Genome-Based Therapeutics: Targeted Drug Discovery and Development: Workshop Summary

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

GENOME-BASED THERAPEUTICS

Targeted Drug Discovery and Development

WORKSHOP SUMMARY

Adam C. Berger and Steve Olson, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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

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SARAH H. BEACHY, Christine Mirzayan Science and Technology Policy Graduate Fellow (August to November 2011)
CLAIRE F. GIAMMARIA, Research Associate
TONIA E. DICKERSON, Senior Program Assistant

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ANDREW N. FREEDMAN, Branch Chief, Clinical and Translational Epidemiology Branch, Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD
GEOFFREY GINSBURG, Director, Center for Genomic Medicine, Institute for Genomic Sciences and Policy, Duke University, Durham, NC
RICHARD J. HODES, Director, National Institute on Aging, Bethesda, MD

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SHARON KARDIA, Professor and Chair of Epidemiology; Director, Public Health Genetics Program; Director, Life Science and Society Program; Co-Director, Center for Public Health and Community Genomics, University of Michigan School of Public Health, Ann Arbor

MOHAMED KHAN, Representative of the American Medical Association; Leader of Radiation Oncology, Vancouver Cancer Centre, BC Cancer Agency, Vancouver, BC, Canada

MUIN KHOURY, Director, National Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, GA

THOMAS LEHNER, Director, Office of Genomics Research Coordination, National Institute of Mental Health, Bethesda, MD

DEBRA LEONARD, Representative of the College of American Pathologists; Professor and Vice Chair for Laboratory Medicine; Director of the Clinical Laboratories; Director of the Pathology Residency Training Program, Weill Cornell Medical Center of Cornell University, New York, NY

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VICTORIA M. PRATT, Chief Director, Molecular Genetics, Quest Diagnostics Nichols Institute, Chantilly, VA

RONALD PRZYGODZKI, Associate Director for Genomic Medicine and Acting Director of Biomedical Laboratory Research and Development, Department of Veterans Affairs, Washington, DC

ALLEN D. ROSES, President and Chief Operating Officer, Cabernet, Shiraz and Zinfandel Pharmaceuticals; and Jefferson–Pilot Professor of Neurobiology and Genetics, Professor of Medicine (Neurology); Director, Deane Drug Discovery Institute; Senior Scholar, Fuqua School of Business, R. David Thomas Executive Training Center, Duke University, Durham, NC

KEVIN A. SCHULMAN, Professor of Medicine and Business Administration; Director, Center for Clinical and Genetic Economics; Associate Director, Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

JOAN A. SCOTT, Executive Director, National Coalition for Health Professional Education in Genetics, Lutherville, MD

DAVID VEENSTRA, Professor, Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy, University of Washington, Seattle

MICHAEL S. WATSON, Executive Director, American College of Medical Genetics and Genomics, Bethesda, MD

DANIEL WATTENDORF, Deputy Chief, Medical Innovations, Department of the Air Force; Program Manager, DARPA/Defense Sciences Office, Arlington, VA

CATHERINE A. WICKLUND, Past President, National Society of Genetic Counselors; Director, Graduate Program in Genetic Counseling; Associate Professor, Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL

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CLAIRE F. GIAMMARIA, Research Associate

TONIA E. DICKERSON, Senior Program Assistant

ANDREW POPE, Director, Board on Health Sciences Policy

Reviewers

This report 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 report as sound as possible and to ensure that the report 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 report:

Jeffrey A. Bluestone, Executive Vice Chancellor and Provost, University of California, San Francisco
Walter M. Capone, Chief Operating Officer, Multiple Myeloma Research Foundation, Norwalk, CT
Steven E. Hyman, Harvard Distinguished Service Professor; Professor of Stem Cell and Regenerative Biology, The Broad Institute, Cambridge, MA
Gary Palmer, Senior Vice President, Medical Affairs and Commercial Development, Foundation Medicine, Inc., Cambridge, MA

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Melvin Worth.**

Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author and the institution.

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The Roundtable wishes to express its gratitude to the expert speakers whose presentations helped outline the challenges in as well as the opportunities for genomics-guided strategies for drug development. The Roundtable also wishes to thank the members of the planning committee for their work in developing an excellent workshop agenda. The project director would like to thank project staff who worked diligently to develop both the workshop and the resulting summary.

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Abbreviations and Acronyms

ALK	anaplastic lymphoma kinase
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFTR	cystic fibrosis transmembrane conductance regulator
CLL	chronic lymphocytic leukemia
CMS	Centers for Medicare & Medicaid Services
DARPA	Defense Advanced Research Projects Agency
FDA	U.S. Food and Drug Administration
FEV	forced expiratory volume
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GWAS	genome-wide association studies
IUO	investigational use only
MMRC	Multiple Myeloma Research Consortium
MMRF	Multiple Myeloma Research Foundation
NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health
NPC	NCATS Pharmaceutical Collection

NSCLC	non-small-cell lung cancer
PwC	PricewaterhouseCoopers
SNP	single nucleotide polymorphism

1

Introduction[1]

The number of new drug approvals has remained reasonably steady for the past 50 years at around 20 to 30 per year (Munos, 2009), while at the same time the total spending on health-related research and development has tripled since 1990 (Scannell et al., 2012). There are many suspected causes for this trend, including increased regulatory barriers, the rising costs of scientific inquiry, a decrease in research and development efficiency, the downstream effects of patent expirations on investment, and the lack of production models that have successfully incorporated new technology (Paul et al., 2010; Scannell et al., 2012). Regardless, this trajectory is not economically sustainable for the businesses involved, and, in response, many companies are turning toward collaborative models of drug development, whether with other industrial firms, academia, or government (IOM, 2011). Introducing greater efficiency and knowledge into these new models and aligning incentives among participants may help to reverse the trends highlighted above, while producing more effective drugs in the process.

New technologies have the potential to open up avenues of development and to identify new drug targets to pursue. Specifically, improved validation of gene–disease associations through genomics research has the potential to revolutionize drug production and lower development costs. Genetic information has helped developers by increasing their understand-

[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 and opinions are those of individual presenters and participants and should not be construed as reflecting any group consensus.

BOX 1-1
Workshop Objectives

The workshop New Paradigms in Drug Discovery: How Genomic Data Are Being Used to Revolutionize the Drug Discovery and Development Process had three broad objectives:

1. To examine the impact of and investment in genetic and genomic technologies and data in drug discovery and development.
2. To examine and discuss the challenges for incorporating genomic technologies into drug development and to explore solutions to remedy those challenges.
3. To discuss and explore how innovative, novel, and global partnerships between academia, industry, foundations, and government can enable the use of genomic information for more efficient and effective drug discovery and development programs.

ing of the mechanisms of disease as well as individual patients' reactions to their medications. Warfarin, Gleevec®, XALKORI®, Kalydeco™, and Zelboraf® are all examples of pharmaceuticals that utilize genetic information to inform dosing or whose activity and effectiveness is determined by inherent genetic properties of the patient or their tumor (i.e., a targeted therapeutic). However, even with these successes there remains skepticism over how useful genomic information will be to the larger drug development process (Pollack, 2010; Wade, 2010). There is a need to identify the success factors for the various models that are being developed, whether they are industry-led, academia-led, or collaborations between the two.

The Roundtable on Translating Genomic-Based Research for Health held a workshop on March 21, 2012, titled New Paradigms in Drug Discovery: How Genomic Data Are Being Used to Revolutionize the Drug Discovery and Development Process. The purpose of the workshop was to examine the general approaches being used to apply genomic-based research results to the discovery and development of new drugs, the successes achieved so far, and the challenges ahead.[2]

STRUCTURE OF THE REPORT

Box 1-1 provides the overall objectives of the workshop. Chapter 2 discusses the current environment for personalized medicine approaches to

[2] The full statement of task can be found in Appendix C.

drug discovery and development. Chapter 3 examines three case studies as illustrations of both the promise and the challenges of genomic-based drug discovery and development. Chapter 4 looks at the application of emerging technologies, such as next-generation sequencing, to this field. Chapter 5 examines several specific evolving paradigms in genomic-based drug development, approval, and prescribing. Finally, Chapter 6 features comments and discussions drawn from throughout the workshop on overcoming the challenges and achieving the promise of genomic-based drug discovery and development.

2

The Current Landscape

Important Points Highlighted by Individual Speakers

- Genomic information has great potential to identify new pathways involved in complex diseases, suggest new therapeutic targets, evaluate adverse drug effects, and identify populations for which a drug is most effective or has the least deleterious effects.
- Pharmaceutical and biotechnology companies have integrated genomics-based strategies for drug discovery, but this has largely not been translated into late-stage development.
- The cost of therapeutic development has increased significantly over the past few decades while the success rate has remained unchanged, and many drug failures often occur after large investments have been made.
- While targeted therapeutics may decrease market size, overall market share may increase, leading to a significant potential advantage for developing stratified medicines.
- Commercial and marketing organizations may need to be aligned with research and development in order to develop a successful commercial model for targeted therapeutics.

GREAT EXPECTATIONS

The advent of the genomic era generated great expectations for drug discovery and development, said Geoffrey Ginsburg of Duke University. Genomic information was expected to provide insights into the underlying biological mechanisms of disease and to highlight biological targets and pathways that would be amenable to new drug discovery. It indicated an approaching ability to stratify populations based on genomic-based biomarkers, leading to better clinical development programs. Genomic data would reveal how individuals might respond to, be resistant to, or have adverse effects from a drug, creating the potential for personalized medicines. As a result of these and other changes, genomic data would increase the efficiency of drug discovery and development, increase the success rate of new drugs, enhance safety, and decrease costs.

The genomic era has made major strides toward delivering on these promises, Ginsburg said. Several genomics-enabled products have been approved in recent years or are in development for use, including three that are described in Chapter 3 of this report: crizotinib for the treatment of non-small-cell lung cancer, pomaglumetad methionil for schizophrenia, and ivacaftor for cystic fibrosis. In addition, academic–industry partnerships have formed to leverage a deep understanding of disease biology from the academic realm and to meld that to product development and commercialization in industry. Precompetitive collaborations, such as the European Innovative Medicines Initiative and programs sponsored by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH), have sought to lay the groundwork for new therapeutics.

CURRENT USE AND POTENTIAL

Nicholas Davies from PricewaterhouseCoopers (PwC) elaborated on the potential and current use of genomic-based drug discovery and development during his presentation in the workshop's initial session. The efficiency and quality of research inputs have undergone huge improvements. The cost of DNA sequencing has dropped by many orders of magnitude and continues to drop. The ability to find targets, screen compounds, and generate chemical libraries is immense. The development of companion diagnostics has made it possible to target patient subpopulations that would be expected to benefit from a specific treatment. As Mark Trusheim from the Sloan School of Management at the Massachusetts Institute of Technology added, in this way patients and providers have more and better treatment options, regulators gain a better sense of risk-benefit comparisons, drug and diagnostic innovators generate more products and profits, and

payers spend less on ineffective therapies. "We see opportunities not just for developers and patients, but for everyone in the cycle. . . . It has to work for everyone or it is not going to work at all as a system."

Both Ginsburg and Davies said that a genomic-based approach continues to have tremendous potential. For example, a recent analysis of genome-wide association studies (GWAS) found that such studies can reveal new pathways involved in complex diseases and suggest potential therapeutic options that had not previously been considered for those indications (Collins, 2011). This analysis also suggested that the off-target or adverse effects of those drugs could be monitored through the analysis of genes discovered through these unbiased genome-wide approaches.

Garret FitzGerald of the University of Pennsylvania added that it has already been demonstrated that genetic information can be used to evaluate adverse drug effects. Studies designed specifically to determine whether particular gene variants can be used to identify individuals at particular risk have been successful for both lumiracoxib and abacavir and required only very small numbers of study participants to do so.

According to recent data from the U.S. Food and Drug Administration (FDA), more than 110 marketed drugs have pharmacogenetic biomarkers on the label (see Table 2-1),[1] and the need for further drugs developed through a genomic-based approach remains strong. As Trusheim observed, many major drugs, including hypertension drugs, heart failure drugs, antidepressants, cholesterol drugs, and asthma drugs, are ineffective for large portions of the population (Spear et al., 2001). Furthermore, ineffective therapies cause substantial harm. Medication-related health problems account for an estimated 3 to 7 percent of hospital admissions (Pirmohamed et al., 2004), and 15 percent of patients experience an adverse drug reaction during hospital stays. An important consequence of these adverse reactions is heightened patient noncompliance.

Oncology has made the most progress in developing personalized medicine (defined in Box 2-1), Davies said, but genomic-based research is also starting to make progress on diseases of the cardiovascular system, central nervous system, and immune system. Metabolic, respiratory, and viral diseases also are starting to yield to this approach, though progress has been slower than expected.

Pharmaceutical companies and biotechnology companies are striving to modernize their drug discovery and development processes. Davies pointed to data from the Tufts Center for the Study of Drug Development (Tufts, 2010) showing that 100 percent of surveyed companies are using a discovery strategy that involves a genetic or genomic approach. Thirty percent

[1] For an up-to-date listing of these drugs, see http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.

TABLE 2-1 Pharmacogenomic Biomarkers in Drug Labels

Drug	Therapeutic Area	Biomarker
Abacavir	Antivirals	HLA-B*5701
Aripiprazole	Psychiatry	CYP2D6
Arsenic Trioxide	Oncology	PML/RARα
Atomoxetine	Psychiatry	CYP2D6
Atorvastatin	Metabolic and Endocrinology	LDL receptor
Azathioprine	Rheumatology	TPMT
Boceprevir	Antivirals	IL28B
Brentuximab Vedotin	Oncology	CD30
Busulfan	Oncology	Ph Chromosome
Capecitabine	Oncology	DPD
Carbamazepine	Neurology	HLA-B*1502
Carisoprodol	Musculoskeletal	CYP2C19
Carvedilol	Cardiovascular	CYP2D6
Celecoxib	Analgesics	CYP2C9
Cetuximab (1)	Oncology	EGFR
Cetuximab (2)	Oncology	KRAS
Cevimeline	Dermatology and Dental	CYP2D6
Chlordiazepoxide and Amitriptyline	Psychiatry	CYP2D6
Chloroquine	Anti-Infectives	G6PD
Cisplatin	Oncology	TPMT
Citalopram (1)	Psychiatry	CYP2C19
Citalopram (2)	Psychiatry	CYP2D6
Clobazam	Neurology	CYP2C19
Clomiphene	Reproductive and Urologic	Rh genotype
Clomipramine	Psychiatry	CYP2D6
Clopidogrel	Cardiovascular	CYP2C19
Clozapine	Psychiatry	CYP2D6
Codeine	Analgesics	CYP2D6
Crizotinib	Oncology	ALK
Dapsone	Dermatology and Dental	G6PD
Dasatinib	Oncology	Ph Chromosome
Denileukin Diftitox	Oncology	CD25
Desipramine	Psychiatry	CYP2D6
Dexlansoprazole (1)	Gastroenterology	CYP2C19
Dexlansoprazole (2)	Gastroenterology	CYP1A2
Dextromethorphan and Quinidine	Neurology	CYP2D6
Diazepam	Psychiatry	CYP2C19
Doxepin	Psychiatry	CYP2D6
Drospirenone and Ethinyl Estradiol	Reproductive	CYP2C19
Erlotinib	Oncology	EGFR
Esomeprazole	Gastroenterology	CYP2C19
Everolimus	Oncology	Her2/neu
Exemestane	Oncology	ER &/PgR receptor

TABLE 2-1 Continued

Drug	Therapeutic Area	Biomarker
Fluorouracil	Dermatology and Dental	DPD
Fluoxetine	Psychiatry	CYP2D6
Fluoxetine and Olanzapine	Psychiatry	CYP2D6
Flurbiprofen	Rheumatology	CYP2C9
Fluvoxamine	Psychiatry	CYP2D6
Fulvestrant	Oncology	ER receptor
Galantamine	Neurology	CYP2D6
Gefitinib	Oncology	EGFR
Iloperidone	Psychiatry	CYP2D6
Imatinib (1)	Oncology	C-Kit
Imatinib (2)	Oncology	Ph Chromosome
Imatinib (3)	Oncology	PDGFR
Imatinib (4)	Oncology	FIP1L1-PDGFRα
Imipramine	Psychiatry	CYP2D6
Indacaterol	Pulmonary	UGT1A1
Irinotecan	Oncology	UGT1A1
Isosorbide and Hydralazine	Cardiovascular	NAT1; NAT2
Ivacaftor	Pulmonary	CFTR (G551D)
Lapatinib	Oncology	Her2/neu
Lenalidomide	Hematology	Chromosome 5q
Letrozole	Oncology	ER &/PgR receptor
Maraviroc	Antivirals	CCR5
Mercaptopurine	Oncology	TPMT
Metoprolol	Cardiovascular	CYP2D6
Modafinil	Psychiatry	CYP2D6
Nefazodone	Psychiatry	CYP2D6
Nilotinib (1)	Oncology	Ph Chromosome
Nilotinib (2)	Oncology	UGT1A1
Nortriptyline	Psychiatry	CYP2D6
Omeprazole	Gastroenterology	CYP2C19
Panitumumab (1)	Oncology	EGFR
Panitumumab (2)	Oncology	KRAS
Pantoprazole	Gastroenterology	CYP2C19
Paroxetine	Psychiatry	CYP2D6
Peginterferon alfa-2b	Antivirals	IL28B
Perphenazine	Psychiatry	CYP2D6
Pertuzumab	Oncology	Her2/neu
Phenytoin	Neurology	HLA-B*1502
Pimozide	Psychiatry	CYP2D6
Prasugrel	Cardiovascular	CYP2C19
Pravastatin	Metabolic and Endocrinology	ApoE2
Propafenone	Cardiovascular	CYP2D6
Propranolol	Cardiovascular	CYP2D6
Protriptyline	Psychiatry	CYP2D6
Quinidine	Antiarrhythmics	CYP2D6
Rabeprazole	Gastroenterology	CYP2C19

continued

TABLE 2-1 Continued

Drug	Therapeutic Area	Biomarker
Rasburicase	Oncology	G6PD
Rifampin, Isoniazid, and Pyrazinamide	Anti-Infectives	NAT1; NAT2
Risperidone	Psychiatry	CYP2D6
Sodium Phenylacetate and Sodium Benzoate	Gastroenterology	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)
Sodium Phenylbutyrate	Gastroenterology	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)
Tamoxifen	Oncology	ER receptor
Telaprevir	Antivirals	IL28B
Terbinafine	Antifungals	CYP2D6
Tetrabenazine	Neurology	CYP2D6
Thioguanine	Oncology	TPMT
Thioridazine	Psychiatry	CYP2D6
Ticagrelor	Cardiovascular	CYP2C19
Tolterodine	Reproductive and Urologic	CYP2D6
Tositumomab	Oncology	CD20 antigen
Tramadol and Acetaminophen	Analgesics	CYP2D6
Trastuzumab	Oncology	Her2/neu
Tretinoin	Dermatology and Dental	PML/RARα
Trimipramine	Psychiatry	CYP2D6
Valproic Acid	Psychiatry	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)
Vemurafenib	Oncology	BRAF
Venlafaxine	Psychiatry	CYP2D6
Voriconazole	Antifungals	CYP2C19
Warfarin (1)	Hematology	CYP2C9
Warfarin (2)	Hematology	VKORC1

SOURCE: U.S. Food and Drug Administration.

