on these problems. I think there is a mismatch in our ability to teach them [that] those problems exist, and the tools aren't readily available," Duyk said.

A MODEL FOR TRANSLATIONAL MEDICINE IN GENOMICS

"I am an unashamed, unabashed optimist for the future of translational medicine," Scott said. The next decade will bring tremendous technological and commercial progress, he suggested. He described how Genomic Health has built a model for translating science into personalized medicine on the basis of the success that it achieved when it brought the multigene, multianalyte Oncotype DX® test to the market to help breast cancer patients and their physicians make treatment decisions.

As stated by other speakers, Scott said, success begins with asking not just interesting scientific questions but also the right clinical question, and that requires listening to physicians and their patients. Bringing translational medicine to clinical practice is feasible, but "it's really hard, it's really painful, it costs a lot of money, and it's not nearly as easy as we all hoped it would be a decade ago." Cancer patients have always been at the center of Genomic Health's business model, and "we fundamentally believe that if we do great things for patients that are really transformational in that patient-physician conversation and drive the way those patients are going to be treated, we'll find a way to get that paid for," Scott said, "Focus on your customers."

Scott discussed how Genomic Health designed its model for product development. "You really need to go sit down with a physician and [his or her] patient and listen to that conversation because that's the conversation that you have to affect," he said. Once the right clinical questions are identified, Genomic Health focuses on high-quality, well-controlled clinical trial data, combined with sound statistical analysis and algorithm development, along with attention to other methodological details. Working closely with physicians is critical, because "you can't go anywhere in health care unless you get the physicians on board." Physicians will make the right decisions for their patients, if they are provided with strong data, Scott said. How physicians view the importance of what is accomplished for their patients matters more than the exact economics, he said.

Genomic Health is seeing successes in translational medicine because it is focused on providing sound clinical data. In theory, Oncotype DX® should have been very attractive to payers because it lowers the cost of cancer care by providing cost-saving information about whether chemotherapy will be useful, but the reason payers supported the test in the end was because it was backed by good clinical data and had the support of physicians, said Scott. By using this model of asking the right clinical questions, Genomic Health now has a similar test for colon cancer, and a test for prostate cancer is under development, said Scott.

The reason for the lack of success in diagnostics development is that the United States is currently underinvesting in this area, Scott said. Devel-

opment of a new drug typically takes more than a decade, costs more than $1 billion, and has an 80 to 90 percent failure rate, he said. In contrast, development of a new diagnostic typically takes 3 to 4 years, costs $100 million to $200 million (when retrospective samples from completed clinical trials are used), and has a success rate close to 90 percent. The diagnostics model is "a much better business model. What if we stopped spending 50 billion or 100 billion dollars a year on research and development of the drugs for diseases we don't understand and spent 10 billion to 20 billion dollars on understanding the disease so we can make that drug development more efficient?" asked Scott.

Change is occurring in the global payment market for diagnostic tests, Scott noted. Regions where health care is not covered—in South America and in parts of Europe and Asia—patients have incentives to spend $3,000 on a test that would provide more information about the chance that they should take on chemotherapy that could cost $20,000, Scott said. "This really will become a global economy as the costs come down very fast."

Technology can be a solution when financing for the development of diagnostic tests is difficult to obtain because of increases in capital costs and hesitance on the part of investors to take risks that they may have been willing to take a few years ago, Scott said. "The cost of DNA sequencing is coming down rapidly and so rapidly that it's having a dramatic shift in how we think of the cost of genetic information," Scott said. The continued development of technologies will make it easier to finance diagnostics companies in the future, he said.

The exponentially declining cost of genome sequencing will have the same transformative effect on translational medicine that the exponentially increasing power of computing has had on digital technologies. Within 10 years, the cost of a complete genome sequence will be less than the price of a single genetic test today. Furthermore, the value of a single genome sequence is much less than the value of many genome sequences, just as the value of a single computer is dwarfed by the power of computers interconnected through the Internet. "Disruption is going to come very, very fast in this field. In fact, it's going to be almost unstoppable, and we should start preparing for when that disruption comes," Scott said.

A New Business Model

Scott said that he had recently joined a new company named InVitae that has the goal of "aggregating all the world's genetic tests into a single assay with better quality and lower cost than [those of] most single gene assays today." Within a few years, the comprehensive test will be able to look at all known Mendelian inherited genetic traits at a low cost. The company believes that genetic testing should be broadly available to everyone.

The price of genetic testing therefore needs to be consumer friendly, and the test needs to be globally available. "There's no country in the world that's going to be able to simply close the walls and say, 'no, our population can't have access to genetic information.' . . . This will become a global economy, especially as the costs come down."

The company also embraces the idea that data should be freely available; patients should have ownership and control over their data, and data should be shared so that others can learn from the data. "As we like to say at InVitae, we don't patent the genes; we set them free. We believe very strongly that patients should own and control their own genetic information, that they should have access to the information, and they should have the rights to determine how it is used. And if that means not at all, that's fine." Data sharing will eventually become part of the medical system, he said. Scott continued, saying that he is not in agreement with the enforcement model of data sharing. It is not needed once people begin to see the incentives and value in sharing their data, as occurred with social media. "I'm fine if [developers] don't want to share their data. . . . I just think it is going to be bad business 10 years from now," said Scott.

5

Role of Advocacy in Facilitating Translation of Basic Scientific Research

Important Points Highlighted by Individual Speakers

- Patient advocacy organizations are uniquely positioned to help convene stakeholders involved in the biomedical research ecosystem to prioritize goals that improve patient outcomes.
- Advocacy groups have identified innovative ways to work with academia and the private sector by encouraging them to embrace novel models for risk sharing.
- Foundations partner with other organizations to promote networks that share and accelerate the identification of treatments for patients.
- Advocacy groups are willing to bear more of the risk on innovative projects to advance early development and generate information that will attract larger funders for the next phase.

The ability to translate research results into outcomes for patients is urgently needed, and patient advocacy groups play a significant role in translating discoveries into patient treatments. Pat Furlong, founding president and chief executive officer of Parent Project Muscular Dystrophy (PPMD), examined the role of patient advocacy organizations within the broad biomedical and health care ecosystem. Todd Sherer, chief executive officer of The Michael J. Fox Foundation for Parkinson's Research (MJFF), described some of the projects and strategies that MJFF has used

to accelerate the translation of novel ideas into improved therapies. Patients need cures today and cannot afford the time to wait, both speakers emphasized; the ability to translate research results into treatments for patients is urgently needed.

ACCELERATING TRANSLATION FOR THOSE WHO NEED IT NOW

PPMD was founded in 1994 to help children who have a progressive, aggressive, and life-limiting disease. Duchenne muscular dystrophy (DMD) affects about 1 in 4,600 boys, causing them to lose muscle function gradually over their lifetime of about 20 or 30 years; about 30 percent of patients also have learning or processing issues, even autism (Liew and Kang, 2013). DMD is an X chromosome–linked disease caused by mutations in a large gene, dystrophin, the product of which is a cytoskeletal protein that binds muscle membrane and helps to maintain muscle cell structure. About 30 percent of cases result from spontaneous mutations (Grimm et al., 2012). Furlong recounted that in 1984, when her sons were diagnosed with the disease, it was predicted that with the recent discovery of the gene responsible for DMD, a cure would be forthcoming in 18 months. Today, after 27 years and the deaths of both her sons, "we don't have a treatment for Duchenne," said Furlong. "It still remains the same: aggressive, progressive, and lethal."