BOX 2-1
Definition

"Personalized medicine" or "stratified medicine," as used by speakers in the workshop, refers to the use of an individual's characteristics, including genetic information, to guide medical decisions regarding prevention, diagnosis, and treatment of disease. This tailoring of medical treatments is based on the ability to classify individuals into subpopulations so that they can benefit from the most efficacious treatments or interventions or be spared from expense or deleterious side effects.

require that all their compounds have an associated biomarker before going into clinical development. More than 80 percent of companies have established strategic partnerships related to personalized medicine, and half have collected DNA samples from clinical trial participants. In addition, companies that have developed genomic and diagnostic technologies have recently been acquired by other companies, suggesting that these approaches continue to be viewed favorably. However, Davies said, in large part these methods are not being employed in late-stage development due to a reluctance on the part of pharmaceutical companies to enable genomic- or genetic-based trials.

One concern about targeted drugs, Trusheim said, has been that they will have smaller markets and therefore attract less investment. But higher efficacy for targeted groups can in fact yield more market share and help minimize the overall reduction in market size (Figure 2-1; Trusheim et al., 2007). Underserved patients may enter the market and look for treatment

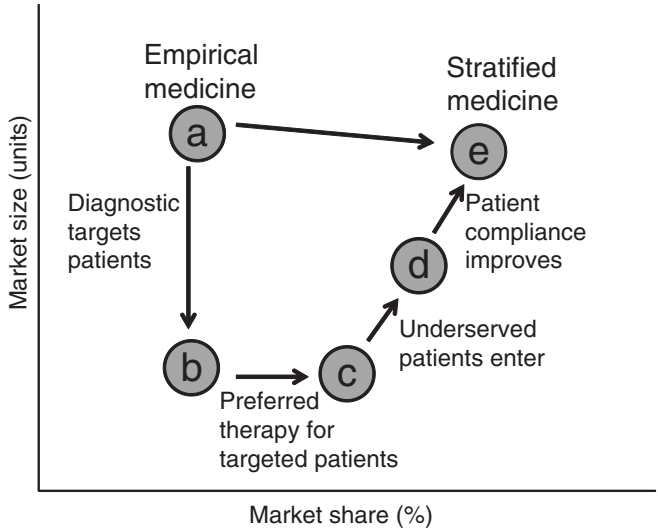

FIGURE 2-1 A number of factors influence the market potential for targeted therapeutics with the prospect of reduced market size leading to increased market share.
NOTE: As defined by Trusheim et al. (2007), an empirical medicine, as opposed to a stratified medicine, is not developed based upon the characteristics of an individual or a subpopulation of individuals. These medicines are based on overall population response and may work for a large or a small amount of individuals without using (either because it is not necessary or one is not available) a methodology to identify which groups may respond.
SOURCE: Trusheim et al., 2007.

if they are more confident that a treatment will work for them. In addition, providers may be more confident to prescribe a drug, especially since possible side effects are outweighed by the benefits. If biomarkers can separate those who will respond from those who will not, a drug will perform much better in the response group, potentially leading to quicker adoption, better patient compliance, more market share, and a higher price premium. This can produce a "niche buster" where the clinical performance of the drug and diagnostic drives commercial performance. For example, a study of the use of trastuzumab and panitumumab in cancer and bapineuzumab in Alzheimer's disease showed a substantial potential economic advantage to using stratified-medicine strategies (Trusheim et al., 2011).

A final consideration in the adoption of personalized medicine, Davies said, is that cost-effective and outcomes-driven therapy will be critical in the future as health care changes. Care will become more preventive, and medicine in general will be more patient-centric. Cost control and value in outcomes will be increasingly important focuses. New therapies may need to be cost neutral, in that they make up for the additional expense of the therapy through reduced costs elsewhere, whether hospital readmissions, surgery, or some other form of care.

THE ECONOMIC CHALLENGE

Genomic-based approaches are an area of promise in an otherwise troubled industry. The success rate for new drugs in the pharmaceutical industry—with success defined as the ability to identify a compound that will be approved and be commercially successful—has remained more or less constant over the last few decades, with occasional upticks, Ginsburg noted (Mullard, 2012). On average, fewer than 1 in 10 compounds entering preclinical testing will be successful. Furthermore, as Davies observed, failures often occur after large investments have been made. In 2010, 45 separate drugs failed in Phase III clinical trials, with the average cost for a Phase III trial being about $100 million. Meanwhile, patents are expiring on profitable drugs, which is further reducing resources. The costs of failures add to development expense and decrease the willingness to invest in the process.

Because of declining productivity, more resources have been needed to produce a constant level of new drugs. According to an analysis in *Nature Reviews Drug Discovery*, productivity in the pharmaceutical industry, measured in terms of output per billion dollars spent, has been decreasing logarithmically (Figure 2-2). This declining productivity has become known as "Eroom's law." "Eroom" is "Moore" spelled backward, and the name is meant to imply a backward version of "Moore's law," the observation made by Intel co-founder Gordon Moore in 1965 that the number of

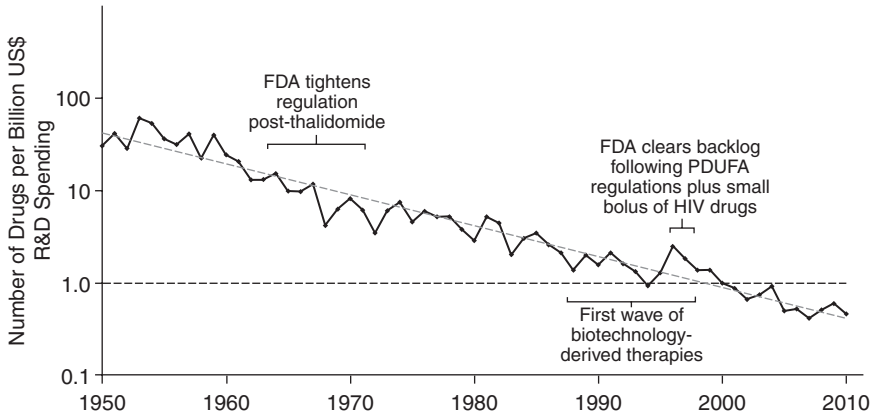

FIGURE 2-2 The number of new drugs approved per billion dollars spent has declined steadily on a logarithmic scale for more than a half-century.
NOTE: FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; PDUFA, Prescription Drug User Fee Act; R&D, research and development.
SOURCE: Scannell et al., 2012.

components in integrated circuits was doubling approximately every year. In the pharmaceutical industry, the output per billion dollars spent has consistently decreased by half every 9 years since 1952.

To remain in the pharmaceutical business, companies and investors need to make money. But the return on capital investment is diminishing to the point that the existing financial model is no longer sustainable, Davies said. The average return on capital after 5 years' sales is currently about $75 million per billion dollars invested, which is clearly not sustainable. A recent report in *Forbes* magazine estimated that some companies are spending upward of $12 billion per launched product (Herper, 2012). As FitzGerald noted, "catastrophe rather than opportunity usually drives radical change . . . and this model is about to change."

According to Davies, the pharmaceutical industry invested an estimated $125 billion in research and development across the industry (Hewitt et al., 2011). An estimated 5 percent of this amount was spent specifically on genetic and genomic research, or about $6 billion including partnerships, acquisitions, and internal research. Companies have slightly different levels and strategies of investment, with some investing more heavily in internal research and some more heavily in external research. As discussed later in this summary and in a prior Roundtable on Translating Genomic-Based Research for Health workshop (IOM, 2011), academic partnerships have become popular, though ways of esti-

mating the value generated by these partnerships remain rudimentary. "Pharma[ceutical companies] and academia need to understand how to work together more effectively and demonstrate that they generate value from [partnering]," Davies said.

CHALLENGES FOR GENOMIC-BASED APPROACHES

Despite its promise, a genomic-based approach to drug discovery and development is surrounded by great uncertainties, as noted by each of the speakers in the workshop's opening session. As FitzGerald pointed out, genomic testing must be shown to influence clinical outcomes to guarantee reimbursement. Adoption will also require substantial physician and patient education, a financial incentive for test development, and patent protection. Davies observed that oncology has been the poster child for a molecular approach to target discovery, diagnosis in the clinic, development of companion diagnostics, and treatment. However, these therapies tend to be expensive, making their value in general medicine uncertain. Furthermore, outside oncology, the value of targeted therapies for the most part remains to be determined. In addition, regulatory constraints are getting tighter, which is an issue for thinking about innovative approaches to bringing medicines to market with companion diagnostics or a targeted approach.

In general, Davies continued, the commercial model for the development of personalized medicines remains immature, with the commercial and marketing organizations within industry retaining a preference to go to market with a more general molecule than with a targeted therapeutic. An analysis by PwC estimates that the companion diagnostic market will reach $42 billion by 2015.[2] "There is a huge market for companion diagnostics," Davies said, "but they are culturally and from a time perspective [off]-kilter with the development cycle and culture of the research and development industry."

Trusheim added that there are countervailing forces at play. Developing both a drug and a diagnostic can take longer, especially given the need to recruit targeted patient pools and synchronize development of the diagnostic; the resulting market may be smaller than for a more general drug; and developers face an increased risk of failure since the drug approval is dependent upon simultaneous approval of the diagnostic. Further complicating the matter, regulatory requirements differ because therapeutics and diagnostics generally fall under different legislative authorities. In addition, product exclusivity concerns raise profitability questions among companies.

[2] For more information, see http://www.pwc.com/gx/en/pharma-life-sciences/pharmaceutical-industry-thought-leadership/pharma-life-sciences-mergers-acquisitions-diagnostics-2011.jhtml.

Patients are prone to confusion regarding the value of genetic and genomic technologies, and providers tend to be untrained in these areas, which slows adoption. Drug reimbursement has been slow, reimbursements for diagnostics remain focused on costs rather than value, and payers do not invest in research and development, even though they benefit from stratification. Many payers and health care providers remain unconvinced that many such therapies improve people's health or are cost-effective.

In addition to its successes, Trusheim said, genomic-based drug development offers cases where these challenges have so far prevailed. For example, no candidate marker for response to bevacizumab has reached a level of performance acceptable to regulators, and genetic tests for warfarin response have not been widely adopted. FitzGerald added that while it is well established that genetic variants impact warfarin metabolism, there is little change in prescribing practices for testing largely because physicians are reluctant to move away from established measures of anticlotting effects. It also still remains to be seen whether there is an impact on clinical outcomes from utilizing this genetic information. Similarly, FitzGerald said, meta-analyses of multiple studies have not suggested a benefit from segregating patients based on genotype in using clopidogrel, which is a medication used to prevent thrombotic events that has a total of $6-$7 billion in annual sales.

Davies stressed the need to consider what the impact on quality and cost of health care will be from genetic or genomic strategies rather than the activity itself. Translating the multitude of genetic and genomic data into a better understanding of disease, improved targets, rapid translation to the clinic, better patient selection, and increased safety will be crucial, he said. FitzGerald noted that "genomic variation is only one hand clapping" and urged that other variables, such as environmental effects, be integrated with genomic information to fully explore the consequences of drug exposure.[3] He also suggested that collaboration with sponsors in small studies that utilize next-generation sequencing and drug-evoked phenotyping of adverse events presents an opportunity for genomic and genetic based strategies.

More generally, Ginsburg concluded, the great expectations generated by the promise of genetic-based drug discovery and development have not always been met (Pollack, 2010). According to a recent article in *Clinical Pharmacology and Therapeutics*, "the level of trust between the different actors in drug development needs to be urgently restored following the disillusionment felt by many that the sequencing of the human genome did

[3] A concept for an integrated data network of genomic and other information is described in *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (NRC, 2011).

not deliver the expected therapeutic breakthroughs" (Goldman, 2012). But there is optimism moving forward as well, Ginsburg said, noting that the same article pointed out that "there is now a unique window of opportunity to tackle these challenges" and a key model for doing so is establishing new models of collaboration among industry, academia, patient groups, regulators, and biotech companies.

3

Case Studies

Important Points Highlighted by Individual Speakers

- The development of drugs and companion diagnostics requires the collection of rigorous and reliable chemical, pharmaceutical, and biological data.
- Candidate gene association studies can identify genetic markers associated with treatment response, generating hypotheses for further testing.
- Small-sample randomized clinical trials can generate valuable data that can be aggregated to generate information similar to that from a large clinical trial.
- Drug and diagnostic development can proceed quickly if the appropriate patient populations can be identified.

The second session of the workshop featured case studies of genomic-based drug discovery and development, two which have gained FDA approval and a third that is still in development. The first example was the use of crizotinib for non-small-cell lung cancer, the second was the use of pomaglumetad methionil for schizophrenia, and the third was the use of ivacaftor for cystic fibrosis. Each of these drugs emerged from a somewhat different development process, depending on the data available, the state of biological understanding, and the nature of the disease. But, together, these three examples demonstrate that genomic-based approaches

can yield new drugs and diagnostics that have substantial benefits for human health.

THE DEVELOPMENT OF CRIZOTINIB FOR TREATMENT OF NON-SMALL-CELL LUNG CANCER

The drug crizotinib provides an excellent example of how a diagnostic test can be used to identify patients who will benefit from a treatment, said Steffan Ho of Pfizer Inc. Crizotinib, which was originally known as PF-02341066 and has the trade name XALKORI, is a small molecule that binds to the catalytic site of kinases and competes with ATP, thereby inhibiting kinase activity. Its primary targets are the receptor tyrosine kinases known as c-MET, ALK, and ROS. It was approved for use by the FDA on August 26, 2011.

As stated in the indications and usage notes for crizotinib, "XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test." The related diagnostic device, which was simultaneously approved for use with crizotinib, is the Abbott Vysis ALK Break Apart FISH Probe Kit, which is described in the package insert as "a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small-cell lung cancer tissue specimens to aid in identifying those patients eligible for treatment with XALKORI (crizotinib)." The device is a Class III diagnostic test, requiring the highest level of rigor and scrutiny, because of the risks associated with its use to inform physicians about how to treat or not treat a patient.

The approval of crizotinib was conditional, Ho noted, because it was based on the response rate. At the time of approval, no data were available that demonstrated improvement in patient-reported outcomes or survival with crizotinib. Additional Phase III clinical studies were under way at the time of the workshop to investigate the hypothesis that crizotinib both improves the response rate and provides a survival advantage.

From the treatment of the first patient deemed to be ALK-positive, approval took just 4 years—a "remarkable accomplishment," Ho said (Figure 3-1). While uncommonly fast compared to most drugs, this timeframe has been fairly common in oncology with targeted therapeutic agents, he added. The development of vemurafenib, imatinib, and trastuzumab—other oncology drugs in which targeted patient populations are identified—also went quickly. "It supports the concept that once we can identify the right population, the clinical efficacy is very clear," he said.

In oncology drug development, the datasets that provide the confidence to move into the clinic include not only the chemical and pharmaceutical

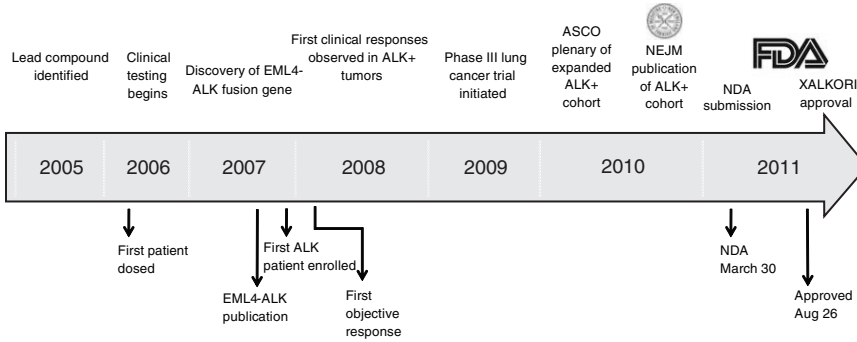

FIGURE 3-1 The development of crizotinib proceeded rapidly from compound identification to target discovery to clinical results to FDA approval.
NOTE: ASCO, American Society of Clinical Oncology; EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; FDA, U.S. Food and Drug Administration; NDA, new drug application; NEJM, *New England Journal of Medicine*.
SOURCE: Ho, workshop presentation, March 21, 2012. Copyright © 2012 Pfizer Inc. All rights reserved.

properties of the drug but also data relevant to the biological setting, Ho said. In the case of crizotinib, more than 700 tumor cell lines were screened for sensitivity to growth inhibition. The results indicated that the drug was active against gastric, esophageal, and lung cancer cell lines that exhibited c-MET amplification; in fact, the drug was originally developed with c-MET as the primary kinase target. It also was found to be active against neuroblastoma with ALK mutation or amplifications, anaplastic large-cell lymphoma with an NPM-ALK fusion, and NSCLC with ALK and ROS alterations. In addition, preclinical tumor models exhibiting dysregulation of c-MET or ALK were highly sensitive to crizotinib. The use of cell models as model systems has limitations, Ho noted, but the regression of tumor cell lines implanted as xenografts into mice provided confidence that the compound could be successful.

In addition, biological understanding of the function of ALK supported the movement of crizotinib into the clinic. Based on the kinase's role in lymphoma, it was known that when ALK undergoes gene rearrangement, it can function as a transforming driver oncogene. In 2007 a team of researchers led by Hiroyuki Mano used a functional genomics screen to demonstrate that ALK is also relevant in NSCLC, being capable of inducing transforming events in 3T3 mouse fibroblast cell lines, tumor growth in mouse models, and malignant transformation in transgenic mice containing the translocated or rearranged ALK gene (Soda et al., 2007).

This study was also followed shortly thereafter by an independent study using a global phosphorylation approach that confirmed the result (Rikova et al., 2007). These basic science results were critical in motivating the development of the drug and shifting the focus of the Phase I development strategy, Ho said.

ALK translocation in lung cancer is a relatively low-frequency alteration, occurring in only about 6 percent of cases (Kris et al., 2011; Riess and Wakelee, 2012). This represents a very low frequency for a stratified medicine approach, Ho observed. For example, with trastuzumab, HER2 amplification is present in about 25 percent of patients. Once the relevant alteration was identified, the clinical trial of crizotinib quickly began to screen for patients who had the ALK translocation. The first patient who was ALK-positive was entered into the trial at the end of 2007. Within a month, the patient's tumor was shrinking. In clinical use, patients have reported symptom relief after just a few doses of crizotinib, suggesting that their tumors began to shrink as soon as the drug reached therapeutic levels in the blood. Furthermore, the overwhelming majority of ALK-positive patients exhibited some level of tumor shrinkage when treated with crizotinib. "Very rapidly we were able to determine that we had targeted the correct oncogene and that we had an active drug," Ho said.

With the demonstration of clinical efficacy, the companion diagnostic test, which initially was laboratory developed, needed further development on a rapid time scale. Within just a few years Abbott Molecular brought forward a test that was suitable for broad clinical use and sufficiently rigorous to enable submission of a PMA application and ultimately to obtain approval as a Class III diagnostic test (Figure 3-2). The development of the diagnostic proceeded in parallel with the clinical trials, so that the data package brought forward to support efficacy included data from patients identified by the final diagnostic test. In this way, the data supported not only the drug approval, but also the diagnostic approval.

Just as with drug candidates, the development of a candidate companion diagnostic test requires rigorous, data-driven evaluation, Ho said. High-quality predictive markers need to be defined that warrant clinical testing, and clinical assays need to be of sufficient quality to test the hypothesis. The transition to the investigational use only (IUO) phase needs to be anticipated, and the decision to pursue IUO development needs to be based on data.