The task of finding treatments is a difficult one. Mutations can occur throughout the 2.4 million base pairs and 79 exons of the gene, resulting in a wide variety of clinical presentations. At the same time, 50 foundations are involved in research on DMD in the United States alone, with annual expenditures on research on the disease being about $25 million. "It's very duplicative," said Furlong, "and this is happening continuously in the rare disease space" around the world.

PPMD funds academic research, but it has found itself mired in disputes over overhead rates and technology transfer agreements. Working with the legal infrastructure of a university "wastes time—time that we don't have," Furlong said. This is an example of how research incentives need to be reevaluated. Academic institutions have actually turned down funding because PPMD's board-directed cost policy could not be adjusted to provide additional funding for overhead expenses. As a result, the foundation has established its own lab to work on validating drug candidates so that it can reduce the risk on some of its investments. This lab offers validation for "any compound at any cost" because of support from PPMD.

Not only do patients and families need therapies right now, but they are also struggling with the economic costs of participating in clinical trials: parents need to take time off from work, hire child care for their other children, and fund travel that might not be supported by trial sponsors.

About 60 percent of DMD patients in the United States are on Medicaid, Furlong said.

PPMD funds several initiatives aimed at finding treatments faster. It supports work in the drug repurposing space, because patients are in such need of therapies that their parents will often try to manage their sons' medical care with information about potential effective therapies that they have learned on the Internet. "The families that I know will share data about their children freely and give it to anyone who can look at [those] data in a thoughtful way and begin to help us change what's happening," said Furlong. They believe that if they are fairly confident about the safety of a compound, it should be tested in trials. "The risk tolerance of this community and the rare disease community is quite high."

Furlong described the work of the Review of Approved Drugs for Duchenne (RADD) working group, which PPMD funds. A precompetitive three-part collaboration among the Nationwide Children's Hospital in Columbus, Ohio, the Children's National Medical Center in Washington, DC, and the European initiative Translational Research in Europe–Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD), RADD is designed to prioritize U.S. FDA–approved drugs for further testing. TREAT-NMD is a global network for the neuromuscular field that provides increased statistical power for research on rare diseases. Through RADD, published literature on preclinical models is annotated and entered into searchable databases, and gene expression data from different models and stages are compiled. One goal is to explain to parents which approaches are valid and which are not, Furlong said.

The TREAT-NMD Advisory Committee for Therapeutics (TACT) is an international network that fosters collaboration among stakeholders with the goal of advancing research and therapeutic development, said Furlong. The TACT model is a comprehensive and integrated one that brings together experts from academia, regulatory agencies, industry, clinical practice, and basic science with parent advocates to discuss proposals in a confidential review setting and inform industry and academia about patient needs. The review process is more than that of a typical academic advisory committee, resulting in greatly increased coordination and credibility among nonprofit organizations, industry, and funders. It also helps enable decisions about when projects are not meeting their milestones and should be concluded.

To improve communication and development efficiency but reduce investment risk, PPMD has diversified its research investments. DuchenneConnect is a patient registry that now has 4,000 entries; personal identifiers are removed from the data, and the information is curated and easily searched. DuchenneConnect is coordinated with clinicians' offices to decrease the time that a physician would need to spend inputting data, and

it is also linked to TREAT-NMD to increase statistical power by including data for patients worldwide. Furlong insisted that every child with DMD and other rare diseases should be in a network "so that we can apply what we know and learn to fly the plane while it's in the air." The organization is also working with Public Library of Science (PLoS) ONE, because it believes that all information generated through its efforts should be fully accessible and not delayed for publication.

Genomic studies are also under way to examine children who are outliers, that is, children who have been self-reported through social networking to be doing better or worse than expected, said Furlong. A task force is also looking at barriers to diagnosis across all pediatric diseases involving muscle weakness, and PPMD developed a website for this called childmuscleweakness.org. A parallel project is being performed by SomaLogic, a company based in Colorado looking at the protein signatures of the disease to accelerate the development of clinical products.

Together, RADD, TACT, and their collaboration with Shire Pharmaceuticals are designed to achieve tangible results in a faster time frame, said Furlong. PPMD's strategic plan for research is to improve the quality of drug candidates entering clinical trials, decrease the time required to test drugs, and thereby buy time for this generation of boys. The foundation will also identify and support drug candidates with the greatest likelihood of success, more quickly recruit subjects for trials by identifying potential subjects and supporting their participation, develop biomarkers and validate new functional endpoints, and encourage the use of centralized institutional review boards.

The identification of markers in early disease would have the most impact for patients if the progression of the illness could be slowed by targeting these markers, Furlong said, but because the disease has so much clinical variability, there likely will not be one single drug to treat DMD. Patients today, not only those with DMD but many others with rare diseases, are waiting for cures, Furlong said. "We also have to think about today because it matters."

RISK SHARING AS A PATH TO PROGRESS

MJFF was founded in 2000 to deliver improved therapies and a cure for Parkinson's disease through creative problem solving and the acceleration of novel research ideas through milestone-driven research. Sherer described some of the projects that MJFF has undertaken and some of the strategies that it uses to achieve these goals. MJFF is 100 percent focused on patients, said Sherer. It seeks to speed treatments that can slow, stop, or reverse the progression of Parkinson's disease; create better treatments for the currently unaddressed or underaddressed symptoms of the disease; and accelerate the

development of treatments to address or avoid the debilitating side effects of current drugs.

MJFF has empowered its staff—nine employees with Ph.D.s and five project managers—with assessing opportunities, designing road maps, setting milestones, and collaborating with investigators to move projects forward, Sherer said. Foundation staff see all the projects so that if there are challenges with one project, the staff can determine if it is common across the disease. If needed, other experts may be consulted to find a solution to the challenge, Sherer said. The internal scientists at the foundation also work with investigators to set up milestones and to terminate projects if a particular approach is not working.

In managing project risk, MJFF does not have an endowment, so each year it needs to return to its donors and justify what it has done. This means that the foundation needs to evolve as it learns from its fundraising and milestone histories to ensure that it is continuing to explore new and innovative areas. Also, as MJFF has grown, it has been able to take on more risk, said Sherer.

Partnerships for Drug Development

Foundations have influenced pharmaceutical companies by encouraging them to embrace novel models for risk sharing, said Sherer. However, development of these models takes time, flexibility, and perseverance. With regard to the need to change the way in which research tools are developed and to change strategies to make data accessible, "this is an area where the licensing and intellectual property [provisions] that universities have put into place are counterproductive and are overvaluing perhaps the commercial value of that asset," Sherer said. "Restrictive-use licenses are limiting standardization and discouraging field-wide use." Duplication of efforts is also wasting valuable resources, he noted. Finally, data availability is necessary, but it does not come for free. Data must be prepared, curated, stored, and distributed; and they have to be of sufficiently high quality to make these investments worthwhile, he said.

Several examples of MJFF's funding of projects in the early translational pathway have resulted in clinical or pharmaceutical partnerships. The first one involved alpha-synuclein. In the late 1990s, genetic studies linked alpha-synuclein, a protein expressed in the brain, to Parkinson's disease. After foundation support of early validation work in animal studies with a European company, the first clinical trial of an alpha-synuclein–based therapy started in 2012. MJFF has provided $2 million to this effort, and that investment led to almost $30 million of additional investment from venture capitalists. However, the translation process has been lengthy, consuming more than a decade. "Our goal is to try to take the risk on

innovative, novel ideas and help build data packages to get them to larger funders," Sherer said.