Ho also observed that the approval of crizotinib was not linked on the label to a specific diagnostic, which opens up the possibility that other diagnostics could be used. But questions would arise in bringing forward a second diagnostic. Data could be generated to prove that the second diagnostic was sufficiently equivalent to the original, but to demonstrate that a second diagnostic was detecting patients who would benefit but were not

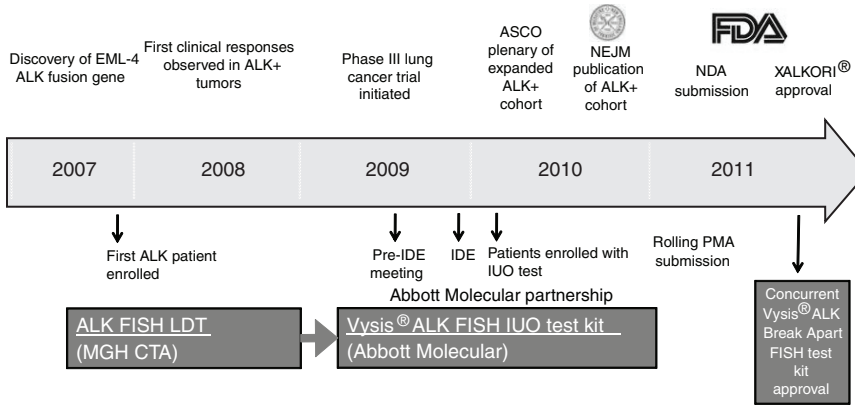

FIGURE 3-2 The development of the diagnostic for ALK alterations also proceeded rapidly from a Phase I laboratory-developed test to PMA approval.
NOTE: ASCO, American Society of Clinical Oncology; EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; FDA, U.S. Food and Drug Administration; FISH, fluorescence in situ hybridization; IDE, investigational device exemption; IUO, investigational use only; LDT, laboratory developed test; MGH CTA, Massachusetts General Hospital clinical trial assay; NDA, new drug application; NEJM, *New England Journal of Medicine*; PMA, premarket approval.
SOURCE: Ho, workshop presentation, March 21, 2012. Copyright © 2012 Pfizer Inc. All rights reserved.

detected by the original diagnostic, new clinical trials would be required. Nevertheless, patients will likely be treated with crizotinib based on results from other than the approved diagnostic test, certainly in other parts of the world. But there will be no formal data supporting those uses. "It raises a lot of interesting questions as far as further development of diagnostic tests."

Ho mentioned the issue of biologic heterogeneity within a patient and within a population. The success of targeted therapy will depend on the source of this heterogeneity. In NSCLC, the population exhibits heterogeneity, which allows population subgroups to be identified. But there is also significant heterogeneity within a tumor, even if one driver mutation within the tumor as a whole is playing a critical role in the cancer. The same situation may apply in other diseases, though this question remains largely unanswered.

The underlying biology of human malignancy is very different from that of other therapeutic indications, Ho said, which has implications for

the potential of stratified medicine. In many cases, today's understanding of the biology of disease is severely limited. As a result, new treatments sometimes move into the clinic in response to hypotheses that are not sufficiently supported. Model organisms provide an opportunity to develop data to support a hypothesis about drug efficacy, whereas moving into the clinic too soon has created challenges for the industry.

"Ultimately, it all requires data," Ho concluded. "One has to have good data to drive those decisions, and good data requires well-designed studies."

USE OF GENETICS TO INFORM DRUG DEVELOPMENT FOR THE TREATMENT OF SCHIZOPHRENIA

Just as genetics is useful for informing drug development for cancers, it is also relevant for other disease states, said Laura Nisenbaum of Eli Lilly and Company. Like cancer, these other diseases can be polymorphic and arise through complex pathways. Diseases like schizophrenia also are polygenic and heritable, and patients have differential responses to treatments.

Schizophrenia is a chronic disabling psychiatric disorder with mortality rates two to three times higher than those in the general population. Even after five decades of modern pharmacotherapy, the clinical management of patients with schizophrenia remains challenging, Nisenbaum said. The efficacy of the currently available drugs to treat the symptoms associated with schizophrenia is still very limited, leading to poor outcomes for these patients, including suicide. Drugs with a greater level of efficacy are needed to increase compliance, reduce adverse effects, and give patients hope for the future.

Recent studies have begun to uncover both common and rare genetic variants that are associated with the disease. But there is as yet no clear understanding of the biological mechanisms that contribute to the disease, Nisenbaum said. Thus, instead of using knowledge of the molecular genetics of the disease, as has been done with cancer, Eli Lilly and Company researchers used knowledge of drug mechanisms to formulate a strategy for the discovery of drug-response markers.

The drug currently being developed for the treatment of schizophrenia by Eli Lilly and Company is called pomaglumetad methionil (hereafter referred to as pomaglumetad). It is an agonist of several group II metabotropic glutamate receptors, in contrast to other available antipsychotics, which target the dopamine D2 receptor, Nisenbaum said. It is thought to work by suppressing excitatory neurotransmission in brain neurocircuits that are dysregulated in schizophrenia.

No specific genetic data were available at the outset of the program to guide the development of the drug, Nisenbaum said. However,

pomaglumetad was known to be active in neurocircuits within the brain, and this information was used to develop the pharmacogenetic strategy to generate hypotheses that could be tested in the clinic. Furthermore, it was felt that any new therapeutic would need to differentiate itself from the available generic and branded competition, leading to significant interest in identifying response markers that could be used to identify patients who would respond better to treatment.

In the original proof-of-concept study, both pomaglumetad and the existing standard-of-care treatment olanzapine significantly decreased the number of symptoms experienced by patients relative to placebo treatment (Patil et al., 2007). However, pomaglumetad did not distinguish itself, based on efficacy, from the standard of care. The developers therefore investigated whether a segment of the population might respond differently to this new type of treatment of schizophrenia. Fortunately, the proof-of-concept study included optional DNA collection for patients, and the collection rate was roughly 70 percent, Nisenbaum stated. Using these DNA samples, a candidate gene association study revealed 16 genetic variants in the serotonin 2A receptor that were associated with differential response to pomaglumetad. In particular, patients who were either homozygous for the rare allele or were heterozygous for a particular single nucleotide polymorphism (SNP) in the receptor had a greater response than patients who were homozygous for the common allele. Similar results were observed in a second clinical trial. This kind of discovery is relatively rare in psychiatric genetics, Nisenbaum said, in that few studies have repeated a finding prospectively in a second clinical trial.

Eli Lilly and Company researchers are now trying to validate the marker in larger registration studies. "You'll have to stay tuned to see how the story plays out," Nisenbaum said.[1] "But we are very excited at the prospect of potentially being able to help tailor something in the psychiatric space where we know that the response rate for these types of drugs is modest."

As genetic markers related to the serotonin 2A receptor are considered for further use in clinical trials, it is necessary to understand additional factors regarding receptor expression, Nisenbaum said. The serotonin variants identified in the proof-of-concept study are all located within a large intron of the serotonin 2A receptor, and the variants do not have an obvi-

[1] Eli Lilly and Company announced results from the first of these studies, H8Y-MC-HBBM, subsequent to the workshop on July 11, 2012. Results indicated that the primary efficacy endpoint had not been met and that neither pomaglumetad nor the active control used, risperidone, had separated from placebo "in either the overall or predefined genetic subpopulation" for the two doses that had been investigated. Further trials are ongoing. Details of the announcement can be found at http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=690836 (accessed August 7, 2012).

ous impact on protein coding. Interestingly, all of the SNPs identified in Caucasian patients lie in tight linkage disequilibrium to one another, and an antisense nested gene is located in this region of the chromosome as well, though the function of the nested gene is not yet known.

An important limitation of the research done to date is that the marker has been identified in one population—non-Hispanic Caucasians—but the genetics of the region are different in African Americans. Researchers now need access to samples from other populations to determine whether the marker is useful for identifying patients from other races and ethnicities.

Because of the limited biological understanding, there was no a priori hypothesis for genetic-based drug discovery and development in this case, Nisenbaum concluded. Rather, hypotheses needed to be generated in Phase II, and these hypotheses then needed to be replicated and validated in Phase III. Also, as was the case with crizotinib, if Phase III results support the need for a companion diagnostic, the development of that diagnostic will need to be timed appropriately so that it does not become the rate-limiting factor for the drug approval.

A GENETIC APPROACH TO THE TREATMENT OF CYSTIC FIBROSIS

Cystic fibrosis is an orphan disease, which differentiates it from cancer and schizophrenia, said Peter Mueller of Vertex Pharmaceuticals. The disease is linked to a genetic defect that leads to an impairment in the ability of cystic fibrosis transmembrane conductance regulator (CFTR) channels to pump chloride and other ions across cell membranes due to either incorrect localization of the protein in the cell or production of nonfunctional proteins. This lack of ion transport causes a variety of adverse outcomes, including the accumulation of a sticky mucus which is characteristic of cystic fibrosis and which eventually leads to chronic infections and death.

More than 1,700 mutations have been linked to impairment of the CFTR channel, which makes gene therapy difficult, Mueller said. Instead, his company has sought to develop small molecules that are orally bioavailable and that improve CFTR function, thereby reducing and halting the progression of the disease.

The mutations responsible for cystic fibrosis can be divided into three categories. People with CFTR gating mutations express channels on the surface of their cells that do not function properly. People with residual CFTR function express a minimal number of channels on their cell surface that do not work optimally. And the largest group consists of people who have almost no CFTR function due to a failure to express channels on cell surfaces.

Understanding the underlying genetics and biology behind the loss of

protein function is essential for progress, Mueller said. Linking the genetics involved with the observed phenotypes pointed to two distinct functional consequences that would need to be corrected to reverse or halt the effects of cystic fibrosis: a lack of surface expression and a lack of transport activity by the CFTR channel. Accordingly, Vertex investigated both potentiators that increase channel activity and correctors that increase the delivery, or trafficking, of CFTR protein to the cell surface. A search of about 10,000 molecules turned up a particular molecule, ivacaftor, that restored function and removed mucus in patient cells with a particular mutation known as G551D. This result was strong enough to take the drug into the clinic.

After negotiations with regulatory agencies in different countries, four studies were conducted: a study in patients 12 and older with the G551D mutation, a similar study in children 6 to 11 years old, a safety study in subjects homozygous for a common cystic fibrosis mutation, and a rollover extension trial of patients who completed two previous trials.

The outcome was "stellar," according to Mueller (Figure 3-3). After just 2 weeks, patients demonstrated a 10 to 12 percent improvement on average in their lung function which persisted throughout the trial (Ramsey et al., 2011). "That never has been seen with any other drug in the respiratory field," Mueller said. "Normally you get about 3 or 4 percent, and then you are really happy." At the same time, sweat chloride concentrations dropped to almost normal levels, indicating an increased function of

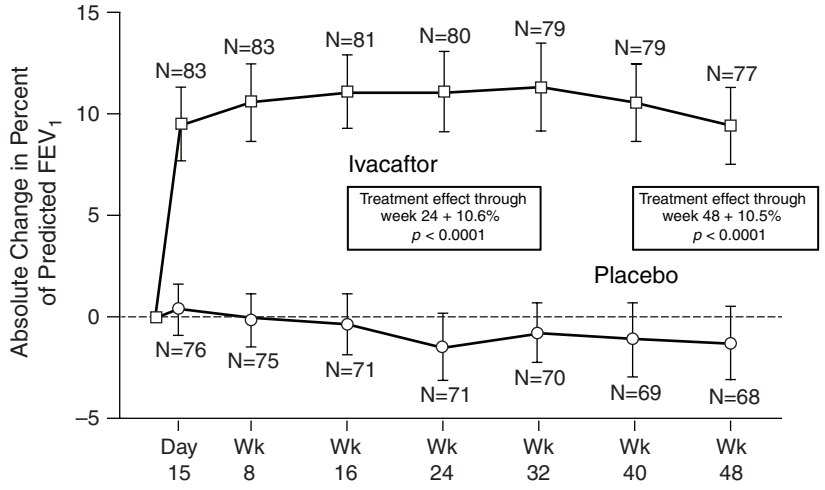

FIGURE 3-3 Administration of ivacaftor produced a rapid and sustained improvement in forced expiratory volume (FEV), which is a measure of lung function. SOURCE: Ramsey et al., 2011.

the channels systemically. Sweat chloride is an indirect rather than a direct measure of what is happening in the lungs, Mueller noted, but more work is being done on validating the results.

Treatment also had other benefits. Most important, it allowed patients to gain weight, which is difficult for cystic fibrosis sufferers because of the high metabolic rate they need to support their breathing. Also, the number of pulmonary exacerbations dropped substantially. Finally, patients taking ivacaftor had fewer adverse events than the patients taking a placebo, and no important safety concerns were identified for the patients on the drug. Even after 3 years on the drug, Mueller noted, patients report that they are still doing well, and these long-term benefits have been confirmed by a new lung imaging technology that uses hyperpolarized helium to measure airflow. Given these results, the drug was approved in just 3 months and 2 days. "There was work on both ends to make it really happen, [but] it's doable. Everybody wanted to get it to the patients."

Only about 5 percent of patients with cystic fibrosis have a gating mutation such as G551D (Figure 3-4). The first need for people with other

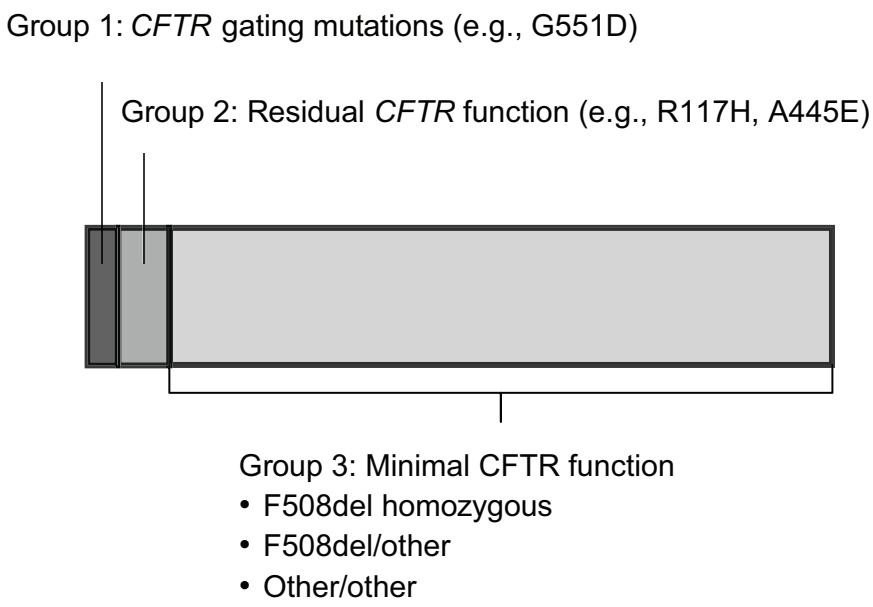

FIGURE 3-4 Approximately 5 percent of people with CFTR mutations have gating mutations such as G551D.
NOTE: CFTR, cystic fibrosis transmembrane conductance regulator.
SOURCE: Mueller, workshop presentation, March 21, 2012; data derived from the Cystic Fibrosis Foundation Annual Patient Registry Report, 2009.

kinds of mutations, Mueller said, is for in vitro data on specific mutations, which can provide the basis for new clinical trials, although he noted that carrying out clinical trials in many cases becomes more complicated since there may only be a few patients with a particular mutation. This applies as well to people who have residual function of CFTR channels. Though their disease tends to be milder, models showing that channel function can be improved can be used to move forward. In some of these cases, combination drugs may be required that enhance channel trafficking as well as conductance. "The hope is, at the end of the day, that almost everybody can benefit from at least the combination regimen and go back to a level that is almost nonsymptomatic," he said. "That's our ultimate goal."

Mueller also noted that ivacaftor was chosen to be extremely selective for the CFTR channel. But this channel plays a role in other conditions, from bronchitis to problems with sperm maturation, which raises the possibility that it could be used in other settings.

Bringing people with cystic fibrosis almost back to normal produces tremendous savings in terms of hospitalization and co-medications, Mueller said. Furthermore, these people are able to go back to work and participate in daily life. Personalized medicine has the potential to make a dramatic difference in a person's life, which creates powerful incentives to create and use such therapies.

One lesson from this experience, Mueller said, is that regulators have a strong interest in bringing the right therapy to the right patients. It is best to involve them early, sometimes across divisions of FDA, and to have a constructive and not adversarial dialogue. Also, regulations and regulators in other parts of the world differ from those in the United States. Harmonized regulatory procedures around the world would bring effective medicines to people faster.

Another important lesson involves the registration of people with a disease. Because cystic fibrosis is an orphan disease, Mueller said, people with the disease are registered, which means they have already been diagnosed and can be approached for the collection of biological samples. It is important for this registry process to be harmonized across different countries, which would help to standardize the data that are gathered and would provide for the wider collection of samples. Data collection and standardization are also occurring through such mechanisms as the Cancer Genome Atlas, Ho said, which is doing multidimensional profiling of a large number of cancer samples. Michelle Penny of Eli Lilly and Company added that during the development of pomaglumetad methionil, the company made the collection of DNA samples mandatory where local regulations and IRB approval allowed, with consents ranging from candidate gene study to whole-genome sequencing. Only by having these

samples available could the company collaborate with partners to do the needed research.

Finally, Mueller made the observation that it was important in cystic fibrosis research to translate results from in vitro systems into the clinic. However, the large number of different mutations complicates the process of finding patients who can benefit from particular therapies. Genotypic and phenotypic strategies need to be combined to facilitate this process.

Small-sample randomized clinical trials known as N-of-1 trials could be a way of generating valuable data (Lillie et al., 2011). First used in the 1960s for behavior research, N-of-1 trials rely on randomized, placebo-controlled, repeated crossovers in a single individual. Remote clinical phenotyping, including ambulatory and home monitoring, has greatly increased the practicality of such trials, and methodologies now exist to aggregate multiple N-of-1 trials to generate information similar to that generated by a large clinical trial. The result would be probability characteristics for markers to use for therapeutic benefit, and discussions are under way with regulatory agencies to enable the use of such information.

"The normal, standard stuff doesn't work when you have only three patients in the world that have one SNP," Mueller said. "We have to be creative and go a new way." New paradigms are needed that can bring benefits to small groups of people. "That's where the world will go, and we will be part of it."

4

Emerging Technologies in Drug Development

Important Points Highlighted by Individual Speakers

- Understanding complex biological networks may require complete genome sequencing of many millions of people.
- In-depth sequencing may be required to find relevant variants with both known and unknown effects.
- Genomic technologies are improving rapidly and soon will be able to provide very rapid sequencing with high sensitivity.
- Complete genomic information may require new regulatory approaches—for example, when considering the approval of new drugs and diagnostics targeted at rare mutations.
- Phase I clinical trials may be enhanced by requiring that all participants have their genomes sequenced so that they can be assigned to different trials.

New paradigms in drug discovery and development rely on new technologies. These include not only DNA sequencers but a wide variety of new tools for gathering, analyzing, and disseminating genetic and genomic information. Three speakers at the workshop discussed technologies now being used and under development for genomic-based drug discovery and development. As they noted, these technologies collectively have the potential to reshape drug development in fundamental ways.

LARGE-SCALE WHOLE-GENOME SEQUENCING

Almost all genetic variants have contextual expression and meaning that depend on other genomic sequences and environmental factors interacting through complex regulatory networks. Given the importance of context, the accurate interpretation and effective use of genetic instructions are impossible with only partial access to genetic codes, said Radoje Drmanac of Complete Genomics. Furthermore, each person has 10,000 to 100,000 family-specific genetic variants along with approximately 100 de novo personal variants in addition to a few million population variants. No comprehensive predefined genetic variant chips can be designed to detect such a wide range of variability.

Whole-genome sequencing provides a maximum level of strictly genetic information, Drmanac said. By providing greater understanding of disease, it has the potential to produce greater efficacy, safety, and overall success in drug development.

Whole-genome sequencing has two main areas of application: biological understanding and genomic medicine. Understanding the molecular and genetic bases of thousands of human diseases, developing better targeted drugs and other therapies, including those for disease prevention, and developing personal genome interpretation software will require the sequencing of millions of genomes, Drmanac said. Today perhaps only 10,000 genomes have been sequenced, so developing a true understanding of disease biology requires sequencing on a much larger scale.

The world contains billions of people, Drmanac noted. "If we're really serious and want to take whole-genome sequencing as the basis for medicine, we need to sequence billions of genomes." But sequencing on that scale will require that the process be industrialized. Small processes may have benefits for specialized applications, but large-scale massively parallel whole-genome sequencing is needed and this must be designed and optimized to achieve high quality and low cost.

Complete Genomics has been developing a turnkey service that enables customers to outsource whole-genome sequencing. Customers send samples to the company and receive data in return. Furthermore, the data received are not just sequences but the fully assembled genome with an annotated list of informative sequence variants, with each base marked as reference, variant, or a no-call. Each variant has a confidence score to balance sensitivity and specificity, and variations in known protein coding and regulatory gene sequences are identified. Drmanac acknowledged that for medical applications it is necessary to include an interpretation of the data, and Complete Genomics is currently working on developing a system for this purpose.

Increasing the sequencing coverage of the DNA makes it possible to call bases for 96 to 97 percent of the genome with very high confidence. However, there are certain regions of the genome that are difficult to sequence, Drmanac said, and within the majority that can be sequenced there are still about 4,200 errors. However, by eliminating the 5 percent of calls that have lower confidence, the error rate for the remaining calls is just 366 per genome, or 1 for every 7 megabases. "We can get to clinical quality, even with our standard process," he said, "and we have other processes that will further improve [quality]."

Complete Genomics expects to be able to sequence 2,000 genomes per month by the end of 2012, up from 800 at the time of the workshop. Better instruments could boost that rate to 100,000 genomes per year, and the company has the goal of being able to do millions of genomes per year. "That's coming," Drmanac said. "We don't need to wait for new inventions. It's just regular improvements."

The company has a diverse base of more than 100 users, including organizations from government, industry, academia, and private industry. These organizations have been using the technology to investigate cancer, de novo mutations, genomic variation and disease, and the potential of translational medicine. "It's a golden age where we can sequence millions of genomes in cancers, in unknown disease, and in frequent disease," Drmanac said. "It can be done in the next 5 to 6 years."

Drmanac proposed the idea of a million-genome project, or perhaps a 10-million-genome project, to understand both health and disease. "Hopefully we can reduce cost at the same time," he added. "It's very difficult and not guaranteed, but I think with the genome we hopefully can do that."

Sequencing capabilities will continue to grow exponentially, both in terms of capacity and accuracy. In a few years, 1,000 times coverage may be routine. A genome sequence could be done at birth—or even preimplantation—to provide a foundation for health care and research throughout life. Understanding of biological function is exploding, and sophisticated software to interpret genomes is undergoing rapid development. Given this rapid growth in understanding and capability, perhaps all people enrolled in clinical trials should have their genomes sequenced to minimize risks and maximize efficiency, Drmanac suggested. Genomic data will need to be integrated with complete transcriptome and epigenome analysis for the relevant tissues of each subject, but whole genome sequencing can provide a foundation to integrate over other kinds of data. In this way, drugs could be developed for distinct genomic states and individual DNA sequences, such as genetically engineered stem cells or drugs that attack only cancer cells with specific DNA signatures.

THE VALUE OF CLINICAL NEXT-GENERATION SEQUENCING TO DRUG DEVELOPERS

For a variety of reasons, the current model of drug development is not sustainable, observed Gary Palmer of Foundation Medicine. Limited amounts of tissue biopsies are available to search and test for informative biomarkers, and screening patients for rare markers is inefficient. Prospective studies are limited by turnaround times for analysis, and retrospective studies can have difficulties securing the appropriate samples. Finally, complex biology requires a better knowledge of disease pathways and thorough interpretation, not just raw data.

These problems can be further exacerbated with clinical cancer samples, Palmer said. Cancerous cells may be only a small fraction of the total sample. Multiple sub-clones of cancer may be present in one sample, and chromosomal gains and losses may modify the abundance of a mutation. As a result, relevant mutations may be rare in a pool of sequenced DNA.

Next-generation sequencing can address many of these issues, Palmer said. In particular, Foundation Medicine was established to help clinicians and pharmaceutical companies screen patients for targeted therapies that are already on the market or that soon will become available. The company works with very small (40 micron) samples of paraffin-embedded tissues from pharmaceutical companies, oncologists, or pathologists. At the time of the workshop, it was analyzing 182 genes that are known to be somatically mutated in cancer, with plans to increase that number to 250 in the near future. "We sequence the heck out of them," Palmer said, with coverage rates averaging close to 900. The analysis is optimized for accuracy and is designed to produce annotation, interpretation, and a clinical report in 14 to 21 days. The analysis identifies point mutations, short insertions and deletions, copy number alterations, and a select number of genomic rearrangements.

The interpretation is particularly important for oncologists, Palmer said. It includes linkage to FDA-approved drugs, either on- or off-label, and connections to clinical trials that are available. In the company's initial stages, interpretation often has involved genetic alterations that need to be curated for the first time, which requires figuring out an alteration's possible effects. "As we're seeing more and more things, that's going to be a more efficient process," he said, "and the turnaround time will get less and less."

The service provided by Foundation Medicine is situated somewhere between whole-genome sequencing and "hotspot testing," which looks for a specific abnormality or group of abnormalities. The company does in-depth sequencing on its panel of selected genes where abnormalities may be of importance. In the process it finds not only expected abnormalities but also other abnormalities that show up repeatedly in different tumors

in varying percentages, which is why the same panel is run for all tumors. Furthermore, many of these abnormalities are actionable, in that they are the target of an FDA-approved drug either on- or off-label. Variants of unknown significance are also identified, although they are not reported. Still, Foundation Medicine is studying these abnormalities to elucidate their role in cancers.

The company has been doing several types of studies with pharmaceutical partners. It is running single-agent clinical trials, longitudinal studies, multiple simultaneous Phase I trials in which individual samples are tested for multiple biomarkers, and analyses of samples from failed Phase III trials that did not meet clinical endpoints but produced evidence of responders for whom a drug might be valuable. "This is very attractive to pharma companies that don't want to let a drug die . . . and see if, in fact, there is a reason that they can move forward," Palmer said.

Pharmaceutical partners have several requirements that they need Foundation Medicine to meet. They want the ability to work with paraffin-embedded tissues so they can retrospectively analyze samples. For prospective studies, they want clinically relevant turnaround times. They want deep sequencing coverage, so that relevant alterations will not be missed. They also want help with genomic insights: What does a particular alteration mean? Finally, they want assistance with computational biology either because they are not able to do it themselves or because they have made the decision to outsource for the technology.

The provision of these services can provide great benefits for the pharmaceutical industry, Palmer said. It can aid in biomarker identification, help stratify patients for clinical trials, help determine resistance markers, enable combination therapies, and assist in resurrecting clinical trials. What next-generation sequencing cannot do is increase the enrollment rate, meaning that very rare but actionable alterations will still require that many patients be screened. Similarly, it cannot overcome problems with statistical power.

Policy makers need to understand the stakes behind this approach to genomic medicine, Palmer said. For example, a separate validation for each marker is not feasible. Next-generation sequencing does not test for a specific marker because thousands of results are possible. As the testing methodology that is being employed at Foundation Medicine could potentially be used as a companion diagnostic for the development of a therapeutic, a clear pathway is needed for these newer technologies.

It is possible that next-generation sequencing will be required in Phase I of all clinical trials, Palmer said. Potential patients could then be placed in the appropriate trial through next-generation sequencing, including combination therapy trials and "case report" trials, so that label extensions could be based on multiple N-of-1 reports.

Finally, oncologists cannot keep up with the deluge of new information that is being generated. For example, even today oncologists are split on whether to try a drug off-label when they find abnormalities in different tumor types. Currently, many patients are not receiving the testing they need, which means that they are not getting proper therapies, and this situation will become worse over time. It will be of critical importance, Palmer said, to have initiatives to educate providers, patients, regulators, payers, and other relevant stakeholders. "There is a lot of potential improvement in patient care that is available by just technology and I think also would lead to improvement in pharma recruitment and [patient outcomes]."

THE USES OF GENOMIC INFORMATION

The development of personalized healthcare approaches depends substantially on the strength of the hypothesis being developed, said Jane Fridlyand of Genentech. Where a strong diagnostic hypothesis exists, a strong scientific rationale allows for patient selection through all stages of development. This situation can provide a relatively fast development path and a relatively straightforward path to approval.

Without a strong diagnostic hypothesis, patient selection is much more difficult. In that case, retrospective data exploration and planning for future data collection need to be emphasized, Fridlyand said.

In many cases, a biomarker and drug have been developed, but it is not clear in which population the drug will work. In this situation the three key challenges are label-enabling trial design and analysis, biomarker cutoff and refinement, and multiple biomarkers and multi-marker tests. The developers of drugs and diagnostics need to decide which patient populations should be tested. These decisions ultimately depend on the scientific rationale and clinical context, Fridlyand said. Key questions include

- What is the clinically meaningful treatment benefit level?
- What is the magnitude in benefits between diagnostic-positive and diagnostic-negative patients?
- What is the risk–benefit evaluation in diagnostic-negative patients, and what are their unmet medical needs?

Biomarker indicators are often continuous, requiring that a threshold be set for selection and refinement of patient groups. The result is a tradeoff between population size and effect size. Often there is no clear best threshold. Instead, the appropriate threshold depends on the clinical risk–benefit, the scientific rationale, and the distribution properties of the biomarker (such as whether it is bimodal). A useful strategy, Fridlyand said, is to

base a threshold on limited data from a Phase II study and then adjust the threshold based on a much larger volume of data from Phase III.

Fridlyand reiterated a point made by Palmer, which is that full clinical validation of each biomarker may not be feasible. Infrequent mutations may be too rare to be validated. For multiplex biomarker signatures, there is no expectation that individual biomarkers will be predictive. A particular pathway activation that modulates the activity of a drug may be activated only when expression of multiple genes in other pathways are on or off, and expression might occur at different prevalences. Instead, it will be necessary to consider alternative clinical and analytical validation, depending on the situation. "It's going to be really hard to show that each of these members of your companion diagnostics are clinically validated," Fridlyand said. "Rather, we have to think about it as a clinical validation for a summary measure."

Analytical validation also raises issues. Testing multiple biomarkers will use up tissues, and eventually patients will not be willing to give more, Fridlyand said. Furthermore, physicians do not want to put patients in trials where they do not think the patient will benefit.

Overcoming these issues will require extensive drug and technology pipelines, effective collaborations, cross-functional teams, and strategic information gathering to provide robust datasets for better-informed and efficient drug development. In addition, said Fridlyand, the development strategy needs to include feedback from development to research in order to improve disease molecular classification and biomarker hypothesis generation.

5

Evolving Paradigms

Important Points Highlighted by Individual Speakers

- The mobilization of patient communities can spur research and lead to the creation of new and more effective therapies.
- Increased collaboration both within FDA and between FDA and other stakeholders has hastened the approval of new drugs and diagnostics.
- The blending of pre- and postmarket environments could combine considerations of safety and efficacy with considerations of clinical effectiveness.

The fourth session of the workshop featured case studies of organizations and initiatives that have furthered genomic-based approaches to drug discovery and development. A prominent theme of these case studies was the importance of collaboration in building the relationships necessary for timely advances. Collaborations can exist both within an organization, such as within FDA, or among organizations. They also can remain within a single sector or span sectors. As is discussed further in the next chapter, collaborative work will be essential to the creation of new paradigms in drug discovery and development.

FOUNDATIONS AND DRUG DEVELOPMENT: AN EXAMPLE

The Multiple Myeloma Research Foundation (MMRF), which was founded in 1998, is the largest private funder of multiple myeloma research, raising over $190 million to date. It funds research around the world, builds community among people affected by multiple myeloma, and partners with the Multiple Myeloma Research Consortium (MMRC), which supports research in 16 institutions to determine which drugs can move from preclinical testing into Phase I and Phase II development and which was founded in 2004. Walter Capone of the MMRF and the MMRC described the organizations and the vision behind their approach.

Multiple myeloma is the second most common blood cancer, affecting 64,000 people in the United States and causing more than 10,000 deaths annually. It occurs largely among older adults, often African American, and predominantly male. In 1998 the average survival period with the disease was 3 years and no drugs were in the pipeline. Today, the average survival period is 7 years, 4 drugs for the disease have been approved, and 9 drugs are in Phase III trials.

MMRF's success has been based on increasingly complex collaborative models to drive drug development. By developing strategic plans and building community, MMRC has accelerated trials and built a tissue bank that includes more than 3,500 samples. Through the Multiple Myeloma Genomics Initiative, more than 80 of these samples have been sequenced and are available through an open-access portal, with plans to sequence 250 samples by the end of 2012. More than 1,000 researchers have accessed the data, and more are expected in the future. Interestingly, while expected mutations were found through the genomic analysis, 4 percent of patients also had activating BRAF mutations, compelling the foundation to examine the use of vemurafenib for treatment of multiple myeloma.

This effort in turn has supported the Multiple Myeloma Personalized Medicine Initiative, which seeks to more fully characterize the range of disease subtypes to enable the development of targeted therapies and potentially curative approaches for patients. Spread across 50 centers and including industry partners, the project combines a 1,000-patient longitudinal study with a companion genomics study that will comprehensively assess the molecular profiles of patient's tumors throughout disease progression and be correlated to clinical interventions, including treatment regimens. The study design allows 3 years for enrollment and includes 5 years of follow-up, and data will be open access with no intellectual property restrictions.

The MMRF is continuing to expand its programs as the network of stakeholders in the field grows more complex. Today, not just academia, industry, and patients are involved but also regulators, physicians, payers, and diagnostic and platform companies. By working with clinicians,

researchers, and a dedicated validation and basic science team, MMRC has increased the success rate of new drugs in Phase I to between 35 and 40 percent, well above the 10 percent success rate in the pharmaceutical industry as a whole. It has partnered with industry to open 37 trials with 20 novel agents, has sped the time to the opening of trials by 60 percent, has reduced the time between Phase I and Phase II trial development and completion by a third through common agreements and dispensing with contracting, and has increased enrollment by 14 percent. MMRC also has expanded its clinical reach well beyond its 16 sites and it has launched an early-access program for the drugs that have gone into the last stages of regulatory review.

The Multiple Myeloma Personalized Medicine Initiative also has taken a collaborative approach. Linking research, clinical, and community activities, it is a multi-year observational study with tissue banking and matching as well as in-depth sequencing work. Information generated by the study is openly available for researchers to identify new targets and biomarkers and to connect researchers with the patient community. The study is putting information in clinicians' and patients' hands, Capone said. "Combining clinical and genomic data in a single platform [will] compel and initiate scientific discoveries that are not possible today."

In the same manner, by mobilizing the multiple myeloma community through a dedicated online portal, the MMRF aims to accelerate and enable personalized therapies. Key features of the online community include groups based on common molecular profiles, the ability to connect with similar patients, a health metrics tracker, tools to help manage the disease, access to educational materials and data, live Web discussions, and clinical trial recruitment tools.

Finally, this approach does not apply just to myeloma, Capone said. It offers a way of bringing information together worldwide from multiple organizations into a common platform that can drive progress for many different diseases. The foremost challenge, Capone said, is collecting and tracking large numbers of patients who have a particular disease or problem. Even in the case of multiple myeloma, only a few thousand patients are being followed. "What if all the patients who were afflicted with a disease were able to become part of and contribute to the community that's going to drive toward a cure ultimately, and in the process be fully engaged in advocating for their own care by having and understanding the latest advances in the field?"

GENOMICS AND REGULATORY SCIENCE

The mandate of FDA is to protect and promote public health, noted Michael Pacanowski of the FDA's Center for Drug Evaluation and Research

(CDER). However, a tension often exists between protection and promotion, between risk aversion and innovation, and between regulation and flexibility while still ensuring that safe and effective drugs are brought to market. However, personalized medicine is changing old ways of thinking about these issues and FDA has been on the leading edge of these changes, Pacanowski said.

Genomic-based drug development creates both promise and challenges. Of the approximately 30 drug approvals in 2011, Pacanowski said, at least a dozen had some type of genomic information included in their clinical development, ranging from dosing based on drug metabolism to exploratory analyses for known biomarkers to co-developed drugs. He noted that several recent drug approvals exhibited features that are likely to become increasingly prominent in the future. For example, the approvals of ivacaftor and crizotinib were very fast, taking just 3 months rather than the more common 6 to 10 months. The approval of ivacaftor also took advantage of partnerships with the Cystic Fibrosis Foundation, which greatly helped in bringing the drug to market quickly.

Drug regulation has been described as the progressive reduction of uncertainty, Pacanowski observed. While genomics may alter the current paradigm, it will not change the need to satisfy the same evidentiary standards that currently exist. In that respect, the advantage of genomic-based drug development is not that it requires fewer data, but that it often has the potential for a higher probability of success. Drug development will shift toward a "quick win, fast fail" model, Pacanowski predicted.

One early way in which CDER has stimulated innovation in the genomic sciences is through the Voluntary Exploratory Data Submission program. This program allowed companies to share data informally without regulatory consequences; to obtain feedback on trial designs, methodologies, and data interpretation; to gain insights into evolving regulatory practices; to provide experience to facilitate policy development; to discuss data elements used to streamline new drug applications; to educate FDA scientists on emerging data and innovative approaches; and to forge partnerships among scientists from different sectors. The agency also prepared guidance on genomic data submissions, which helped companies navigate the drug application process, and established a Biomarker Qualification Program, which promoted the development of biomarkers that are broadly applicable to multiple drug developers. Furthermore, recent negotiations over the Prescription Drug User Fee Act have created the potential for funding to enhance the agency's biomarker and genomic teams.

Internal changes at FDA have spurred these advances. Since 2008, CDER and the Center for Devices and Radiological Health (CDRH) have greatly increased their communication and have harmonized their procedures. In addition, new guidances have been issued on such topics as

developing companion diagnostics and early-stage and clinical pharmacogenomic studies. Currently under development is guidance on enrichment strategies when using selected populations.

Partnerships have been and will continue to be critical at FDA, as emphasized in its most recent strategic plan, Pacanowski said (FDA, 2011). Areas where this is particularly true include the effective development of qualified tools and surrogate biomarkers, creating a drug safety research infrastructure, and carrying out comparative effectiveness research. Such partnerships can take many forms, including industrial consortia, academic collaborations, government-catalyzed partnerships, or contracts with payers to do postmarketing research. Pacanowski noted that developing partnerships with clinical practice societies will be of importance to the agency because these groups will play a large role in determining what is considered standard of care for personalized medicine.

In the past, precompetitive collaborations have been an elusive goal, but barriers are being overcome to establish such partnerships. Successful examples include the international Serious Adverse Event Consortium and the Predictive Safety Testing Consortium from C-Path. "It is possible to put together these partnerships and have effective outputs," Pacanowski said.

FDA has been and will continue to be committed to personalized medicine and individualized therapeutics, Pacanowski concluded. "It is part and parcel to rational and sound drug development and will probably be applied in almost every scenario in the coming decades."