A second project involved the provision of a $5 million grant to a Vanderbilt University researcher. The funding allowed target validation, animal testing, and a drug discovery effort that has yielded a series of molecules targeting a neurotransmitter receptor for glutamate. In 2012, Vanderbilt University announced a major collaboration with Bristol-Myers Squibb to move the therapy forward into the clinic. In this case, MJFF will receive a portion of the licensing fee and will allocate it to direct further investments in its research, which is the first time that it has used this model, said Sherer.

Sherer described another program that is developing a novel drug to reduce dyskinesia, or impairment of the ability to control voluntary movement, which may appear as a lack of coordination, a common side effect of treatment in patients with Parkinson's disease. MJFF funded early target validation work and formed a partnership with a company developing molecules that interact as an antagonist to glutamate receptor 5. The company recently completed a Phase II trial showing the efficacy and safety of the drug for use as a treatment for dyskinesia in patients with Parkinson's disease, and both parties are working to find a pharmaceutical partner.

MJFF will also take risks on technical approaches for therapeutic development. It formed a collaboration with Ceregene to conduct a series of clinical trials on a gene therapy approach focused on neurotropic factors, said Sherer. Results from this study are expected in 2013.

Development of Research Tools

In addition to these research projects, Sherer described the development of research tools to accelerate the translational process. The Parkinson's Progression Markers Initiative is a large-scale natural history and biomarker study for patients newly diagnosed with Parkinson's disease. MJFF has invested $45 million to bridge the gap between industry, nonprofit organizations, and private individuals. Data are available through a website in real time, as are biological samples. Thirteen pharmaceutical partners are now helping to support the study and the use of the data, which are available to all researchers.

MJFF is also investing in laboratory tools to accelerate the development of therapeutics for Parkinson's disease outside of the traditional model of providing a grant to an academic laboratory. For example, through a collaboration with The Jackson Laboratory, MJFF provides openly available animal models generated by any grantee. These models are thoroughly characterized and housed at The Jackson Laboratory. Similarly, it has supported the development of research tools like viral vectors and antibodies

and made them available as well. One advantage of this initiative is that people are using the same tools so that data can be compared across laboratories, Sherer said.

Finally, Sherer described the Fox Trial Finder, which matches volunteers—both those with Parkinson's disease and controls—to clinical trials. Matching is based on demographic characteristics, medication history, diagnosis duration, and other attributes. Volunteers can connect directly—online and anonymously—with members of a trial team through secure messaging to learn more. Almost 12,000 people signed up for the trial finder in the course of a year. MJFF is working to extend the tool from English-speaking countries to other countries. "The idea is to have volunteers at the ready as you launch new trials and studies," Sherer said.

A DRUG DEVELOPMENT ECOSYSTEM

Patient advocacy groups are part of a much larger ecosystem, which Furlong defined as a community of stakeholders (universities, companies, patient organizations, patients, and government agencies) that exist in conjunction with the nonliving components of their environment (e.g., regulations, economic factors, reimbursement potential), all of which interact as a system. PPMD seeks to fill in or strengthen the missing or weak pieces of the ecosystem, such as preclinical research, the clinical infrastructure, and education, and to accelerate interactions among the system's components. It also seeks new paradigms that can deliver change more quickly than the existing system.

PPMD has a patient advisory group that helps make decisions about which projects will be funded, and the groups tend to pursue projects that sound promising, even if those projects are risky. Engaging patients in decision making helps them understand the process by which ideas are pursued and either accepted or rejected, said Furlong. The advisory group generates interesting ideas and discussion: patients "want to come to a table with people that they respect and feel that they have a definite interest in what they would like to accomplish," Furlong indicated. The basic scientists "listen, and then they begin to think in a different realm, and sometimes new ideas are generated that make maybe a little more sense than the initial proposal. So it's a way to engage the community," said Furlong.

Advocacy groups are changing, said Sharon Terry, Roundtable co-chair and president and chief executive officer of Genetic Alliance. Young parents do not necessarily sign up for a foundation and send in $50 per year. They join a Facebook group, find a local group at the library, or join affinity groups for other interests that their children share. People are aggregating themselves in ways that the disease groups have not yet prepared for, which will lead to the decline of groups that cling to old models, Terry said.

"Foundations can play an important role as a major player representing the patients in this ecosystem," Sherer concluded. Foundations need to be part of the conversation on how the basic science research model needs to change to remind the community that the reason for funding biomedical research is to help patients. He added that "we have highly motivated academic researchers that volunteer their time, take lower indirect costs, share their tools, share their data, and are happy and excited in their careers to be a part of this effort. It's [about] being part of something bigger than just their own projects."

6

Strategies for Change

During the course of the workshop, several topics consistently arose during the presentations and subsequent discussions. Many of these topics also emerged in the final session of the workshop, a panel session that featured discussants William Rutter, chief executive officer of Synergenics, and workshop speakers Geoffrey Duyk, Daniel Geschwind, and Todd Sherer. This final chapter of the workshop summary highlights the major themes and identifies specific strategies for improving the efficiency and effectiveness of the translation of genomic science (see Box 6-1).

ALIGNING INCENTIVES FOR CHANGE

Tension in connecting basic and translational sciences exists because of the difference between their inherent missions. For example, many neuroscientists are interested in learning about how the brain works to gain new knowledge, not necessarily because the information would help treat a disease, Geschwind noted. Understanding the basic science is critical, and that should not be overlooked in the discussion of translational research, he said. However, the current system is designed to incentivize novelty through the publication of papers in scientific journals, and that does not necessarily translate to social benefit, such as improved treatments for patients. The replication of results has value, and, in fact, the scientific method relies upon it, but "the incentives just aren't aligned" to do this sort of work, said Geschwind.

A system in which the important replication of data is rewarded with academic promotion may be what is needed to improve interactions along

BOX 6-1
Pathways to Improving Genomic Science Translation[a]

- Funding milestone and outcome-driven research is key to supporting the current state of technology with a more efficient biomedical research system. (Liu)
- As a starting point for the systemwide integration of genomic science, general practitioners could have the most impact for embracing genomics and bioinformatics as decision support tools. (Huntsman)
- Research goals and incentives need to be aligned for the effective translation of genomic science. (Geschwind)
- Universities should consider including collaborative benchmarks as part of the criteria for academic promotion to align tenure as an incentive for translational research. (Liu)
- Scientists should make better use of the high-quality data and resources that are already publicly available and should be encouraged to share their own data for reuse to accelerate translation. (Butte)
- The sharing and reuse of data should be incentivized through funding and publication mechanisms. (Butte)
- Competition among teams, as opposed to individuals, can encourage multidisciplinary, collaborative efforts and be an effective tool for achieving grand translational challenges. (Burke)
- Incorporation of multidisciplinary systems biology approaches to integrate genetic and phenotypic data will yield rapid progress for understanding complex diseases. (Geschwind)
- Patient advisory groups can convene stakeholders to help focus research on projects that are most likely to provide patients with treatments today. (Furlong)
- Many advocacy groups are now participating in research, but enlistment of these groups needs to be frictionless, and the information needs to be aggregated broadly to reduce the risk of fragmenting diseases so much that use of a systems-level approach to translation is not possible. (Terry)
- By managing innovative risk-sharing research models, advocacy groups can build evidence that is more likely to produce treatments that result in private-sector investment and development. (Sherer)
- Progress in bringing products to market can be accelerated if the risk of investment is improved by adjustment of the health care ecosystem to adapt to new technology, improved globalization, and restructured regulation and reimbursement policies. (Duyk)
- New business models built on global networking, investments in disease prevention diagnostics, and continued technological development will have a transformative effect on translational medicine and cost-effectiveness. (Scott)
- Data will be made freely available if patients are given the right to own and control their genomic data; enforcement strategies will not be necessary to encourage data sharing because patients will realize the value of sharing their information. (Scott)

[a]The statements, recommendations, and opinions expressed here are those of the individual presenters and participants and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

the basic science and translational pathways. The difficulty is that some journals have policies disallowing publication of reanalyzed data. Realignment in all areas is needed to line up goals and incentives for the effective translation of genomic science, from analysis and sharing and replication of data to grant proposal evaluation, publication, and academic promotions, Geschwind noted.

Redefining Criteria for Tenure

Although it was recognized that tenure is not the only mechanism for promotion that should be considered for change, the idea of reevaluating the criteria used to determine tenure was discussed often during the workshop. As a starting point, universities could define a specific process and goals for achieving tenure that could include a collaborative research piece, Liu said.

A workshop participant pointed to institutions that have changed incentives for tenure. For example, the University of Wisconsin system altered its tenure criteria to require that faculty engage in outreach to the community, and the University of Georgia system has done something similar. With strong leadership to put new incentives in place, changes are possible, he said. Important stakeholders to be included as part of the discussion to effect these changes would be university presidents and professor unions, Duyk said. Participants also discussed the fact that professional societies are key to shifting incentives, as they can make recommendations to convey what is important to the societies' membership.

Catalyzing Change Through Funding, Collaboration, and Goal Setting

As a first step to improve the translation of basic science, Geschwind suggested that if funding agencies, such as the National Institutes of Health (NIH), were to demand data sharing or collaborative multidisciplinary research, behaviors would change. "People will follow the money," he said. To incentivize data sharing, funding agencies must recognize that it is a priority, in the sense that funding needs to be specifically allocated for sharing so that there is no excuse not to share the information. To accomplish this, NIH and other organizations could convene short-term working groups to achieve implementation milestones in no more than a year to enforce the requirement that all funded proposals participate in data sharing, Geschwind said.

Advocacy groups have a lesson on resource sharing to teach scientists, as many patients voluntarily share their medical information and in so doing have changed how data sharing is thought about, Geschwind observed. The advocacy groups would be essential for this process because

they could emphasize the importance of sharing information for those who really need to see research results turn into clinical applications quickly, Geschwind said. Advocacy organizations are particularly well suited for determining who is working on particular projects and they also can play a major role in the reorientation of incentives, Liu said.

Regulatory agencies could also encourage data sharing. Rutter called attention to a recent report of the President's Council of Advisors on Science and Technology that recommended accelerated approval for some therapeutics, thereby allowing patients and physicians to decide if they would like to take greater risks (PCAST, 2012). Rutter suggested that "as a trade-off for the accelerated approval, mandatory data sharing would be a condition" to provide full transparency of the data. A recent Institute of Medicine consensus study recommended making omics-based datasets available and more transparent (IOM, 2012). Encouraging the sharing of data would be a more efficient way to develop drugs, said Rutter, in addition to the mechanisms being used by organizations today.

Although sharing of data and resources is needed, it is a difficult balance to achieve because tension also exists between collaboration and competition. Although some competition is needed, multidisciplinary efforts are often needed to achieve grand goals, Geschwind said. Competition among teams, as opposed to individuals, can be a very effective tool for making progress, Burke said.

Duyk cited the Human Genome Project as a successful example of teams setting specific, clear goals. In addition to incentivization of individuals, "appropriate incentives [should be given] to institutions that are creating a culture of teamwork and an effective mechanism involving a large team that is moving a translational research agenda," Burke said. To address the issue of working in teams and how sharing among universities and industry could be of benefit to both, Sherer pointed to a tension between top-down versus bottom-up management of the research enterprise. Today, medical academic research is largely a bottom-up free-agent enterprise. The establishment of teams of experts to provide some top-down guidance for defining goals and providing clear, time-dependent milestones that can be held accountable to the taxpayers and others who fund the research would be beneficial, he said.

Even though many systematic changes are needed, these will take time. It must not be overlooked that those with diseases now need accelerated development of treatments in the short term, Sherer said. He asked, "If we have human data, do we even need a transgenic animal model," for example? "Can we figure out some way to do this faster to get results more quickly? That's something we shouldn't miss as we are making recommendations that might change 20 or 25 years from now." The global infectious disease community provides case studies of how change can occur more

rapidly for self-organizing and how new technology can be used to create solutions to immediate issues, Duyk said. Perhaps rapid response teams would be useful in this case, too.

Training of the next generation of scientists to operate in an innovative culture that connects basic and translational science teams was also discussed. Young people need to hear that leadership and management skills are important, said Duyk. If a young researcher wanted to take three courses in the business school, he or she would probably not be encouraged to do so, as this would distract from time dedicated to science. "You have to tell people what you think is important. You have to incent people, whether it's economically or otherwise, to do the right thing. And be careful. You can send the wrong messages very easily," said Duyk. Sherer said that not everyone needs to be an innovator, a leader, a project manager, or a cutting-edge scientist. "You have to figure out what are the opportunities for people and then provide the training for those. Not everyone wants to lead their own lab. They may want to be part of the team."

Innovation in the current research system could also be catalyzed through the funding of fellowship grants and awards. MacArthur and Markey fellowships and awards from the Defense Advanced Research Projects Agency are examples of ways to provide promising researchers and institutions with enough funding and freedom to explore and innovate, Duyk said. NIH funds New Innovator and Pioneer Awards as well. Success then begets more success, especially because other people in a system tend to follow winners. The distribution of funding over a broad range of recipients will not necessarily allow for the creation of an effective research model that people will follow, Duyk suggested. Similarly, a grand challenges approach can attract talent to problems that need to be solved, especially if this approach outlines a clear problem that needs to be solved and a prize is awarded as an incentive.

A BETTER MODEL FOR INDUSTRY–ACADEMIA COLLABORATION

Change that would help translate discoveries could also come from achievement of better industry–academia collaboration. Achievement of such collaboration is often a difficult task because of conflicts of interest, Sherer said. Duyk observed that pharmaceutical companies are interested in investing money in academia, because it is cheaper than investing in biotechnology companies for some activities. However, complex conflict-of-interest rules can hinder such investments. The availability of better guidelines for collaboration that would address university technology transfer issues would also be useful. Technology transfer offices in universities need staff who can make good decisions and negotiate win-win agreements. The interface between the public and private sectors needs to be more functional, Duyk said.

The model for translational research that the California Institute for Quantitative Biosciences (known as QB3) uses to foster innovation without distracting from the business models of pharmaceutical companies could be considered, said Rutter. QB3 is a joint project between the University of California, San Francisco, the University of California, Berkeley, and the University of California, Santa Cruz, which merged the efforts of the faculties of the three universities. The faculty network brings expertise in a range of disciplines and a central facility provides services in support of bioscience entrepreneurs. QB3 provides laboratory space, professional development training, mentorship, and legal services for those innovators who would like to start a business. Almost 60 companies have emerged from the initiative and are either still part of the network or have expanded. NIH could facilitate the development of similar facilities around core areas of technology and expertise, Rutter suggested.