PHARMACY BENEFIT MANAGEMENT AND PHARMACOGENOMICS

In the current paradigm of drug discovery and development, the premarket environment and the postmarket environment are separate and distinct (Figure 5-1). Companies try to get regulatory approval for a drug and then hope that patients and providers will use it and that payers will pay for it. Increasingly, there are examples in which there is regulatory success but commercial failure, said Felix Frueh of the Medco Research Institute.

This paradigm will change, Frueh predicted. In the future, the premarket environment and postmarket environment will be blended (Figure 5-2). Companies will receive information from payers early in the drug development process. Considerations of efficacy and safety will interact with considerations of not just clinical utility but clinical effectiveness. The logistics of deploying a new therapy will be a factor—including, for example, off-label uses. The stakeholders in the drug development process will be confronted with a new set of questions, Frueh said, and it will be necessary to assess how this new paradigm will influence drug development.

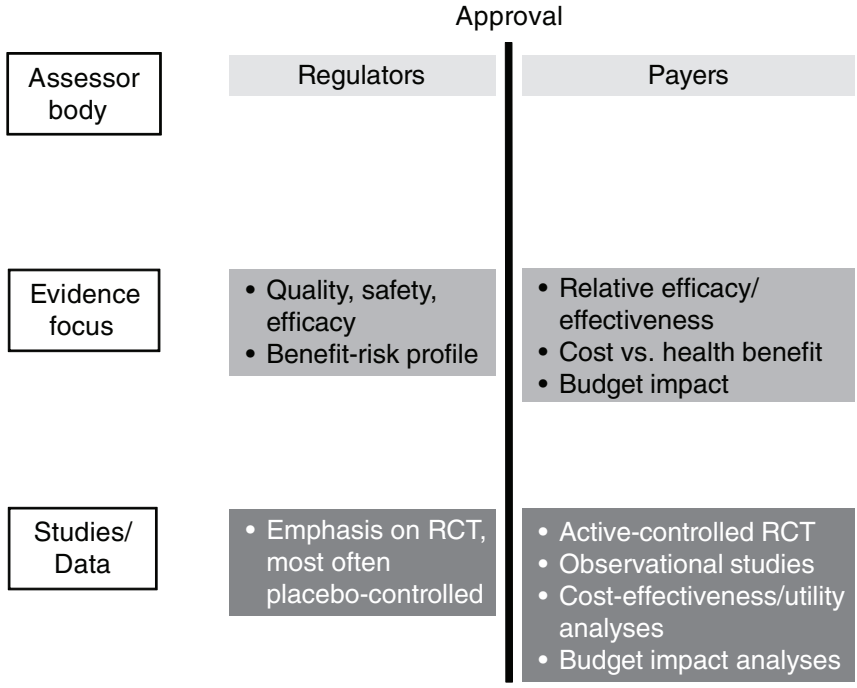

FIGURE 5-1 In the current paradigm of drug discovery and development, the approval of a drug rigidly separates the domains of regulators and payers.
NOTE: RCT, randomized control trial.
SOURCE: Adapted from Eichler et al., 2010.

These changes will affect regulators and payers as much as they will industry and government, Frueh said. Today, regulators are increasingly interested in comparative data and outcomes research. The demand for more safety data cannot be met entirely by randomized controlled trials, so regulators in the United States and Europe have set up sentinel networks to assess postmarket data. Reimbursement bodies are calling for value-based pricing that is tied to the demonstration of comparative effectiveness in the real world. In Germany, for example, the Federal Joint Committee requires drug makers to demonstrate greater efficacy for a new compound before they can charge more.

Strategic partnerships are also emerging to generate and access post-market data. Pfizer, for example, has teamed with Medco to use large patient databases to perform both retrospective and prospective research on personalized therapies. In this way clinical trials can be designed to answer not only regulatory questions but questions that are relevant for the payer,

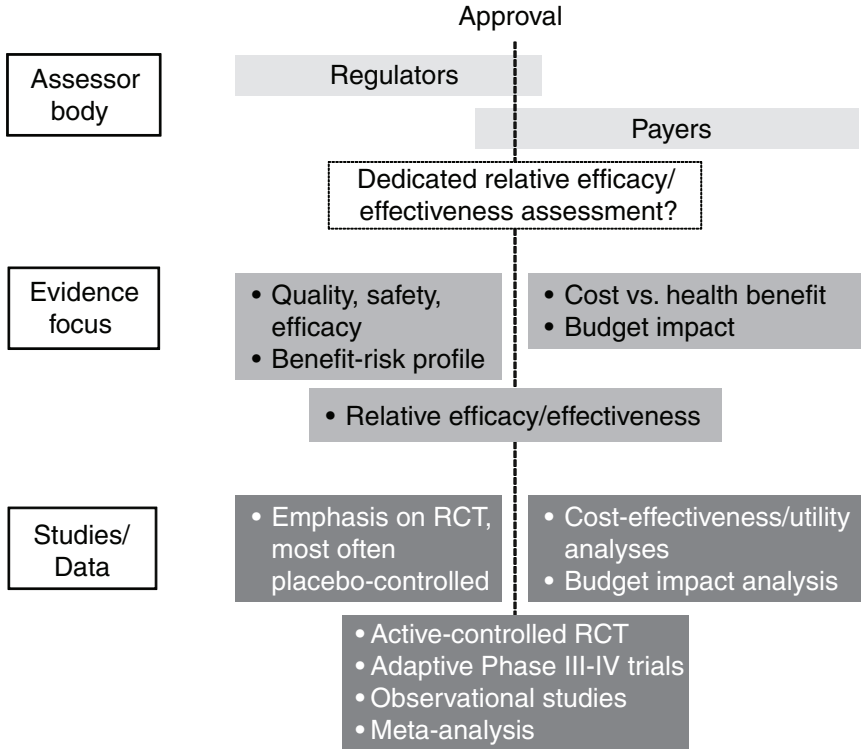

FIGURE 5-2 In the future, the responsibilities of regulators and payers could overlap, resulting in a dynamic interplay between evidence generation and drug approval.
NOTE: RCT, randomized control trial.
SOURCE: Adapted from Eichler et al., 2010.

such as whether the right clinical endpoint has been selected. Similarly, questions of comparative effectiveness can be addressed, such as whether an older drug (for example, clopidogrel) that is about to go off patent is safer and more effective than a new and more expensive drug (for example, prasugrel) for people with particular genetic backgrounds. While not the primary concern of payers, economic questions also take on significance in these analyses, Frueh said. All of this information can also be important for drug developers who need to make decisions about whether and how to proceed with the development of a particular compound. Companies could utilize a personalized medicine methodology to identify an unmet medical need, for example. Developers could approach payers early about creating programs to identify patients who are unlikely to benefit from a drug already on the market but could benefit from a newly developed drug.

Frueh concluded with several provocative thoughts emphasizing the role of payers:

- Comparative-effectiveness evaluations will become increasingly required by payers because of the need to demonstrate that a new treatment is better than the standard of care.
- What if payers were to cover a drug only if it actually works?
- Payers will progressively move toward employing coverage with evidence development.
- Can payers act to encourage patients to participate in clinical trials or even help in recruitment?
- What if payers were to co-sponsor clinical trials or provide pharmacy, lab, and outcome data for research?
- Could payers partner with industry to develop more personalized medicines faster?

Over the next 5 years, Frueh said, the answers to these questions could reshape relationships in the drug discovery and development system. For example, if payers across the board were to embrace the coverage-with-evidence-development paradigm, "that would really change the way that we'd be looking at drugs and diagnostics."

REPURPOSING OF DRUGS

The NCATS Pharmaceutical Collection (NPC) is a comprehensive resource of 3,800 approved and investigational medicines that was designed to facilitate the repurposing of medicines by the scientific community.[1] As a recent paper states, the NPC is "a definitive, complete, and non-redundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening" (Huang et al., 2011).

Christopher Austin of NCATS at NIH demonstrated how the NPC can be used. Drugs approved in different jurisdictions throughout the world can be accessed. Searches can look for indication, target, drug name, and so on. A search on "migraine," for example, returned 14 drugs that are approved worldwide. Clicking on a particular drug gives the mechanism of action, known targets, the regulatory status in different countries, and other information.

To demonstrate the utility of the collection for drug repurposement, Austin cited a recent example of successfully identifying a drug that could potentially be used for the treatment of chronic lymphocytic leukemia (CLL),

[1] The NPC can be accessed at http://tripod.nih.gov/npc.

which accounts for about 15,000 new diagnoses per year in the United States. In partnership with the University of Kansas and the Leukemia & Lymphoma Society, NCATS screened the NPC collection for effects against CLL patient cells as well as against cells from normal donors. Some drugs killed the CLL cells from all patients, while some killed the cells from only some of the patients. Subsets of these drugs were less effective or ineffective in killing normal donor cells. One particular drug called Auranofin was originally approved for the treatment of rheumatoid arthritis in 1984. Reverse pharmacology revealed the mechanism of action of the drug, and three clinical trial sites are now active.

The principal lesson Austin drew from this experience is that effective translation requires collaboration. The partnership benefited by the marriage of funding sources, expertise, project management, and the early incorporation of technology transfer agreements which allowed for rapid movement in establishing the trials. In fact, less than a year passed between signing the partnership agreement and the dosing of the first patients. "This is a great example of how, [through] a team effort, we were able to move forward."

One complication in the repurposing of drugs is that about 90 percent of the drugs in the pharmaceutical collection are generic. For these drugs, paying for a registration trial to expand the indication can be a barrier. In addition, regulatory issues can impede the repurposing of on-patent or abandoned drugs. For example, one might wish to know if the new indication is related to the original mechanism of action or if it is related to an unexpected or unrelated mechanism. Or if the mode of delivery is the same. To answer such questions, it is typically the case that data are needed from the firm that originally created the drug.

Public policy changes may be necessary to encourage drug repurposing. For example, establishing exclusivity could allow the licensing of a discovery to a for-profit organization to take a drug through registration. Also, it is never too early to start thinking about reimbursement strategies, Austin said, because the goal is to get the drug to patients.

A Value Maximization Path, or ValueMaP, is under development to provide guidance in pursing drug repurposing. This guidance draws on examples of what has worked in previous projects, such as rational repurposing based on knowledge of disease pathogenesis and drug pharmacology. In addition, in selected cases computational approaches have been able to identify promising pathways or patterns (Sirota et al., 2011).

Partnerships need comprehensive and complementary expertise at every step of the process, Austin said. When the process breaks down, it often does so in the experimental medicine space, such as in the early clinical trials. Other problems have arisen when repurposing is based solely on animal models, when computational approaches are used without experi-

mental testing, and when phenotypic screens are done without a prospective plan for translating the results to humans.

Repurposing generic drugs provides a tremendous opportunity to improve human health without great additional costs, Austin concluded. But new funding paradigms may be necessary to make such drugs available to patients.

6

Forging Collaborative Strategies for the Development of Personalized Medicine

Important Points Highlighted by Individual Speakers

- New paradigms in drug discovery and development will be achieved only through the collaborative efforts of multiple groups.
- Successful collaborations require a shared and compelling vision along with a well-defined timeline and deliverables, and each party in a collaboration needs to benefit.
- A particular focus of collaboration needs to be the establishment of biorepositories, databases, patient repositories, and other information resources for drug development.
- Universal participation in biomedical research is a goal that would require overcoming major obstacles, but it would generate an enormous amount of safety and efficacy data that would benefit everyone.

Throughout the workshop, individual presenters and workshop attendees commented on the changes that would be necessary for new paradigms in drug discovery and development to take root and flourish. As with the examples described in the previous chapter, most of these changes involve the establishment of collaborations within a broad "ecosystem" of public and private stakeholders.

In the final session of the workshop, four presenters described pathways toward effective collaborations: Deborah Dunsire of Millennium Pharmaceuticals, Inc.; Victor Dzau of Duke University and Duke University Health System; Margaret Hamburg of the FDA; and Kathy Hudson of the NIH. This chapter summarizes their remarks along with those of other workshop participants who addressed the broad issues associated with collaborative strategies for the development of personalized medicine.

THE NEED FOR COLLABORATION

Translating genomic discoveries into patient benefits is a "team sport," Dunsire said. No one organization has all the capabilities and resources needed to realize the promise of personalized medicine. Only through partnerships can success be achieved.

This collaboration needs to extend from the research laboratory to the clinic, Dunsire added. As such, collaborations can involve a very wide range of stakeholders, including industry, academia, regulators, health care providers, and patient organizations. A particularly important set of stakeholders that should be part of these collaboration efforts, Dzau said, consists of the various payers, such as the Centers for Medicare & Medicaid Services (CMS). Payers should be eager for evidence that a particular approach would save money. "That conversation has to occur," Dzau said.

Austin emphasized that a successful collaboration requires a shared vision. In the collaboration among NCATS, the University of Kansas, and the Leukemia & Lymphoma Society, all of the partners had experience with drug development and shared knowledge of the process. In addition, the project used management practices standard in industry, with project managers in each of the three institutions who worked closely together to ensure that the project met its timelines.

Each party to a collaboration needs to benefit, even though each has different capabilities, Frueh said. "You need to look at what everybody brings to the table and really define the benefit to each entity, to each party, that participates." On this issue, Pacanowski pointed to the importance of clear deliverables. "Knowing what to expect as a product that would benefit all of the [partners] is probably the most critical piece." Finally, Capone observed that the vision must be not only shared but compelling in order to motivate and align the partners.

Frueh made the point that a balance needs to be drawn between less formal and more formal arrangements to reduce the demands on the members of a collaboration. In addition, the larger any group gets, the more complex it gets. Davies observed that companies need to focus on what they do well. "Are we spreading ourselves too thin?" he asked. "Is there an area where we can have more impact than other areas?"

Many collaborations occur in the precompetitive space where all partners can benefit from new knowledge without losing competitive advantage. Foundations can play a central role in such collaborations, Capone said, because the absence of a profit motive can keep the focus on the science and on the benefits to patients. In that regard the parties to a collaboration need to recognize the potential threats to a collaborative enterprise. For example, efforts to protect intellectual property, either by industry or academic partners, can stymie partnerships and thereby limit scientific advances. If all the information generated by a partnership is available, no party feels that it is being disadvantaged versus other parties in the group. Transparency requires effective governance structures and accountability. If these cannot be achieved, Capone said, it may be necessary to find different partners.

FDA INITIATIVES

A particularly important partner in many collaborations is the FDA, which was represented at the workshop by its commissioner, Margaret Hamburg. The FDA has been working with sponsors, patient groups, and academia to get into the marketplace new products that represent the opportunities of personalized medicine, she said. These collaborative efforts have generated real benefits for patients with treatments being developed that affect the underlying mechanism of disease rather than treating symptoms, such as with ivacaftor, and that affect the appropriate use of medications, as represented by the more than 110 drugs that now have genetic information on their labels.

Research collaborations will be increasingly important to the FDA in the future, because it does not have the resources to do all of the research needed to develop the regulatory tools and knowledge needed for the agency to do its job as efficiently and effectively as possible, Hamburg said. Biomarkers need to be identified, characterized, and validated. Standards for whole-genome sequencing and SNP panels need to be established. Innovative clinical trial designs need to be developed that are faster, cheaper, more adaptive, and use smaller populations of patients, particularly in projects to identify subpopulations of patients that can benefit from a drug or that would react poorly to a drug.

One complication for the FDA is that many potential therapies cut across its traditional domains of product activity. The combination of a diagnostic with a therapeutic intervention falls into two centers within the FDA with different regulatory frameworks. The FDA's challenge is to deal with such products in ways that "are efficient and reflective of where the science is and where these products are," Hamburg said. The FDA will continue to work with its sponsors to break down barriers to co-development and to help create an effective scientific and business framework.

Information about underlying genetic traits and markers can be applied to help determine whether drugs will be effective as well as to predict their toxicological effects. It is important to feed this type of information as well as knowledge about why drugs have failed in the past back into earlier parts of the drug development process so that if a drug will fail it is identified as early as possible, not after hundreds of millions of dollars have been spent. While the FDA is not allowed to share the confidential commercial information it receives, the agency is working with companies to make this information more available to inform drug development and applications of existing drugs, Hamburg said.

The FDA has many opportunities to apply better computational approaches, improved data mining techniques, better pattern recognition strategies, and other cutting-edge techniques to identify promising applications of existing drugs and better-defined pathways for drug development. Such applications of cutting-edge science will often require bringing together people with different perspectives and different expertise.

Hamburg concluded her formal remarks by pointing to the complex ecosystem involved in biomedical product development and innovation. Many policies besides regulatory policies affect this ecosystem, including intellectual property protections, access to capital, reimbursement policies, and direct government investments. All of these policies matter, said Hamburg. "If we're going to have success in realizing the opportunities in science, we need to be thinking about investing in and supporting the ecosystem that will be the engine of success."

NCATS INITIATIVES

Another increasingly important partner in collaborative efforts will be NCATS, which was represented at the workshop by its acting deputy director, Kathy Hudson. The mission of NCATS is to catalyze the generation of innovative methods and technologies in order to enhance the development, testing, and implementation of diagnostics and therapeutics. The goal is to develop the tools that will make drug discovery and development better, faster, and cheaper, Hudson said. "We are not in the drug development business."

This is a nontraditional approach for NIH. It requires working collaboratively with all of the 27 NIH institutes and centers that are each conducting translational research; with its sister agencies, including the FDA; with industry; with patients; and with academic medical centers. "[Collaboration] is really essential and vital to our success," Hudson said.

Hudson mentioned several examples of innovative work that NCATS is undertaking in a precompetitive space. Like the FDA, NCATS has an interest in new kinds of clinical trials that are faster, cheaper, and involve smaller

groups. A resource it can use to develop such trials is the set of institutions that have received Clinical and Translational Science Awards, which represents 60 of the best academic medical centers in the country networked together to do human subjects research across a range of diseases. The second example she mentioned is NCATS's project in drug repurposing—described in the previous chapter—which is seeking to find beneficial compounds with known safety profiles that companies have abandoned, with all of the work done under a set of pre-negotiated three-way agreements with the pharmaceutical companies, academic universities, and the NIH. This will alleviate some of the barriers to entering into a formal agreement and speed the process of setting up the initiative. Finally, NCATS is working with FDA and the Defense Advanced Research Projects Agency (DARPA) to develop a chip that will closely mimic the physiological behavior of normal tissues. The goal is to develop a validated tool that companies and academic medical centers can use to test the responses of tissues to specific compounds, allowing compounds to be tested in vitro before testing them in humans.

NCATS is taking a DARPA-like approach to the drug repurposing and "tissue on a chip" projects. Both will be milestone-driven with funding removed if goals are not met.

BIOSPECIMENS AND DATABASES

The evolving landscape of genomics creates a tantalizing opportunity to bring forward medicines that are more effective because of the ability to identify patients for whom a particular drug will work best or have the least downside risk, Dunsire said. However, data are not always available to truly select therapies as a routine. Establishing biorepositories, databases, patient registries, and other information resources will allow drugs to be reevaluated as new information is derived. Examples like the collaboration between Millennium Pharmaceuticals and the Multiple Myeloma Research Foundation on the latter's Personalized Medicine Initiative discussed in Chapter 5 show what is possible, Dunsire said. Patients with the same genetic condition can be targeted, and patients with other mutations can be encouraged to participate in different trials. Patients can donate specimens and data at diagnosis and throughout the progression of their disease. In this case, a patient advocacy organization is driving inclusion, but other mechanisms could be equally or more effective.