QB3 is a good example of how lean development could be valuable for the translation process, according to Rutter. Relatively small groups could initiate a project and carry it out under low-cost conditions until it becomes robust enough to be supported by venture capital or other groups. Several small companies also could be managed collectively, which would allow oversight by experienced managers in industry or a management group. Such strategies could help address the time-cost differential for development.

In addition to thinking about when to develop a research finding for clinical use, it is also just as important to know when to cease a project. Duyk said that researchers are too soft about terminating projects and reorienting their organizations. "We're about to go through a financial crisis that's going to take a generation, probably, to resolve. And we should use that as an opportunity to rethink and make some hard decisions."

FINAL WORDS

"We have to use those tools and figure out how we can get maximum impact out of the medical process," said Duyk. "I think we don't have enough iteration. If every drug development program is a rocket shot to the moon, you're not going to do a lot of rocket shots to the moon." To transform the translational pathway, "we have to really think about 21st-century solutions." Terry added, "The solution is going to be us. . . . It will be somehow resolved within this kind of community, [with] this kind of group of stakeholders."

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Appendix A

Workshop Agenda

Improving the Efficiency and Effectiveness of Genomic Science Translation: A Workshop

December 3, 2012

The Beckman Center of the National Academies
100 Academy
Irvine, CA

Workshop Objectives:

- To examine how basic science can best be positioned to foster successful translation of early genomic discoveries.
- To explore the challenges in and identify potential opportunities for improving the efficacy of the translation process.
- To define pathways for moving innovative basic science forward.

8:30–8:45 A.M. **WELCOMING REMARKS AND CHARGE TO WORKSHOP SPEAKERS AND PARTICIPANTS**

Wylie Burke, Roundtable Co-Chair
Professor and Chair,
Department of Bioethics and Humanities
University of Washington, Seattle

Sharon Terry, Roundtable Co-Chair
President and Chief Executive Officer
Genetic Alliance

8:45–10:20 A.M. **SESSION I: CONNECTING BASIC RESEARCH AND HEALTH CARE NEEDS**

Discussion Provocateur:
William J. Rutter
Chairman/Chief Executive Officer and Founder
Synergenics, LLC

8:45–9:05 A.M. **Genomics to Health**
Edison Liu
President and Chief Executive Officer
The Jackson Laboratory

9:05–9:25 A.M. **Genomics and Personalized Cancer Treatment**
David G. Huntsman
Associate Professor of Medicine
University of British Columbia

9:25–10:15 A.M. **Discussion with Speakers and Attendees**

10:15–10:20 A.M. **Session Distillation and Potential Next Steps**
William J. Rutter
Chairman/Chief Executive Officer and Founder
Synergenics, LLC

10:20–10:35 A.M. **BREAK**

10:35 A.M.–12:10 P.M. **SESSION II: MOVING BASIC SCIENCE FORWARD**

Discussion Provocateur:
Robert L. Nussbaum
Chief, Division of Medical Genetics
Department of Medicine and Institute of Human Genetics
University of California, San Francisco

10:35–10:55 A.M. **Discovering New Drugs and Diagnostics from 300 Billion Points of Data**
Atul Butte
Chief and Associate Professor of Systems Medicine, Department of Pediatrics
Stanford University School of Medicine

10:55–11:15 A.M.	**Translating Genetic and Genomic Research in Neuropsychiatric Conditions: Lessons from Autism Research** *Daniel Geschwind* *Gordon and Virginia MacDonald Distinguished Chair in Human Genetics and Professor of Neurology and Psychiatry,* *University of California, Los Angeles, School of Medicine*
11:15 A.M.–12:05 P.M.	**Discussion with Speakers and Attendees**
12:05–12:10 P.M.	**Session Distillation and Potential Next Steps** *Robert L. Nussbaum* *Chief, Division of Medical Genetics* *Department of Medicine and Institute of Human Genetics* *University of California, San Francisco, School of Medicine*
12:10–1:00 P.M.	**WORKING LUNCH**
1:00–2:35 P.M.	**SESSION III: THE ROLE OF INDUSTRY AND VENTURE CAPITAL** **Discussion Provocateur:** *Wylie Burke, Roundtable Co-Chair* *Professor and Chair* *Department of Bioethics and Humanities* *University of Washington, Seattle*
1:00–1:20 P.M.	**Lost in Translation: The Systematic and Comprehensive** *Geoffrey Duyk* *Partner and Managing Director* *TPG Biotech*
1:20–1:40 P.M.	**Translating Genomic Science into Clinical Practice: Time for Innovative Business Models** *Randy Scott* *Chairman and Chief Executive Officer* *InVitae*

1:40–2:30 P.M.	**Discussion with Speakers and Attendees**
2:30–2:35 P.M.	**Session Distillation and Potential Next Steps** *Wylie Burke, Roundtable Co-Chair* *Professor and Chair* *Department of Bioethics and Humanities* *University of Washington, Seattle*
2:35–4:10 P.M.	**SESSION IV: THE ROLE OF ADVOCACY IN FACILITATING BASIC SCIENTIFIC RESEARCH** **Discussion Provocateur:** *Sharon Terry, Roundtable Co-Chair* *President and Chief Executive Officer* *Genetic Alliance*
2:35–2:55 P.M.	**Purpose of Advocacy—Helping to Solve Important Problems** *Pat Furlong* *Founding President and Chief Executive Officer* *Parent Project Muscular Dystrophy*
2:55–3:15 P.M.	**Bridging the Gap Between Basic and Clinical Research** *Todd Sherer* *Chief Executive Officer* *The Michael J. Fox Foundation for Parkinson's Research*
3:15–4:05 P.M.	**Discussion with Speakers and Attendees**
4:05–4:10 P.M.	**Session Distillation and Potential Next Steps** *Sharon Terry, Roundtable Co-Chair* *President and Chief Executive Officer* *Genetic Alliance*
4:10–4:25 P.M.	**BREAK**
4:25–5:30 P.M.	**SESSION V: NEXT STEPS**

4:25–5:30 P.M. **LEADING THE STRATEGY FOR MORE EFFICIENT AND EFFECTIVE TRANSLATION**

Discussion Provocateur:
Geoffrey Ginsburg
Director, Center for Genomic Medicine
Institute for Genomic Sciences & Policy
Duke University

Discussants:
William J. Rutter
Chairman/Chief Executive Officer and Founder
Synergenics, LLC

Daniel Geschwind
Gordon and Virginia MacDonald Distinguished Chair in Human Genetics and Professor of Neurology and Psychiatry,
University of California, Los Angeles, School of Medicine

Geoffrey Duyk
Partner and Managing Director,
TPG Biotech

Todd Sherer
Chief Executive Officer,
The Michael J. Fox Foundation for Parkinson's Research

5:30–5:45 P.M. **SESSION VI: CONCLUSION**

5:30–5:45 P.M. **CONCLUDING REMARKS**

Wylie Burke, Roundtable Co-Chair
Professor and Chair
Department of Bioethics and Humanities
University of Washington, Seattle

Sharon Terry, Roundtable Co-Chair
President and Chief Executive Officer
Genetic Alliance

5:45 P.M. **ADJOURN**

Appendix B

Speaker Biographical Sketches

Wylie Burke, M.D., Ph.D., is professor and chair of the department of bioethics and humanities at the University of Washington. She received a Ph.D. in genetics and an M.D. from the University of Washington and completed a residency in internal medicine at the University of Washington. She was a medical genetics fellow at the University of Washington from 1981 to 1982. Dr. Burke was a member of the department of medicine at the University of Washington from 1983 to 2000, where she served as associate director of the internal medicine residency program and founding director of the University of Washington's Women's Health Care Center. She was appointed chair of the department of medical history and ethics (now the department of bioethics and humanities) in October 2000. She is also an adjunct professor of medicine and epidemiology and a member of the Fred Hutchinson Cancer Research Center. She is a member of the Institute of Medicine and the Association of American Physicians and is a past president of the American Society of Human Genetics. Dr. Burke's research addresses the social, ethical, and policy implications of genetics, including the responsible conduct of genetic and genomic research, genetic test evaluation, and the implications of genomic health care for underserved populations. She is director of the University of Washington Center for Genomics and Healthcare Equality, a National Human Genome Research Institute Center of Excellence in Ethical, Legal, and Social Implications research, and co-director of the Northwest-Alaska Pharmacogenomic Research Network.