Hamburg noted that a wide variety of information, including that derived from registries, could be used in both prospective and retrospective analyses. Reports of adverse effects, information about existing clinical trial networks, and identified potential patient populations all could be valuable resources. "All of these things make us better positioned to ask and answer critical questions in a timely and cost-effective way and strengthen the

infrastructure that is so critical for our ability to maintain a cutting-edge position in these important areas of science," she said. Dzau added that a strong electronic health record and a robust information technology rapid learning health care system also need to be developed to make a difference in drug discovery and development.

Hamburg also pointed to the many ways in which new technologies can forge connections with patients and collect information, potentially at lower cost than through clinical trials. For example, data collection could be pushed closer to the patient for some diseases. This "is an area where we feel we need to open our thinking," she said. Similarly, Dunsire said, different registries and databases can be linked in the precompetitive space.

Both phenotypic and genomic data, Dzau said, need to be gathered from multiple patient populations, including those suffering from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, cardiovascular disease, and other diseases, not just cancer. The intention must be to apply information so that everyone is placed into a subpopulation. This will be how linkages between diseases are identified and will facilitate novel applications for existing drugs or the development of new therapeutics.

Efforts to construct and link such information sources are under way, though much more needs to be done. One pressing question, Dzau said, is "Should we biobank every single patient who comes through the door? Should we sequence everybody? These kinds of questions come up every single day for us." A related question is whether patients should have to opt out of engaging in research instead of choosing to opt in. If people had to opt out rather than opting in, much larger banks of specimens and data would be available to do anonymized research.

Dzau proposed the creation of a national consortium of academic centers in which particular centers would choose diseases, cohorts, or pathways they want to study in depth. The consortium could include NIH, FDA, and CMS as well. Cohorts could be of sufficient size to do phenotyping and molecular imaging in detail and centers could be supported by both government and industry with sharing of data.

Major impediments would need to be overcome to build such a resource of specimens and data. Wylie Burke from the University of Washington pointed out that patients have expectations about such issues as re-consent, learning what happened with their samples, and the return of results. There are also cultural sensitivities which factor into low minority participation, she said. Hudson noted that NIH is trying to provide human subjects protection and regulations to remove some of the impediments to participation. More broadly, Dzau observed, such a system would have to be related to the larger issues of health care delivery and reform.

Austin pointed to the value of having all of the data available on currently approved drugs in a public database, at least for generic drugs.

Having such data available would make it possible to narrow candidate drugs for a condition beyond the possibilities that can be identified without such data. It also would allow for the review of safety and efficacy data in repurposing drugs. These data are now available, but they belong to private companies, which constrains their release.

The FDA also has a tremendous amount of data developed as part of drug development projects, but it does not have the infrastructure, the resources, or the authority to analyze these data and make them available. Austin pointed out that having only summary data released by the FDA would not be acceptable since the analyses could not be verified. One option, said Pacanowski, might be for the FDA to draw together the parties that own the data to work out legal agreements so the data can be used. "That would potentially be very valuable."

The allocation and protection of intellectual property are troublesome issues, however. For example, Trusheim observed that the developers of diagnostics can create tremendous value but are often poor at capturing that value. Instead, payers, patients, and drug developers collect much of that value. Only when diagnostic companies have strong intellectual property protection have they been able to force other partners to pay what a diagnostic is worth. Additionally, Austin said, many owners of the data believe that their release would be detrimental. For their part, private companies do not have an upside in releasing data that might be used to undercut the value of a compound. "Even when they would want to do it, they can't."

Companies need the exclusive use of data that they generate to receive returns on their investment. Otherwise, the development costs have to be paid up front. "It's one or the other," Austin said.

REDUCING HEALTH DISPARITIES

Hamburg said that a criticism sometimes made of personalized medicine is that it will serve only elites, but personalized medicine has at least the potential to do the opposite and help reduce the health disparities that exist among population groups today. By understanding more about the mechanisms and natural history of diseases, researchers can help uncover the reasons why groups differ in their susceptibility to disease and in their responses to therapy.

Hudson agreed, adding that intergroup differences emphasize the need for much more widespread participation in research. Minorities are still underrepresented in many clinical studies and NIH has many projects to increase participation, although the results have been "depressing." The Clinical and Translational Science Awards have a specific focus on health disparities along with community engagement and implementa-

tion research. Also, the new National Institute of Minority Health and Health Disparities has created new programs to address disparities. "I am optimistic that they are really going to be able to make some real catalytic changes," Hudson said.

Dunsire observed that the response of population groups to drugs can differ not only within the United States but around the world. Phase I trials cannot be done just in the United States and Europe, with the drug then being taken around the world, because the drug can act differently with different populations. Health disparities do not necessarily arise from genetic factors, she said, but genetic factors need to be taken into account. Dzau agreed, adding that the social, cultural, and environmental influences on health point to the need to involve social scientists in collaborations. For instance, one way of involving social scientists would be to have anthropologists help develop culturally specific ways of encouraging participation and gathering information in research.

PATIENT AND PHYSICIAN EDUCATION

Particular attention needs to be directed toward patients and physicians in the drug development ecosystem, several presenters said. According to Ginsburg, only 5 percent of oncology patients are currently in clinical trials in the United States. Patients need to be educated about why their tissues are needed, how they will be used, and how that use could change treatments, Dunsire said. She noted that we are at a critical junction for patients regarding their understanding of the importance of participation and the benefits for doing so. Hudson said that a much better job needs to be done of communicating to prospective participants what the potential value and risk is to them for participating in research. "Ideally, we would all be, as patients, also participating in research."

A national dialogue about research participation could enhance the ability "to get people to participate and sign that form that says, 'Yes, I would like my tissue and my clinical information to be a part of future research studies,'" Hudson said.

AN EMPHASIS ON THE SCIENCE

In his concluding remarks, Ginsburg pointed out that the workshop began with an industry in crisis. It ended with a discussion of how collaborative efforts could lead the way toward a new era of drug discovery and development that could provide immense benefits to human health.

The essential resource that will enable this transformation is scientific knowledge, Ginsburg said. "We need to understand the biological underpinnings of the diseases and the pathways that we're trying to affect."

References

Collins, F. S. 2011. Reengineering translational science: The time is right. *Science Translational Medicine* 3(90):90cm17.

Eichler, H. G., B. Bloechl-Daum, E. Abadie, D. Barnett, F. König, and S. Pearson. 2010. Relative efficacy of drugs: An emerging issue between regulatory agencies and third-party payers. *Nature Reviews Drug Discovery* 9(4):277–291.

FDA (Food and Drug Administration). 2011. *Advancing regulatory science at FDA: A strategic plan*, http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf (accessed June 18, 2012).

Goldman, M. 2012. The Innovative Medicines Initiative: A European response to the innovation challenge. *Clinical Pharmacology and Therapeutics* 9(3):418–425.

Herper, M. 2012. The truly staggering cost of inventing new drugs. *Forbes*, February 10.

Hewitt, J., J. D. Campbell, and J. Cacciotti. 2011. Beyond the shadow of a drought: The need for a new mindset in pharma R&D. *Oliver Wyman*, http://www.oliverwyman.com/media/OW_EN_HLS_PUBL_2011_Beyond_the_Shadow_of_a_Drought%283%29.pdf (accessed June 19, 2012).

Huang, R., N. Southall, Y. Wang, A. Yasgar, P. Shinn, A. Jadhav, D. T. Nguyen, and C. P. Austin. 2011. The NCGC pharmaceutical collection: A comprehensive resource of clinically approved drugs enabling repurposing and chemical genomics. *Science Translational Medicine* 3(80):80ps16.

IOM (Institute of Medicine). 2011. *Establishing precompetitive collaborations to stimulate genomics-driven product development*: *Workshop summary*. Washington, DC: The National Academies Press.

Kris, M. G., B. E. Johnson, D. J. Kwiatkowski, A. J. Iafrate, I. I. Wistuba, S. L. Aronson, J. A. Engelman, Y. Shyr, F. R. Khuri, C. M. Rudin, E. B. Garon, W. Pao, J. H. Schiller, E. B. Haura, K. Shirai, G. Giaccone, L. D. Berry, K. Kugler, J. D. Minna, and P. A. Bunn. 2011. Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: The NCI's Lung Cancer Mutation Consortium (LCMC). *Journal of Clinical Oncology* 29(Suppl 18):CRA7506. http://meeting.ascopubs.org/cgi/content/abstract/29/18_suppl/CRA7506?sid=582aea71-36a2-4117-96c7-9e783602272f (accessed June 19, 2012).

Lillie, E. O., B. Patay, J. Diamant, B. Issell, E. J. Topol, and N. J. Schork. 2011. The N-of-1 clinical trial: The ultimate strategy for individualizing medicine? *Personalized Medicine* 8(2):161–173.

Mullard, A. 2012. FDA drug approvals. *Nature Reviews Drug Discovery* 11(2):91–94.

Munos, B. 2009. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery* 8(12):959–968.

NRC (National Research Council). 2011. *Toward precision medicine: Building a knowledge network for biomedical research and a new taxonomy of disease*. Washington, DC: The National Academies Press.

Patil, S. T., L. Zhang, F. Martenyi, S. L. Lowe, K. A. Jackson, B. V. Andreev, A. S. Avedisova, L. M. Bardenstein, I. Y. Gurovich, M. A. Morozova, S. N. Mosolov, N. G. Neznanov, A. M. Reznik, A. B. Smulevich, V. A. Tochilov, B. G. Johnson, J. A. Monn, and D. D. Schoepp. 2007. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized Phase 2 clinical trial. *Nature Medicine* 13(9):1102–1107.

Paul, S. M., D. S. Mytelka, C. T. Dunwiddie, C. C. Persinger, B. H. Munos, S. R. Lindborg, and A. L. Schacht. 2010. How to improve R&D productivity: The pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery* 9(3):203–214.

Pirmohamed, M., S. James, S. Meakin, C. Green, A. K. Scott, T. J. Walley, K. Farrar, B. K. Park, and A. M. Breckenridge. 2004. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18,820 patients. *British Medical Journal* 329(7456):15–19.

Pollack, A. 2010. Awaiting the genome payoff. *New York Times*, June 14, B1.

Ramsey, B. W., N. G. Davies, E. McElvaney, E. Tullis, S. C. Bell, P. Dřevínek, M. Griese, E. F. McKone, C. E. Wainwright, M. W. Konstan, R. Moss, F. Ratjen, I. Sermet-Gaudelus, S. M. Rowe, Q. Dong, S. Rodriguez, K. Yen, C. Ordoñez, J. S. Elborn, and VX08-770-102 Study Group. 2011. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *New England Journal of Medicine* 365(18):1663–1672.

Riess, J. W., and H. A. Wakelee. 2012. Metastatic non-small cell lung cancer management: Novel targets and recent clinical advances. *Clinical Advances in Hematology & Oncology* 10(4):226–234. http://www.clinicaladvances.com/article_pdfs/ho0412_reiss.pdf (accessed June 18, 2012).

Rikova, K., A. Guo, Q. Zeng, A. Possemato, J. Yu, H. Haack, J. Nardone, K. Lee, C. Reeves, Y. Li, Y. Hu, Z. Tan, M. Stokes, L. Sullivan, J. Mitchell, R. Wetzel, J. Macneill, J. M. Ren, J. Yuan, C. E. Bakalarski, J. Villen, J. M. Kornhauser, B. Smith, D. Li, X. Zhou, S. P. Gygi, T. L. Gu, R. D. Polakiewicz, J. Rush, and M. J. Comb. 2007. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 131(6):1190–1203.

Scannell, J. W., A. Blanckley, H. Boldon, and B. Warrington. 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery* 11(3):191–200.

Sirota, M., J. T. Dudley, J. Kim, A. P. Chiang, A. A. Morgan, A. Sweet-Cordero, J. Sage, and A. T. Butte. 2011. Discovery and preclinical validation of drug indications using compendia of public gene expression data. *Science Translational Medicine* 3(96):96ra77.

Soda, M., Y. L. Choi, M. Enomoto, S. Takada, Y. Yamashita, S. Ishikawa, S. Fujiwara, H. Watanabe, K. Kurashina, H. Hatanaka, M. Bando, S. Ohno, Y. Ishikawa, H. Aburatani, T. Niki, Y. Sohara, Y. Sugiyama, and H. Mano. 2007. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 448(7153):561–566.

Spear, B. B., M. Heath-Chiozzi, and J. Huff. 2001. Clinical application of pharmacogenetics. *Trends in Molecular Medicine* 7(5):201–204.

Trusheim, M. R., E. R. Berndt, and F. L. Douglas. 2007. Stratified medicine: Strategic and economic implications of combining drugs and clinical biomarkers. *Nature Reviews Drug Discovery* 6(4):287–293.

Trusheim, M. R., B. Burgess, S. X. Hu, T. Long, S. D. Averbuch, A. A. Flynn, A. Lieftucht, A. Mazumder, J. Milloy, P. W. Shaw, D. Swank, J. Wang, E. R. Berndt, F. Goodsaid, and M. C. Palmer. 2011. Quantifying factors for the success of stratified medicine. *Nature Reviews Drug Discovery* 10(11):817–833.

Tufts Center for the Study of Drug Development. 2010. Personalized medicine is playing a growing role in development pipelines. *Impact Reports* 12(6).

Wade, N. 2010. A decade later, genetic map yields few new cures. *New York Times*, June 12, A1.

Appendix A

Workshop Agenda

New Paradigms in Drug Discovery: How Genomic Data Are Being Used to Revolutionize the Drug Discovery and Development Process—A Workshop

March 21, 2012

20 F Street NW Conference Center
20 F Street, NW
Washington, DC 20001

WORKSHOP OBJECTIVES

- To examine the impact of and investment in the use of genetic and genomic data in drug development.
- To discuss how genomic and genetic data have been and will be used in the drug development process to improve aspects such as target identification, clinical trial design, pharmacogenomic approaches, biomarker development, and understanding of disease biology.
- To investigate the economic drivers, incentives, and models for genomic-based strategies for drug development.

8:30–8:35 A.M. **WELCOMING REMARKS**

Wylie Burke, *Roundtable Chair*
Professor and Chair, Department of Bioethics and Humanities, University of Washington

8:35–8:45 A.M. **CHARGE TO WORKSHOP SPEAKERS AND PARTICIPANTS**

Geoffrey Ginsburg
Director, Center for Genomic Medicine, Duke University

8:45–10:15 A.M. **CURRENT LANDSCAPE**

Session Moderator: Aidan Power, Pfizer Inc.

8:45–9:00 A.M. **Current Use of Genetic and Genomic Strategies in Drug Development**

Nicholas Davies
Partner, Pharmaceutical and Life Sciences Practice, PwC

9:00–9:15 A.M. **Economic Incentives for Genetic and Genomic Strategies**

Mark Trusheim
Visiting Scientist and Executive-in-Residence, MIT Sloan School of Management; President, Co-Bio Consulting

9:15–9:30 A.M. **Perceived Challenges in Genomic-Based Drug Development**

Garret A. FitzGerald
Professor of Medicine and Pharmacology and McNeil Professor in Translational Medicine and Therapeutics; Associate Dean for Translational Research; Chair, Department of Pharmacology; Director, Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine

9:30–10:15 A.M.	**Discussion with Speakers and Attendees**
10:15–10:30 A.M.	BREAK
10:30 A.M.–12:15 P.M.	**DRUG DISCOVERY AND DEVELOPMENT: CASE STUDIES OF GENOMICS-BASED DRUG DEVELOPMENT**
	Session Moderator: Michelle Penny, Eli Lilly and Company
10:30–10:50 A.M.	**Development of Crizotinib for Treatment of Non-Small-Cell Lung Cancer**
	Steffan N. Ho, Director, Translational Oncology, Pfizer Inc.
10:50–11:10 A.M.	**Use of Genetics to Inform Drug Development of a Novel Treatment for Schizophrenia**
	Laura Nisenbaum, Senior Research Advisor, Pharmacogenomics, Translational Medicine and Tailored Therapeutics, Eli Lilly and Company
11:10–11:30 A.M.	**A Genetic Approach to the Treatment of Cystic Fibrosis**
	Peter Mueller, Executive Vice President, Global Research and Development; Chief Scientific Officer, Vertex Pharmaceuticals Incorporated
11:30 A.M.–12:15 P.M.	**Discussion with Speakers and Attendees**
12:15–1:00 P.M.	WORKING LUNCH

1:00–2:15 P.M. **UTILITY OF EMERGING GENOMICS TECHNOLOGY IN DRUG DEVELOPMENT**

Session Moderator: Geoffrey Ginsburg, Duke University

1:00–1:15 P.M. **Large-Scale Whole-Genome Sequencing for Disease Understanding, Drug Development, and Genomic Medicine**

Radoje Drmanac
Co-Founder and Chief Scientific Officer, Complete Genomics

1:15–1:30 P.M. **Clinical Next Generation Sequencing—Value to Drug Developers**

Gary Palmer
Senior Vice President, Medical Affairs and Commercial Development, Foundation Medicine

1:30–1:45 P.M. **Pharma Perspective**

Jane Fridlyand
Senior Statistical Scientist, Genentech

1:45–2:15 P.M. **Discussion with Speakers and Attendees**

2:15–4:15 P.M. **EVOLVING PARADIGMS**

Session Moderator: Sharon Terry, Genetic Alliance

2:15–2:30 P.M. **Foundations and Drug Development**

Walter Capone
Chief Operating Officer, Multiple Myeloma Research Foundation

2:30–2:45 P.M. **Genomics and Regulatory Science**

Michael Pacanowski
Team Leader, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

2:45–3:00 P.M. BREAK

3:00–3:15 P.M. **Repurposing of Drugs**

Christopher Austin
Director of the Division of Pre-Clinical Innovation; Scientific Director, NIH Center for Translational Therapeutics; National Center for Advancing Translational Sciences, National Institutes of Health

3:15–3:30 P.M. **Pharmacy Benefit Management and Pharmacogenomics**

Felix W. Frueh
President, Medco Research Institute

3:30–4:15 P.M. **Discussion with Speakers and Attendees**

4:15–5:30 P.M. **LEADING THE STRATEGY FOR PERSONALIZED MEDICINE: PHARMA, GOVERNMENT, ACADEMIA—HOW DO WE ALL WORK TOGETHER?**

Session Moderator: Thomas Lehner,
National Institute of Mental Health, National Institutes of Health

Discussants:

Deborah Dunsire
President and Chief Executive Officer, Millennium: The Takeda Oncology Company

Victor Dzau
Chancellor for Health Affairs, Duke University; President and Chief Executive Officer, Duke University Health System

Margaret Hamburg
Commissioner, U.S. Food and Drug Administration

Kathy Hudson
Deputy Director for Science, Outreach, and Policy; Acting Deputy Director, National Center for Advancing Translational Sciences, National Institutes of Health

5:30–5:45 P.M. **CONCLUDING REMARKS**

Geoffrey Ginsburg
Director, Center for Genomic Medicine, Duke University

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

Appendix B

Speaker Biographical Sketches

Christopher P. Austin, M.D., is scientific director at the National Institutes of Health (NIH) Center for Translational Therapeutics (NCTT), and director of the Division of Preclinical Innovation at the National Center for Advancing Translational Sciences, U.S. NIH. The NCTT's mission is both to translate basic science discoveries into new treatments, particularly for rare and neglected diseases, and to develop new technologies and paradigms by which therapeutic development is done. The NCTT's programs span the spectrum of translational science from RNAi biology to small molecule probe discovery to drug development, including genome-wide RNAi, the NIH Chemical Genomics Center (NCGC), the Therapeutics for Rare and Neglected Diseases (TRND) program, and the Bridging Interventional Development Gaps (formerly the NIH-RAID) program. The NCGC is an ultra-high-throughput screening, informatics, and chemistry center that profiles small molecule libraries for biological activity using its quantitative high-throughput screening (qHTS) technology and develops novel compounds as probes of biology and starting points for the development of new drugs for rare and neglected diseases. The NCGC is a partner with the National Toxicology Project, the Environmental Protection Agency, and the Food and Drug Administration in the Toxicology in the 21st Century Program, which is developing in vitro signatures for in vivo toxicity endpoints. The TRND program develops small molecules and biologics from lead to clinical proof of concept for rare and neglected diseases. Before joining NIH in 2002, Dr. Austin directed research programs in genomics-based target discovery, pharmacogenomics, and neuropsychiatric drug development at Merck, with a particular focus on schizophrenia. Dr. Austin received his

A.B. in biology summa cum laude from Princeton and his M.D. from Harvard Medical School. He completed clinical training in internal medicine and neurology at the Massachusetts General Hospital and finished a postdoctoral fellowship in genetics at Harvard.