Atul Butte, M.D., Ph.D., is chief of the division of systems medicine and associate professor of pediatrics and, by courtesy, medicine and computer

science at Stanford University and the Lucile Packard Children's Hospital. Dr. Butte trained in computer science at Brown University, worked as a software engineer at Apple and Microsoft, received an M.D. at Brown University, trained in pediatrics and pediatric endocrinology at Children's Hospital Boston, and then received a Ph.D. in health sciences and technology from Harvard Medical School and the Massachusetts Institute of Technology. Dr. Butte is also a founder of Personalis, which provides clinical interpretations of whole-genome sequences, and NuMedii, which finds new uses for drugs. The Butte laboratory builds and applies tools that convert more than 300 billion points of molecular, clinical, and epidemiological data that have been measured by researchers and clinicians over the past decade into diagnostics, therapeutics, and new insights into disease. To facilitate this method, the Butte laboratory has developed tools to automatically index and find genomic datasets based on the phenotypic and contextual details of each experiment to deconvolve multi-cellular samples, and to perform these calculations on the Internet cloud. Dr. Butte has authored more than 120 publications and delivered more than 140 invited presentations in personalized and systems medicine, biomedical informatics, and molecular diabetes, including 30 at the National Academy of Sciences, Institute of Medicine, National Institutes of Health (NIH), or NIH-related meetings. Dr. Butte's research has been featured in the *New York Times* and the *International Herald Tribune* (2008), the *Wall Street Journal* (2010 to 2012), and the *San Jose Mercury News* (2010). Dr. Butte has received several awards, including the 2012 FierceBiotech IT "Top 10 Biotech Techies" award and the 2011 National Human Genome Research Institute Genomic Advance of the Month.

Geoffrey Duyk, M.D., Ph.D., is a partner and managing director of TPG Biotechnology. Prior to joining TPG Biotechnology in 2004, Dr. Duyk served on the board of directors and was president of research and development at Exelixis, Inc., where he led a group of more than 550 people focused on the discovery and development of small-molecule therapeutics. Prior to his work at Exelixis, Inc., he was one of the founding scientific staff at Millennium Pharmaceuticals, Inc. As vice president of Genomics at Millennium Pharmaceuticals, Inc., Dr. Duyk was responsible for building and leading the informatics, automation, DNA sequencing, and genotyping groups as well as the mouse and human genetics group. Prior to this, Dr. Duyk was an assistant professor at Harvard Medical School in the department of genetics and assistant investigator of the Howard Hughes Medical Institute. While at Harvard Medical School, Dr. Duyk was a co–principal investigator in the National Institutes of Health (NIH)-funded Cooperative Human Linkage Center. Dr. Duyk has been and continues to be a member of numerous NIH panels and oversight committees focused

on the planning and execution of the Human Genome Project and has been elected to the board of directors of the American Society of Human Genetics. Dr. Duyk graduated from Wesleyan University in 1980 with a B.A. in biology and was elected to Phi Beta Kappa. He holds a Ph.D. and an M.D. from Case Western Reserve University and completed his medical and fellowship training at the University of California, San Francisco (UCSF). While at UCSF, he was a fellow of the Lucille P. Markey Foundation and was also awarded a postdoctoral fellowship from the Howard Hughes Medical Institute. Dr. Duyk currently serves on the boards of directors of Aerie Pharmaceuticals, Inc.; Alphabet Energy, Inc.; Amyris; Beta Renewables; DNAnexus, Inc.; Elevance Renewable Sciences, Inc.; Fourteen22, Inc.; Galleon Pharmaceuticals, Inc.; Genomatica; and Karos Pharmaceuticals, Inc., and is a board observer at Ultragenyx Pharmaceutical, Inc.

Pat Furlong, B.S.N., is the founding president and chief executive officer of Parent Project Muscular Dystrophy (PPMD), the largest nonprofit organization in the United States solely focused on Duchenne muscular dystrophy (Duchenne). The mission of PPMD is to end Duchenne. PPMD accelerates research, raises its voice in Washington, DC, demands optimal care for all young men, and educates the global community. Duchenne is the most common fatal genetic childhood disorder, which affects approximately 1 out of every 3,500 boys each year worldwide. It currently has no cure. When doctors diagnosed her two sons, Christopher and Patrick, with Duchenne in 1984, she did not accept "there's no hope and little help" as an answer. She immersed herself in Duchenne, working to understand the pathology of the disorder, the extent of research investment, and the mechanisms for optimal care. Her sons lost their battle with Duchenne in their teenage years, but she continues to fight—in their honor and for all families affected by Duchenne. In 1994, Ms. Furlong, together with other parents of young men with Duchenne, founded PPMD to change the course of Duchenne and, ultimately, to find a cure. Today, she continues to lead the organization and is considered one of the foremost authorities on Duchenne in the world.

Daniel Geschwind, M.D., Ph.D., is the Gordon and Virginia MacDonald Distinguished Chair in Human Genetics and is a professor of neurology and psychiatry at the University of California, Los Angeles (UCLA), School of Medicine. He is director of the Neurogenetics Program and the Center for Autism Research and Treatment and co-director of the Center for Neurobehavioral Genetics at UCLA. Dr. Geschwind obtained an A.B. in psychology and chemistry at Dartmouth College and M.D. and Ph.D. degrees at Yale School of Medicine prior to completing his internship, residency (neurology), and postdoctoral fellowship at UCLA. He joined the UCLA faculty in 1997. His laboratory works to improve understanding of human

neuropsychiatric diseases, such as autism and neurodegenerative diseases. The lab's approach relies heavily on systems-level integration involving computational and bioinformatic methods, in addition to wet laboratory experimentation. Dr. Geschwind has also put considerable effort into fostering the development of large-scale collaborative patient resources for genetic research and data sharing. He is a strong advocate for sharing of data and biomaterials, having provided scientific oversight for the Autism Genetic Resource Exchange. He sits on several scientific advisory boards, including the Faculty of 1000 Medicine, the Executive Committee of the American Neurological Association, and the National Institutes of Health Council of Councils. He received the Derek Denny-Brown Neurological Scholar Award from the American Neurological Association in 2004 and the Scientific Service Award from Autism Speaks in 2007 and is a member of the Institute of Medicine.

Geoffrey Ginsburg, M.D., Ph.D., is the founding director for genomic medicine at Duke University and assumed his current position in the Duke Institute for Genome Sciences & Policy in 2004. He is also the founding executive director of the Center for Personalized Medicine, established in the Duke University Health System in 2010. He is currently professor of medicine and pathology at the Duke University Medical Center. While at Duke, Dr. Ginsburg has pioneered translational genomics, initiating programs in genome-enabled biomarker discovery, longitudinal registries with linked molecular and clinical data, biomarker-informed clinical trials, and the development of novel practice models and implementation research for the integration of genomic tools in heath care systems. He is an internationally recognized expert in genomics and personalized medicine, with more than 200 published papers and funding from the National Institutes of Health (NIH), the U.S. Department of Defense, the Defense Advanced Research Projects Agency, the Bill & Melinda Gates Foundation, and industry. In 1990, he joined the faculty of Harvard Medical School, where he was director of preventive cardiology at Beth Israel Hospital, and led a laboratory in applied genetics of cardiovascular disease at Children's Hospital. In 1997 he joined Millennium Pharmaceuticals Inc. as senior program director for cardiovascular diseases and was eventually appointed vice president of molecular and personalized medicine, where he was responsible for developing pharmacogenomic strategies for therapeutics, as well as biomarkers for disease and their implementation in the drug development process. He has received a number of awards for his research accomplishments, including the Innovator in Medicine Award from Millennium in 2004 and the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005. He is a founding member and former board member of the Personalized Medicine Coalition, a senior consulting editor for the *Journal of the*

American College of Cardiology, an editor for the *HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition, he is the editor of *Genomic and Personalized Medicine* (Elsevier), whose first edition was published in 2009. He has been a member of the Secretary of Veterans Affairs Advisory Council on Genomic Medicine and the National Advisory Council for Human Genome Research at NIH. He is currently an international expert panel member for Genome Canada; a member of the Board of External Experts for the National Heart, Lung, and Blood Institute; a member of the Institute of Medicine's Roundtable on Translating Genome-Based Research for Health; and a member of the External Scientific Panel for the Pharmacogenomics Research Network. He was recently appointed to the Advisory Council for the newly established National Center for Advancing Translational Sciences at NIH. He received an M.D. and a Ph.D. in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, Massachusetts. He subsequently pursued postdoctoral training in clinical cardiovascular medicine at Beth Israel Hospital and in molecular biology at Children's Hospital as a Bugher Foundation Fellow of the American Heart Association.

David G. Huntsman, M.D., F.R.C.P.C., F.C.C.M.G., is a professor in the departments of pathology and laboratory medicine and obstetrics and gynaecology at the University of British Columbia and is the Dr. Chew Wei Memorial Professor of Gynaecologic Oncology. He is a staff pathologist at the British Columbia Cancer Agency (BCCA) and a consulting pathologist at the Vancouver General Hospital (VGH). Dr. Huntsman is currently the director of the British Columbia multidisciplinary ovarian cancer research team, medical director of the Centre for Translational and Applied Genomics at the BCCA, and co-director of the Genetic Pathology Evaluation Centre at the Jack Bell Research Centre, VGH. Dr. Huntsman's research has led to the development of predictive and prognostic tissue-based cancer biomarkers for ovarian cancer and a wide variety of other tumor types. His team created a blueprint for subtype-specific ovarian cancer control and has been a leader in the application of novel genomics technologies to ovarian cancer. As collaboration is critical in his field, Huntsman happily leads and engages in a wide number of multidisciplinary research groups. Most recently, he has been working on the creation of a broad-based personalized medicine initiative for British Columbia.

Edison Liu, M.D., is the president and chief executive officer of The Jackson Laboratory. Prior to joining the Laboratory, Dr. Liu was the founding executive director of the Genome Institute of Singapore (GIS) from 2001 to 2011. GIS grew into one of the leading genomics research institutes globally, comprising 27 laboratory groups and a staff of 270. Between

1997 and 2001, he was the scientific director of the National Cancer Institute's Division of Clinical Sciences in Bethesda, Maryland, where he was in charge of the intramural clinical translational science programs. From 1987 to 1996, Dr. Liu was a faculty member at the University of North Carolina at Chapel Hill, where he was director of the Lineberger Comprehensive Cancer Center's Specialized Program of Research Excellence in Breast Cancer, director of the Laboratory of Molecular Epidemiology at the School of Public Health, chief of medical genetics, and chair of the Correlative Science Committee of the National Cooperative Clinical Trials group Cancer and Leukemia Group B. Dr. Liu's own scientific research has focused on the functional genomics of human cancers, particularly breast cancer, uncovering new oncogenes and deciphering the dynamics of the regulation of genes that modulate cancer biology on a genomic scale. He has authored more than 300 scientific papers and reviews and has co-authored 2 books. He obtained a B.S. in chemistry and psychology, as well as an M.D., at Stanford University. He served his internship and residency at Washington University's Barnes Hospital in St. Louis, Missouri, followed by an oncology fellowship at Stanford University. From 1982 to 1987 he was at the G.W. Hooper Foundation, University of California, San Francisco.

Robert L. Nussbaum, M.D., focuses his research efforts on three main areas: (1) the genetic contribution to Parkinson's disease; (2) the rare X-linked disease known as the oculocerebrorenal syndrome of Lowe, characterized by congenital cataracts, Fanconi syndrome of the renal proximal tubules, neurological dysfunction, and developmental delay; and (3) the value of personalized medicine through the application of genetic and genomic approaches to improving patient care. Dr. Nussbaum seeks to evaluate if and how genetic and genomic information about an individual can effectively be used to improve health care by improving outcomes, reducing adverse reactions, lowering costs, and promoting health through risk education. As chief of the Division of Medical Genetics in the Department of Medicine and as a faculty member in the Institute of Human Genetics at the University of California, San Francisco, Dr. Nussbaum is seeking to develop collaborative research efforts with clinicians-researchers interested in studying how the application of genomics can improve patient care.

William J. Rutter, Ph.D., is chair, chief executive officer, and founder of Synergenics, LLC, which owns or controls a portfolio of biotechnology companies at various stages of development. Dr. Rutter, with two colleagues, founded Chiron Corporation in 1981, a pioneering biotech firm that developed the first recombinant vaccine (for hepatitis B); that was the first to sequence of the HIV genome in 1984; and that discovered, cloned, and sequenced the hepatitis C virus in 1987. Chiron also developed quantitative

diagnostic tests for determination of viral loads, a new concept that opened the way for the development of therapeutic drugs and vaccines against these viruses. In 1995, the Swiss pharmaceutical company Ciba-Geigy acquired 49 percent of Chiron in a transformative transaction. Subsequently, Sandoz merged with Ciba-Geigy to form Novartis. Dr. Rutter joined the Novartis Board of Directors and remained with Chiron until 1998. Novartis purchased the remaining portion of Chiron in 2005. Dr. Rutter played a key role in developing the University of California, San Francisco (UCSF), into a major scientific institution. He joined UCSF as head of its new department of biochemistry and biophysics in 1968 and helped build the science enterprise during the period of major developments in recombinant DNA technology, based on the discoveries of colleague Herbert Boyer and Stanley Cohen of Stanford University. After the formation of Chiron, he became director of UCSF's Hormone Research Institute, a post that he retained until 1989, when he joined Chiron full-time. He has published more than 380 scientific articles and holds more than 25 patents. Dr. Rutter is a member of the National Academy of Sciences and the American Academy of Arts and Sciences and has received numerous awards for his contributions to science and the biotechnology industry.