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 (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 responsible conduct of genetic and genomic research, genetic test evaluation, and 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.

Walter Capone, M.B.A., is the chief operating officer of the Multiple Myeloma Research Foundation (MMRF) and the Multiple Myeloma Research Consortium (MMRC). He oversees the core business operations of the MMRF and as part of the executive committee executes the growth initiatives outlined in the organization's strategic plan. He has 20 years of pharmaceutical and biotechnology leadership experience in the areas of commercial development, operations, finance, marketing, and sales in the United States and internationally. Prior to joining the MMRF, he was the vice president of commercial development and operations at Progenics Pharmaceuticals. He previously worked at a number of entrepreneurial pharmaceutical and biotechnology ventures throughout the United States and Europe including Trimeris, Triangle Pharmaceuticals, and Cyanamid Benelux. He started his career at leading global pharmaceutical companies including Lederle, Wyeth, and Bristol-Myers Squibb. He received his B.A. in international relations

from Brown University and he has an M.B.A. in finance and international business from Columbia University Business School.

Nicholas Davies, Ph.D., is a partner in the pharmaceutical and life sciences practice at PricewaterhouseCoopers (PwC), responsible for pharmaceutical and research and development strategy. He has been a key figure in the pharmaceutical life sciences consulting and pharmaceutical industry for over 16 years and possesses extensive knowledge spanning research, development, commercial and marketing, and the external payer, access, and regulator environments. Prior to joining PwC, Dr. Davies was responsible for global research and development strategy at Pfizer and led a number of key research and development transformations, integrations, and mergers. As a former PwC management consultant and IBM business consulting research and development leader, he led and delivered complex engagements in major mergers and acquisitions, extensive restructuring and downsizing, research and development productivity projects, personalized medicine and diagnostics strategies, portfolio and decision making strategies, outsourcing, clinical research organization and partnering strategies, operational strategies in discovery and clinical development, enterprise risk management, Asia and emerging market strategies, out- and in-licensing, and commercial assessments of pipeline assets. He has also led research laboratories and departments at Novartis and AstraZeneca. Dr. Davies gained his Ph.D. in immunology and genetics at Cambridge University, UK.

Radoje Drmanac, Ph.D., is a co-founder of Complete Genomics and has served as chief scientific officer since July 2005. In 2001, Dr. Drmanac co-founded Callida Genomics, Inc., a DNA sequencing company, and served as Callida's chief scientific officer from 2001 to 2004 and as its president since 2004. In 1994, Dr. Drmanac co-founded Hyseq, Inc., a DNA array technology company that became Hyseq Pharmaceuticals, Inc. and later merged with Variagenics, Inc. to become Nuvelo, Inc., and served as its senior vice president of research from 1994 to 1998 and as its chief scientific officer from 1998 to 2001. Prior to that, Dr. Drmanac served as a group leader at Argonne National Laboratory. Dr. Drmanac received a B.S., M.S., and Ph.D. in molecular biology from the University of Belgrade.

Deborah Dunsire, M.D., has been the president and chief executive officer of Millennium Pharmaceuticals Inc., since July 2005. In 2008 Millennium was acquired by Takeda Pharmaceuticals of Japan, becoming the global oncology center of excellence for Takeda under her leadership. Dr. Dunsire joined Millennium from her role as senior vice president and North American region head of the oncology business unit of Novartis. Prior to her move to the United States in 1994, Dr. Dunsire worked in the global headquarters

of Sandoz in Switzerland managing launch and growth of global products in the field of immunology and dermatology. She joined Sandoz in South Africa in 1988 as a clinical researcher and expanded her résumé to include portfolio and specialty market management. Dr. Dunsire is a member of the board of directors of Allergan Inc. and serves as a director of the Biotechnology Industry Organization where she co-chairs the Committee on Reimbursement and serves as a member of the executive committee. Her not-for-profit board memberships include CancerCare Inc.; the Gabrielle's Angel Foundation for Cancer Research; and the Boston Museum of Science, where she chairs the investment review board; and she is also a member of the Massachusetts General Hospital research advisory council. She served as a director of the Pharmaceutical Research and Manufacturers of America from 2005 to 2008 and as a director of the California Healthcare Institute from 2002 to 2005. Dr. Dunsire was the 2001 recipient of the American Cancer Society Excalibur Award, the 2000 recipient of the Health Care Business Women's Association Rising Star Award, the 2009 Health Care Business Women's Association Woman of the Year Award, the 2011 Massachusetts Biotechnology Organization's Innovative Leadership Award, and the 2011 Golden Door Award from the International Institute of New England. She received a Ph.D. honoris causa from Worcester Polytechnic Institute in 2007. Dr. Dunsire graduated as a physician from the University of Witwatersrand in Johannesburg, South Africa.

Victor J. Dzau, M.D., is the chancellor for health affairs and James B. Duke Professor of Medicine at Duke University and the president and chief executive officer of Duke University Health System. Dr. Dzau was previously the Hersey Professor of Theory and Practice of Medicine and chairman of medicine at Harvard Medical School's Brigham and Women's Hospital and the chairman of the department of medicine at Stanford University. Dr. Dzau has made a significant impact on medicine through his seminal research in cardiovascular medicine, his pioneering work in the discipline of vascular medicine, and recently his leadership in health care innovation. His important work on the renin angiotensin system (RAS) paved the way for the contemporary understanding of RAS in cardiovascular disease and the development of RAS inhibitors as therapeutics. Dr. Dzau also pioneered gene therapy for vascular disease and was the first to introduce DNA decoy molecules to block transcription as gene therapy in vivo. Recently his seminal work on stem cell "paracrine mechanism" provided novel insights into stem cell biology and therapy. As a leader of academic medicine, Dr. Dzau's vision is that academic health centers must lead the transformation through innovation, translation, and globalization. To achieve this vision he has established the Duke Translational Medicine Institute, Duke Global Health Institute, Duke Initiative in Health Innovation, and Duke National Univer-

sity of Singapore Graduate Medical School in Singapore. Among his honors and recognitions are the prestigious Gustav Nylin Medal from the Swedish Royal College of Medicine; the Max Delbruck Medal from Humboldt University, Charite and Max Planck Institute; the Commemorative Gold Medal from Ludwig Maximillian University of Munich and Frey-Werle Foundation; the Inaugural Hatter Award from the Medical Research Council of South Africa; the Polzer Prize from the European Society of Sciences and Arts; the Ellis Island Medal of Honor of the USA; the Novartis Award for Hypertension Research; the Distinguished Scientist Award from the American Heart Association (AHA); and the 2010 AHA Research Achievement Award for his contributions to cardiovascular biology and medicine. He has received six honorary doctorates. He serves on the council of the Institute of Medicine of the National Academy of Sciences, the board of directors of Research America, and the board of health governors of the World Economic Forum. He is also board chair of the Association of Academic Health Centers. He has chaired the NIH Cardiovascular Disease Advisory Committee as well as the Council of Atherosclerosis, Thrombosis and Vascular Biology of the AHA, and has served on the advisory council to the director of NIH.

Garret A. FitzGerald, M.D., FAHA, is the McNeil Professor in Translational Medicine and Therapeutics at the University of Pennsylvania in Philadelphia, where he chairs the Department of Pharmacology and directs the Institute for Translational Medicine and Therapeutics (ITMAT). Dr. FitzGerald trained in medicine at University College Dublin and its teaching hospitals and in statistics at Trinity College in Dublin and the London School of Hygiene. Following fellowships at the Royal Postgraduate Medical School in London, the Max Planck Institute in Cologne, and Vanderbilt University, Dr. FitzGerald joined the faculty at Vanderbilt and eventually led the Division of Clinical Pharmacology as the William Stokes Professor of Experimental Therapeutics. He moved in 1991 to lead the Department of Medicine and Experimental Therapeutics at University College, Dublin, and then returned in 1994 to the United States to take up direction of the Center for Experimental Therapeutics and the General Clinical Research Center as the Robinette Professor of Cardiovascular Medicine at Penn. These structures were subsumed into ITMAT when it was founded in 2004, anticipating the funding of clinical and translational research centers 2 years later by the NIH. ITMAT has grown to more than 650 members and supports research programs, faculty recruitment, education, and infrastructural developments relevant to translational research. Dr. FitzGerald has served as chair of the Department of Pharmacology at Penn. The department is routinely placed in the top three in NIH funding in the United States and supports a graduate group in pharmacological sciences with about 90 students.

Dr. FitzGerald's research has been characterized by an integrative approach to elucidating the mechanisms of drug action, drawing on work in cells, model organisms, and humans. His work contributed substantially to the development of low-dose aspirin. He was the first to describe the dose-dependent suppression by aspirin of thromboxane and prostacyclin biosynthesis in vivo and to discover that inhibition of platelet cyclooxygenase by low-dose aspirin occurred in the presystemic circulation and to characterize the interaction by which non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen could interact with and undermine cardioprotection from aspirin. Dr. FitzGerald's group was the first to predict and then mechanistically explain the cardiovascular hazard from NSAIDs. Since his first prediction of a potential hazard, based on clinical pharmacological studies 12 years ago, evidence consistent with the mechanism proposed—suppression of COX-2 derived prostacyclin—has emerged from multiple studies in model systems, including many genetically manipulated mice created by his group; human genetics; randomized comparisons amongst NSAIDs; and seven placebo-controlled trials of three structurally distinct NSAIDs designed to be specific for inhibition of COX-2. Aside from this work, Dr. FitzGerald has also discovered many products of lipid peroxidation and established their utility as indices of oxidant stress in vivo. Using this methodology he demonstrated that conventional doses of vitamins E and C have no impact on lipid peroxidation in healthy individuals with intact endogenous antioxidant defense, that social consumption of alcohol has a pro-oxidant effect, and that suppression of lipid peroxidation retards atherogenesis in mice. His laboratory was the first to discover a molecular clock in the cardiovascular system and has contributed substantially to our understanding of the importance of peripheral clocks in the regulation of cardiovascular and metabolic function.

Dr. FitzGerald's papers have been published in journals such as *Cell*, *Science*, *Nature*, the *New England Journal of Medicine*, the *Lancet*, *JAMA*, *PNAS*, *JCI*, and *Nature Medicine* and have been cited more than 30,000 times. He has also published on science policy in the lay and professional press and is an occasional sports commentator for *Il Manifesto*. He has been awarded honorary degrees from University College Dublin and the Universities of Edinburgh and Frankfurt. Among his awards are the Harvey Medal, the Boyle Medal, the Taylor Prize, and the Cameron Prize. Dr. FitzGerald serves on the peer review advisory committee of the NIH, the science board of the FDA, and the drug forum of the Institute of Medicine.

Jane Fridlyand, Ph.D., is a senior statistical scientist in the Department of Biostatistics at Genentech/Roche. Dr. Fridlyand received her Ph.D. in statistics in 2001 from the University of California, Berkeley; her dissertation was focused on the applications of statistics to high-dimensional

biological data, including sequencing, genotyping, and early expression microarrays. She continued on to a postdoctoral position at the University of California, San Francisco (UCSF) Cancer Center where she developed novel methods for the analyses of genome-wide copy-number data. In 2003 she transitioned to a faculty position at the Department of Epidemiology and Biostatistics at UCSF. Dr. Fridlyand's main area of research included development of new approaches to the integration of different modalities of high-dimensional genomic and genetic data in cancer with the aim of identifying novel tumor subtypes relevant to disease etiology and prognosis. Dr. Fridlyand has co-authored more than 50 peer-reviewed publications and multiple book chapters, was a key contributor to a number of funded NIH applications, and has been an invited speaker at many national and international meetings. In 2007, Dr. Fridlyand joined early clinical development, oncology, at Genentech. In the past 5 years, her work has focused on developing strategies for incorporation of biomarkers into clinical development programs. Currently she leads global biometrics efforts at Roche in personalized health care.

Felix W. Frueh, Ph.D., is president of the Medco Research Institute, leading Medco's real-world, outcomes-based research in personalized medicine. Dr. Frueh was associate director for genomics at the FDA and managing partner at Stepoutside Consulting and held senior positions at Transgenomic and Protogene Laboratories. He is a member of the board of the Personalized Medicine Coalition and TcLand Expression, Inc. and is adjunct faculty at the Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina. Dr. Frueh held faculty appointments in the departments of pharmacology and medicine at Georgetown University in Washington, DC, and was a fellow at Stanford University and the University of Basel, Switzerland, where he also received his Ph.D. in biochemistry.

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. Dr. Ginsburg is currently professor of medicine and pathology at 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. With a strong commitment to interdisciplinary science he has led projects to develop predictive models for common complex diseases using high-dimensional genomic data

as well as collaborations with engineering groups to develop novel point of care sensors.

Dr. Ginsburg's work spans oncology, infectious diseases, cardiovascular disease and metabolic disorders. His research is addressing the challenges for translating genomic information into medical practice using new and innovative paradigms and the integration of personalized medicine into health care. He is an internationally recognized expert in genomics and personalized medicine with over 200 published papers and funding from NIH, DOD, DARPA, the 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 University 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.

Dr. Ginsburg 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, the Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health, and a member of the External Scientific Panel for the Pharmacogenomics Research Network. Dr. Ginsburg has recently been appointed to the Advisory Council for the newly established National Center for Advancing Translational Sciences at NIH and has recently been nominated to serve on the World Economics Forum's Global Agenda Council on Personalized and Precision Medicine. Dr. Ginsburg received his M.D. and Ph.D. in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, Massachusetts. Subsequently, he 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.

Margaret A. Hamburg, M.D., is the 21st commissioner of the U.S. Food and Drug Administration (FDA). As the top official at the FDA, Dr. Hamburg is committed to strengthening programs and policies that enable the agency to carry out its fundamental mission—to protect and promote the public health. Only the second woman ever to serve as commissioner, Dr. Hamburg earned her M.D. from Harvard Medical School and completed her residency at what is now New York Presbyterian Hospital–Weill Cornell Medical Center. She conducted neuroscience research at Rockefeller University in New York and at the National Institute of Mental Health and later focused on AIDS research as assistant director of the National Institute of Allergy and Infectious Diseases. In 1991, after just a year in the New York City Department of Health, Dr. Hamburg was named its commissioner. During her 6-year tenure she implemented rigorous public health initiatives that tackled the city's most pressing crises head-on, including improved services for women and children, a needle-exchange program to combat HIV transmission, and the nation's first public health bioterrorism defense program. The most celebrated achievement during her leadership was her aggressive approach to the city's tuberculosis epidemic, which led to an 86 percent decline in drug-resistant TB in just 5 years. In 1997, 3 years after she was elected one of the youngest-ever members of the Institute of Medicine, President Bill Clinton named Dr. Hamburg assistant secretary for planning and evaluation in the U.S. Department of Health and Human Services, where she served until the end of the Clinton administration. She then became founding vice president for biological programs at the Nuclear Threat Initiative, a foundation dedicated to reducing the threat to public safety from nuclear, chemical, and biological weapons. President Barack Obama nominated Dr. Hamburg for the post of FDA commissioner on March 14, 2009. As the commissioner of food and drugs, Dr. Hamburg has emphasized the critical role of innovation in meeting the nation's rapidly growing public health needs. She provided leadership for the implementation of three groundbreaking measures: the Family Smoking Prevention and Tobacco Control Act, a 2009 law that gives FDA the authority to regulate the manufacture, distribution, and marketing of tobacco products; the Food Safety Modernization Act of 2011, which changed the focus of food safety measures from responding to food-borne outbreaks of illness to preventing them; and a thorough review of the system for the evaluation and approval of medical devices. Beyond these specific undertakings, Dr. Hamburg has set the agency's paramount course for fulfilling two central public health tasks. She has launched a nationwide public-private effort to strengthen regulatory science as a means for advancing the development and evaluation of innovative, breakthrough medical products, and she is leading FDA's transformation into a global regulatory agency capable of ensuring the safety and quality of imported food, drugs, and medical devices. Commissioner

Hamburg is committed to ensuring that FDA is poised to meet the public health challenges of the 21st century.

Steffan N. Ho, M.D., Ph.D., is currently director of translational oncology at Pfizer Inc. He received a Ph.D. in immunology and an M.D. from the Mayo Clinic. He completed a residency in pathology at the Stanford University Medical Center and a postdoctoral fellowship in the Howard Hughes Medical Institute, also at Stanford. Dr. Ho was on the faculty at the University of California, San Diego, School of Medicine in the Department of Pathology and the Department of Cellular and Molecular Medicine. He subsequently led the development of the translational oncology group at Biogen Idec. In his current position at Pfizer, Dr. Ho plays a leadership role in integrating translational research efforts with experimental medicine strategies to define mechanism of action, understand pharmacodynamic relationships, identify rational therapeutic combinations, and investigate predictive biomarker hypotheses. He has focused on integrating drug and diagnostic development strategies, including the coordination of strategic collaborations supporting predictive diagnostic test development. He also functions as the translational oncology lead for the Xalkori program.

Kathy L. Hudson, Ph.D., is the deputy director for science, outreach, and policy at the National Institutes of Health (NIH) where she oversees the activities of the associate directors for communications and public liaison, legislative policy and analysis, and science policy. In addition, Dr. Hudson works with NIH leadership to develop and implement new strategic and scientific initiatives and is the NIH liaison with the U.S. Department of Health and Human Services. She also represents the NIH—and the NIH director—in high-level collaborations and negotiations with other federal agencies, such as FDA, Centers for Disease Control and Prevention, and the White House Office of Science and Technology Policy, as well as with private research institutions, patient voluntary organizations, and professional societies. In addition to her role in the Office of the Director at NIH, in December 2011 Dr. Hudson became the acting deputy director of the new National Center for Advancing Translational Sciences (NCATS) at NIH. She also serves as the acting director of the Office of Strategic Communications, Alliances, and Policy at NCATS. Dr. Hudson holds a Ph.D. in molecular biology from the University of California, Berkeley, an M.S. in microbiology from the University of Chicago, and a B.A. in biology from Carleton College.

Thomas Lehner, Ph.D., M.P.H., is the director of the Office for Genomics Research Coordination and chief, Genomics Research Branch at the National Institute of Mental Health (NIMH), National Institutes of Health

(NIH). He oversees and coordinates all efforts associated with genomics research for NIMH and is the principal advisor to the NIMH director and the NIMH scientific director for issues related to genetics and genomics. A native of Vienna, Austria, he received a Ph.D. in genetics from the University of Vienna and an M.P.H. in epidemiology from Columbia University. He completed his doctoral training in the laboratory of Jurg Ott at Columbia University and later moved to the Rockefeller University where he worked with Jeff Friedman as the Associate Director of the Starr Center for Human Genetics and as senior research scientist affiliated with the Laboratory for Statistical Genetics. He has also served as an infectious disease epidemiologist for the City of New York and as director of science and research for a subsidiary of Millennium Pharmaceuticals. Since joining NIMH in 2004, Thomas has been instrumental in expanding the NIMH genomics portfolio and the NIMH Repository at Rutgers University while also promoting the team science approach in genomics by forging international collaborative efforts and consortia.

Peter Mueller, Ph.D., joined Vertex in July 2003. As executive vice president, global research and development, and chief scientific officer, he provides strategic oversight for Vertex's worldwide drug discovery research programs, pharmaceutical development, quality assurance and control, and pharmaceutical operations as well as clinical and nonclinical development, regulatory, and medical affairs. Key areas of Vertex's research and development are hepatitis C (HepC), cystic fibrosis (CF), immune-mediated inflammatory diseases (IMIDs), cancer, and neurological diseases, which led in 2011 to the successful approval and launch of INCIVEK (HepC), a NDA/MAA submission for KALYDECO (CF) with FDA approval in January 2012 and several proof of clinical concept candidates in various disease areas. Prior to coming to Vertex, Dr. Mueller served as senior vice president, research and development, for Boehringer Ingelheim Pharmaceuticals, Inc., where he was responsible for the development of all drug candidates of the company's worldwide portfolio in North and South America, Canada, and Japan, beginning in 1997. He also led research programs in the areas of immunology, inflammation, cardiovascular disease, and gene therapy on a global basis. During his time with Boehringer Ingelheim (BI), Dr. Mueller oversaw the discovery of numerous development candidates, held several positions in basic research, medicinal chemistry, and management in different centers of BI worldwide. Dr. Mueller received both an undergraduate degree and a Ph.D. in chemistry at the Albert Einstein University of Ulm, Germany, where he also holds a professorship in theoretical organic chemistry. He completed fellowships in quantum pharmacology at Oxford University and in biophysics at Rochester University. Special fields of study are synthetic organic chemistry, computational chemistry (cheminformat-

ics and bioinformatics), RNA-biophysics, atherosclerosis research, IMIDs, neurodegenerative diseases, infection, oncology, gene/epigenetic technology, and management strategies. He is a board member of various scientific and political societies, such as the Gesellschaft Deutscher Chemiker and Verband Chemische Industrie; the Royal Society of Chemistry; the U.S.-India Chamber of Commerce Biotech, Pharma & Medical Devices Council; the Industrial Research Institute; RNA-the Society; the Association of Strategic Alliance Professionals; the American Association for the Advancement of Science; and the Harvard Accelerator Fund. Before he left Connecticut to join Vertex, Dr. Mueller was also a member of Governor Roland's Council on Economic Competitiveness and Technology for the State of Connecticut.

Laura K. Nisenbaum, Ph.D., is senior research advisor in translational medicine and tailored therapeutics at Eli Lilly and Company. She received a Ph.D. in neuroscience from the University of Pittsburgh in 1991. Prior to this, Dr. Nisenbaum received a Fulbright Scholarship to study neuroscience in Cologne, Germany. Before joining Lilly, she completed postdoctoral fellowships at the National Institute of Mental Health and the University of Tennessee College of Medicine. In addition she was an assistant professor in the Department of Physiology and Neurobiology at the University of Connecticut from 1995 to 1998. Dr. Nisenbaum joined Lilly in 1998 and while there she has made significant contributions to drug discovery and development for the treatment of psychiatric and neurological disorders, especially schizophrenia. She has developed and implemented molecular profiling methodologies for novel target validation and biomarker development. In addition, Dr. Nisenbaum has applied pharmacogenomics across the neuroscience drug development portfolio to help tailor Lilly drugs for the right patient, leading to improved individual patient outcomes.

Michael A. Pacanowski, Pharm.D., M.P.H., is a clinical pharmacologist and team leader of the genomics group in the Office of Clinical Pharmacology at the FDA. Dr. Pacanowski received his Pharm.D. from the Philadelphia College of Pharmacy. He then completed clinical training at Bassett Healthcare in Cooperstown, New York, and a clinical research fellowship in cardiovascular pharmacogenomics at the University of Florida, where he also received his M.P.H. Dr. Pacanowski's expertise is in the area of genetic epidemiology and public health genomics, specifically as related to pharmacogenomic strategies in drug development and utilization. At the FDA, he oversees review of investigational and new drug applications, contributes to regulatory policy development, and conducts research that supports FDA's core public health mission.

Gary Palmer, M.D., J.D., M.B.A., M.P.H., is a medical oncologist with a career spanning three decades in oncology, initially as a clinician in both the academic and community settings and then as a biotech industry executive with diagnostic and therapeutic experience. Currently, he is the senior vice president of medical affairs and commercial development at Foundation Medicine. Dr. Palmer joined Foundation Medicine from On-Q-ity, where he was chief medical officer and head of development for DNA repair marker development and circulating tumor cell technology. He also served as vice president of medical affairs at Genomic Health, Inc., where he was instrumental in the commercialization of the Oncotype DX breast cancer assay. Prior to Dr. Palmer's tenure with Genomic Health, he held leadership positions at Kosan Biosciences and Salmedix, Inc. He also spent 5 years at Amgen, Inc., where he was involved in the clinical development and commercialization of Neupogen, Neulasla, and Aranesp. Prior to joining industry, he served as director of the Medical Breast Service at the University of California, Davis, Cancer Center and chief of medical oncology at Mercy Health System, Sacramento. Dr. Palmer received a B.A. from Yale University and an M.D. from the Stanford University School of Medicine. He completed his internal medicine training at the Boston City Hospital and his oncology fellowship at the Massachusetts General Hospital. He also holds an M.B.A. from the University of California, Davis, an M.P.H. from the University of California, Los Angeles, and a J.D. from Concord Law School. He is a licensed physician and a member of the State Bar of California.

Michelle Ann Penny, Ph.D., is a senior director in the translational medicine group at Eli Lilly and Company. She received her Ph.D. in genetics from the University of Birmingham, UK, in 1993. After a postdoctoral fellowship in the virology division at the National Institute of Medical Research, Mill Hill, London, she joined the Imperial College London, Department of Medical and Community Genetics where she was a postdoctoral research scientist until taking a lectureship role in human molecular genetics in 1998 as course leader for two master of science programs in human molecular genetics and molecular genetics with genetic counseling. Her academic research career focused on the study of complex polygenic diseases, particularly autoimmune disease and susceptibility to infection. In 2002 Dr. Penny joined the clinical pharmacogenomics group at Pfizer in Sandwich, UK, and moved to New London, Connecticut, in 2006 to take on the role of oncology molecular medicine lead until 2009, when she moved to Indianapolis to lead the pharmacogenomics work at Eli Lilly and Company.

Aidan Power, M.B., B.Ch., M.Sc., M.R.C.Psych., has been vice president and head of PharmaTx Precision Medicine since January 2008. Precision

medicine represents a synthesis of all the emerging technologies and operations (computational science, imaging, pharmacogenomics, metabolomics, proteomics, physiological measurements, and diagnostics) that form the scientific basis of emerging approaches to the development of personalized medicine. Graduating in medicine from the University College Cork, Ireland, Dr. Power trained as a psychiatrist in England and joined Pfizer in the United Kingdom in 1993, working on the antidepressant Sertraline and the antipsychotic Ziprasidone. In 2002 Dr. Power relocated to Pfizer Global Research and Development Headquarters in New London, Connecticut, where he headed clinical pharmacogenomics. For the last 3 years he has headed up molecular medicine (now PharmaTx Precision Medicine), which has been integrating molecular studies across disease areas as well as developing diagnostics for critical programs in the Pfizer product pipeline.

Sharon Terry, M.A., is president and CEO of the Genetic Alliance, a network dedicated to improving health through the authentic engagement of communities and individuals. She is the founding CEO of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). Following the diagnosis of their two children with PXE in 1994, Sharon, a former college chaplain, and her husband, Patrick, founded and built a dynamic organization that enables ethical research and policies and provides support and information to members and the public. Along with the other co-inventors of the gene associated with PXE (ABCC6), she holds the patent for the invention, and with the assignment of all rights to PXE International, is its steward. She co-directs a 33-lab research consortium and manages 52 offices worldwide for PXE International. Ms. Terry is also a co-founder of the Genetic Alliance Registry and Biobank (GARB). It is a lay-owned and lay-managed biologic samples and data repository catalyzing translational genomic research on genetic diseases. GARB works in partnership with academia and industry to develop novel diagnostics and therapeutics to better understand and treat these diseases. Ms. Terry is at the forefront of consumer participation in genetics research, services, and policy and serves as a member of many of the major governmental advisory committees on biomedical research, including the Health Information Technology Standards Committee for the Office of the National Coordinator for Health Information Technology, liaison to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children and the National Advisory Council for Human Genome Research, NHGRI, NIH. She serves on the boards of the Institute of Medicine's Health Sciences Policy Board, National Coalition for Health Professional Education in Genetics, the Coalition for 21st Century Medicine, and the International Rare Disease Research Consortium. She is on

the editorial board of *Genetic Testing and Biomarkers*, *Biopreservation and Biobanking*, and the Google Health and Rosalind Franklin Society Advisory Boards. Ms. Terry is the chair of the Coalition for Genetic Fairness that was instrumental in the passage of the Genetic Information Nondiscrimination Act and is co-chair of the Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health. 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 also an Ashoka Fellow. Ms. Terry is committed to personal transformation as a catalyst for the system change needed to improve health and wellness.

Mark Trusheim is a visiting scientist and executive in residence at the Massachusetts Institute of Technology (MIT) Sloan School of Management. He has been a special government employee for the FDA's Office of the Commissioner and is the founder and president of Co-Bio Consulting, LLC. He holds degrees in chemistry from Stanford University and management from MIT. Mr. Trusheim's research focuses on regional innovation industry economic clusters and modeling the introduction of new innovations in health care, such as stratified medicines, to inform public policy, corporate strategy, and product development programs. He is a former member of the Massachusetts Biotechnology Council's board of directors, which helps its more than 500 members succeed in the state. In 2004 he further served as the interim president of the council, leading its successful legislative agenda, its expansion of MassBioEd education programs, and its continued membership growth. Co-Bio Consulting focuses on biotechnology public policy, corporate development, and financing. Co-Bio Consulting helps life sciences firms secure partners and rapidly move their research to market by connecting strategy formation to action. The firm also helps facilitate academic, government, and industry consortia to grow life sciences economic clusters. Clients include established biopharma firms, start-up biotechs, universities, and government agencies. As an entrepreneur, Mr. Trusheim founded and was the first president and chief executive officer of Cantata Laboratories. Cantata marketed clinical diagnostics and pharmaceutical biomarker services based on its biochemical profiling platform. Prior to Cantata, Mr. Trusheim worked at Monsanto/Pharmacia, culminating his career there as co-president and chief operating officer of Cereon Genomics, LLC. Located in Cambridge, Massachusetts, Cereon was created in 1997 by Monsanto as part of a $500 million collaboration with Millennium Pharmaceuticals. Prior to his position at Cereon, Mr. Trusheim

was responsible for Monsanto's external genomics relationships and held roles of vice president in the health and wellness sector, marketing director in Searle Pharmaceutical, and director in the agriculture division strategy. Mr. Trusheim spent the first half of his career in the high-tech industry working at Wang Laboratories in computer hardware and at the startup Kenan Systems Corporation, which focused on developing quantitative models and artificial intelligence–based applications for large corporations and government agencies.

Appendix C

Statement of Task

An ad hoc planning committee will plan and conduct a public workshop that will examine the impact of and investment in the use of genetic and genomic data in drug development. The workshop will feature presentations and discussions from an array of stakeholders which may include leaders from academia, industry, and governmental organizations. The goal of the workshop will be to discuss how genomic and genetic data has been and will be used in the drug development process to improve aspects such as target identification, clinical trial design, pharmacogenomics approaches, biomarker development, and understanding disease biology. The workshop will also investigate the economic drivers, incentives, and models that use genomics in drug development. 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

Brian Abbott
AstraZeneca Pharmaceuticals

Nathan Adams
Defense Threat Reduction Agency, Department of Defense

Margaret Anderson
FasterCures

Euan Ashley
Stanford University

Christopher Austin
National Center for Advancing Translational Sciences, National Institutes of Health

Sarah Beachy
National Cancer Institute, National Institutes of Health

Judith Benkendorf
American College of Medical Genetics

Anahita Bhathena
Abbott Laboratories

Paul Billings
Life Technologies

Bruce Blumberg
Kaiser Permanante

Denise Bonds
National Heart, Lung, and Blood Institute, National Institutes of Health

Ann Bonham
Association of American Medical Colleges

Kristopher Bough
National Institute on Drug Abuse, National Institutes of Health

Joann Boughman
American Society of Human Genetics

Khaled Bouri
U.S. Food and Drug Administration

Linda Brady
National Institutes of Health

Apryl Brown
Wayne County Community College District

Wylie Burke
University of Washington

Walter Capone
Multiple Myeloma Research Foundation

Carolyn Carroll
STAT TECH Inc.

Christine Carter
Society for Women's Health Research

C. Thomas Caskey
Baylor College of Medicine

Chia-Chien Chiang
Human Genome Sciences, Inc.

Lisa Chong
Science

Melina Cimler
Illumina

Sara Copeland
Health Resources and Services Administration

Sean David
Stanford University School of Medicine

Nicholas Davies
PricewaterhouseCoopers LLP

Silvana Dean
U.S. Food and Drug Administration

Jamie Driscoll
National Institute of Mental Health, National Institutes of Health

Rade Drmanac
Complete Genomics

Deborah Dunsire
Millennium: The Takeda Oncology Company

Victor Dzau
Duke University Health System

Peggy Eastman
Oncology Times

Amy Efantis
Boehringer Ingelheim Pharmaceuticals, Inc.

Raith Erickson
Complete Genomics

Cynthia Ewel
Medco Research Institute

W. Gregory Feero
National Human Genome Research Institute, National Institutes of Health

Mandy Field
Children's National Medical Center

Gary Filerman
Atlas Health Foundation

Ross Filice
U.S. Food and Drug Administration

Kelly Filipski
National Cancer Institute

Andrew Fish
AdvaMedDx

Garret FitzGerald
Perelman School of Medicine, University of Pennsylvania

Cathy Fomous
National Institutes of Health

Richard Forshee
U.S. Food and Drug Administration

Jane Fridlyand
Genentech

Felix Frueh
Medco Research Institute

Dean Gaalaas
EdgeBio

Ron Galloway
Method Content LLC

John Gardenier
Independent

Turkan Gardenier
Pragmatica Corporation

Fathia Gibril
U.S. Food and Drug Administration

Geoffrey Ginsburg
Duke University

Andrea Giuffrida
National Institutes of Health

Evan Hadley
National Institute on Aging, National Institutes of Health

Margaret Hamburg
U.S. Food and Drug Administration

Steffan Ho
Pfizer Inc.

Carolyn Hoban
Multiple Myeloma Research Foundation

Damon Hostin
Complete Genomics

Florence Houn
Celgene

Kathy Hudson
National Center for Advancing Translational Sciences, National Institutes of Health

Sheikh Mohammed Shariful Islam
International Centre for Diarrhoeal Disease Research, Bangladesh

Jean Jenkins
National Human Genome Research Institute, National Institutes of Health

Justin Johnson
EdgeBio

Carolyn Jones
Biogen Idec

Thea Kalebic
Millennium: The Takeda Oncology Company

Francis Kalush
Center for Devices and Radiological Health, U.S. Food and Drug Administration

Sharon Kardia
University of Michigan

Nobuko Katagiri
U.S. Food and Drug Administration

John Kehne
Translational Neuropharmacology Consulting LLC

John Kenten
Mesoscale Diagnostics

Mohamed Khan
British Columbia Cancer Agency

Muin Khoury
Centers for Disease Control and Prevention

Chava Kimchi-Sarfaty
U.S. Food and Drug Administration

Roger Klein
Esther & Hyman Rapport Philanthropic Trust

Hon-Sum Ko
U.S. Food and Drug Administration

Susan Koester
National Institute of Mental Health, National Institutes of Health

Kathy Kopnisky
National Institutes of Health

Courtney Lang
Pepperdine University

Thomas Lehner
National Institute of Mental Health, National Institutes of Health

Debra Leonard
Weill Cornell Medical Center

Emily Levy
Synergy Partners

Michelle Lewis
Johns Hopkins University

Len Lichtenfeld
American Cancer Society

Michele Lloyd-Puryear
Office of Rare Diseases Research, National Institutes of Health

Laurence McCarthy
Scientific Technologies & Solutions, LLC

Michael McCaughan
RPM Report

Robert McCormack
Veridex, LLC

Kathryn McLaughlin
Health Resources and Services Administration

Melodi McNeil
Abbott Laboratories

Amy Miller
Personalized Medicine Coalition

Helen Moore
National Cancer Institute, National Institutes of Health

Richard Morris
National Institutes of Health

Peter Mueller
Vertex Pharmaceuticals

Arnulfo Muralles
American Association for the Advancement of Science

Laura Nisenbaum
Eli Lilly and Company

Lolita O'Donnell
Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury

Steve Olson
Independent Consultant

Michael Pacanowski
U.S. Food and Drug Administration

Gustavo Palacios
Center for Genomic Sciences

Gary Palmer
Foundation Medicine

Lydia Pan
Pfizer Inc.

Gillian Parrish
FasterCures

Praveen Pendyala
Center for Studying Health System Change

Michelle Penny
Eli Lilly and Company

Margaret Piper
BlueCross BlueShield Association

Laura Povlich
U.S. House of Representatives

Aidan Power
Pfizer Inc.

Arundeep Pradhan
Oregon Health & Science University

Victoria Pratt
Quest Diagnostics

Ronald Przygodzki
Department of Veterans Affairs

Drena Reaves-Bey
Parenting Before Conception

Cynthia Reilly
American Society of Health-System Pharmacists

Jon Retzlaff
American Association for Cancer Research

Max Robinowitz
U.S. Food and Drug Administration

Bob Roehr
British Medical Journal

Allen Roses
Duke University

Deborah Runkle
American Association for the Advancement of Science

Lisa Schlager
Facing Our Risk of Cancer Empowerment

Derek Scholes
National Human Genome Research Institute, National Institutes of Health

Amber Scholz
President's Council of Advisors on Science and Technology

Joan Scott
National Coalition for Health Professional Education in Genetics

Sam Shekar
Northrop Grumman

Vijaya Simhadri
Center for Biologics Evaluation and Research, U.S. Food and Drug Administration

Tania Simoncelli
U.S. Food and Drug Administration

Dee Simons
Biogen Idec

James Sorace
U.S. Department of Health and Human Services

Ansalan Stewart
U.S. Department of Health and Human Services

Carol Stinson
AstraZeneca Pharmaceuticals

Katherine Johansen Taber
American Medical Association

Zivana Tezak
U.S. Food and Drug Administration

Barry Thompson
American College of Medical Genetics

Javier Torres-Roca
H. Lee Moffitt Cancer Center

Mark Trusheim
MIT Sloan School of Management

Kenneth Tucker
Tauri Group, Inc.

Simona Volpi
National Human Genome Research Institute, National Institutes of Health

Amelia Warner
Merck

Daniel Wattendorf
Department of the Air Force

Jill Wechsler
Pharmaceutical Executive Magazine

Cole Werble
RPM Report

Catherine Wicklund
Northwestern University

Erin Wilhelm
Georgetown University

Hui-Hsing Wong
U.S. Department of Health and
Human Services