Randy Scott, Ph.D., is chair and chief executive officer of InVitae Corporation, a privately owned company focused on bringing comprehensive genetic information into routine medical practice for millions of people. Prior to joining InVitae, Dr. Scott founded Genomic Health in 2000 and led the company as CEO for 9 years with a focus on improving the quality of treatment decisions for patients with cancer. In addition, Dr. Scott was a cofounder and chief scientific officer for Incyte from 1991 to 2000. An author of more than 40 scientific publications, the holder of 20 patents, and the recipient of numerous awards, Dr. Scott holds a B.S. degree in chemistry from Emporia State University and a Ph.D. in biochemistry from the University of Kansas.

Todd Sherer, Ph.D., is the chief executive officer of The Michael J. Fox Foundation for Parkinson's Research (MJFF), reporting to the board of directors. Formally trained as a neuroscientist, he directs the organization's research strategy and is responsible for the organization's overall scientific and fundraising direction to speed treatment breakthroughs and a cure for Parkinson's disease. Dr. Sherer has been a key architect of the foundation's strategy to define high-priority research areas for Parkinson's disease—therapeutic targets and approaches that are the closest or the most critical to practical relevance in patients' daily lives—to leverage donor-raised capital to push projects in these areas toward the clinic. He has played a major role in the foundation's efforts to increase the phar-

maceutical industry's investment in Parkinson's disease drug development and engage the patient community to encourage and expand participation in clinical research. Today he is one of the world's foremost experts on the science and business of Parkinson's disease drug development, speaking frequently on these topics at conferences, to the media, and to members of the Parkinson's disease community. Dr. Sherer's work with the foundation began in 2003, when, as a postdoctoral fellow at Emory University in Atlanta, Georgia, he was awarded MJFF funding to investigate the role of environmental factors in Parkinson's disease. He joined the foundation's staff full-time as associate director of research programs in April 2004. He was promoted to vice president of research programs in June 2006 and chief program officer in November 2010, finally assuming the role of chief executive officer in May 2011. Dr. Sherer is a member of the board of directors of the Parkinson's Action Network and participates in the Institute of Medicine of the National Academies Forum on Neuroscience and Nervous System Disorders. He is a collaborating scientist for the Coalition Against Major Diseases and a member of the CINAPS Advisory Committee at the National Institute of Neurological Disorders and Stroke, National Institutes of Health. In addition, Dr. Sherer was selected to join the National Center for Advancing Translational Sciences Council and the Cures Acceleration Network Review Board at the National Institutes of Health. During his career as a bench researcher, Dr. Sherer published more than 30 peer-reviewed articles in scientific journals. He earned a Ph.D. in neuroscience from the University of Virginia and holds a B.S. in psychology from Duke University in Durham, North Carolina.

Sharon Terry, M.A., is president and chief executive officer of the Genetic Alliance, a network of more than 10,000 organizations, 1,200 of which are disease advocacy organizations. Genetic Alliance improves health through the authentic engagement of communities and individuals. It develops innovative solutions through novel partnerships, connecting consumers to smart services. She is the founding CEO of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). As codiscoverer of the gene associated with PXE, she holds the patent for *ABCC6* and has assigned her rights to the foundation. She developed a diagnostic test and is conducting clinical trials. Ms. Terry is also a cofounder of the Genetic Alliance Registry and Biobank. She is the author of more than 90 peer-reviewed articles. In her focus at the forefront of consumer participation in genetics research, services, and policy, she serves in a leadership role on many major international and national organizations, including the Institute of Medicine (IOM) Board on Health Sciences Policy, the National Coalition for Health Professional Education in Genetics Board, and the International Rare Disease Research Consortium

Interim Executive Committee, and is a member of the IOM Roundtable on Translating Genomic-Based Research for Health. She is on the editorial boards of several journals. She was instrumental in the passage of the Genetic Information Nondiscrimination Act. In 2005, she received an honorary doctorate from Iona College for her work in community engagement, the first Patient Service Award from the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy in 2007, the Research!America Distinguished Organization Advocacy Award in 2009, and the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011. She is an Ashoka Fellow.

Appendix C

Statement of Task

An ad hoc planning committee will plan and conduct a public workshop to discuss ways to improve the efficiency and effectiveness of translation of basic genomic discoveries. The goal of the workshop will be to advance discussions among a broad array of stakeholders, including academic and clinical researchers, policy makers, industry representatives, and others. The planning committee will develop the workshop agenda, select and invite speakers and discussants, and moderate the discussions. An individually authored summary of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures.

Appendix D

Registered Attendees

Euan Ashley
Stanford University

Scott Beck
Mayo Clinic

Paul Billings
Life Technologies

Bruce Blumberg
Kaiser Permanente Northern California

Heather Brown
Blue Cross and Blue Shield Association

Wylie Burke
University of Washington, Seattle

Atul Butte
Stanford University

Melina Cimler
Illumina

Sean David
Stanford University

Vamil Divan
Credit Suisse

Michael Dougherty
American Society of Human Genetics

Geoffrey Duyk
TPG Biotech/ART

Samir Elamrani
Wilson Sonsini Goodrich & Rosati

Patricia Furlong
Parent Project Muscular Dystrophy

Daniel Geschwind
University of California, Los Angeles

Geoffrey Ginsburg
Duke University

William Gunn
Mendeley

Carolyn Hoban
Multiple Myeloma Research Foundation

Julia Hoeng
Philip Morris International

Eric Hoffman
Children's National Medical Center

Gillian Hooker
Johns Hopkins University/ National Human Genome Research Institute Genetic Counseling Training Program

David Huntsman
British Columbia Cancer Agency

Elizabeth Iorns
Science Exchange

Samuel Johnson
Kaiser Permanente Colorado

Mohamed Khan
British Columbia Cancer Agency

Jana Klauer
Private Practice in Nutrition and Obesity

Roger Klein
Cleveland Clinic Foundation

Gabriela Lavezzari
P*h*RMA

Edison Liu
The Jackson Laboratory

Robert McCormack
Veridex, LLC

Kelly Marie McVearry
Northrop Grumman Health IT

C. Douglas Monroe
Kaiser Permanente

Jan Nowak
NorthShore University HealthSystem

Robert Nussbaum
University of California, San Francisco

Jyotishman Pathak
Mayo Clinic

Vijay Pillai
Oracle Health Sciences

Victoria Pratt
Quest Diagnostics

Ronald Przygodzki
U.S. Department of Veterans Affairs

Laura Lyman Rodriguez
National Human Genome Research Institute

Allen Roses
Duke University

Helena Rubinstein
Independent

William Rutter
Synergenics, LLC

Danielle Scelfo
Genomic Health

Sheri Schully
National Cancer Institute

Joan Scott
National Coalition for Health Professional Education in Genetics

Randy Scott
InVitae Corporation

Cecili Sessions
Air Force Medical Support Agency

Sam Shekar
Northrop Grumman

Todd Sherer
The Michael J. Fox Foundation for Parkinson's Research

Pamela Shiao
Azusa Pacific University

Moyra Smith
University of California, Irvine

Kathryn Johansen Taber
American Medical Association

Weimin Tang
CrownBio

Sharon Terry
Genetic Alliance

James Thompson
McKesson

David Veenstra
University of Washington, Seattle

Michael Watson
American College of Medical Genetics and Genomics

Thomas White
University of California, Berkeley

Catherine Wicklund
Northwestern University

Dave Wilson
Oracle

Dara Wright
Affymetrix