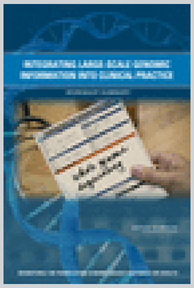

Integrating Large-Scale Genomic Information into Clinical Practice: Workshop Summary

ISBN
978-0-309-22034-7

100 pages
6 x 9
PAPERBACK (2012)

Steve Olson, Sarah H. Beachy, Claire F. Giammaria, and Adam C. Berger, Rapporteurs; Roundtable on Translating Genomic-Based Research for Health; Institute of Medicine

INTEGRATING LARGE-SCALE GENOMIC INFORMATION INTO CLINICAL PRACTICE

WORKSHOP SUMMARY

Steve Olson, Sarah H. Beachy, Claire F. Giammaria, and
Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
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THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This project was supported by contracts between the National Academy of Sciences and the American College of Medical Genetics (unnumbered contract); American Medical Association (unnumbered contract); American Nurses Association (unnumbered contract); Blue Cross and Blue Shield Association (unnumbered contract); Centers for Disease Control and Prevention (Contract No. 200-2011-38807); College of American Pathologists (unnumbered contract); Department of the Air Force (Contract No. FA7014-10-P-0072); Department of Veterans Affairs (Contract No. V101(93) P-2238); Eli Lilly and Company (Contract No. LRL-0028-07); Genetic Alliance (unnumbered contract); Health Resources and Services Administration (Contract No. HHSH250201100119P); Johnson & Johnson (unnumbered contract); Kaiser Permanente (unnumbered contract); National Cancer Institute (Contract No. N01-OD-4-2139, TO#189); National Heart, Lung, and Blood Institute (Contract No. N01-OD-4-2139, TO#189); National Human Genome Research Institute (Contract No. N01-OD-4-2139, TO#189 and 264); National Society of Genetic Counselors (unnumbered contract); and Pfizer Inc. (Contract No. 140-N-1818071). Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number-13: 978-0-309-22034-7
International Standard Book Number-10: 0-309-22034-3

Additional copies of this report are available from The National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

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Suggested citation: IOM (Institute of Medicine). 2012. *Integrating Large-Scale Genomic Information into Clinical Practice: Workshop Summary.* Washington, DC: The National Academies Press.

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

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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:

James P. Evans, Bryson Distinguished Professor of Genetics & Medicine, Department of Genetics, University of North Carolina at Chapel Hill
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Harold J. Fallon,** Dean Emeritus of the University of Alabama at Birmingham School of Medicine. 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.

Acknowledgments

The support of the sponsors of the Institute of Medicine Roundtable on Translating Genomic-Based Research for Health was crucial to the planning and conduct of the workshop Integrating Large-Scale Genomic Information into Clinical Practice. Federal sponsors are the Centers for Disease Control and Prevention; Department of the Air Force; Department of Veterans Affairs; Health Resources and Services Administration; National Cancer Institute; National Heart, Lung, and Blood Institute; and National Human Genome Research Institute. Non-federal sponsorship was provided by the American College of Medical Genetics, American Medical Association, American Nurses Association, Blue Cross and Blue Shield Association, College of American Pathologists, Eli Lilly and Company, Genetic Alliance, Johnson & Johnson, Kaiser Permanente, National Society of Genetic Counselors, and Pfizer Inc.

The Roundtable wishes to express its gratitude to the expert speakers whose presentations helped outline the challenges and opportunities in integrating large-scale genomic information into clinical practice. 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. Christine Mirzayan Science and Technology Policy Fellow Sarah H. Beachy was involved in writing and editing of the report, as was research associate Claire F. Giammaria. Tonia E. Dickerson arranged meetings and handled administrative tasks that resulted in a highly successful workshop.

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Abbreviations and Acronyms

ATM	automated teller machine
BRCA1	breast cancer 1, early onset
BRCA2	breast cancer 2, early onset
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CDG	congenital disorders of glycosylation
CK	creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
CLL	chronic lymphocytic leukemia
CMAMMA	combined malonic and methylmalonic aciduria
CMD	congenital muscular dystrophy
CPMC	Coriell Personalized Medicine Collaborative
CT	computed tomography
EGFR	epidermal growth factor receptor
EMR	electronic medical record
FDA	U.S. Food and Drug Administration
FISH	fluorescent in situ hybridization
HCM	hypertrophic cardiomyopathy
HIV	human immunodeficiency virus

ICOB	Informed Cohort Oversight Board
IRB	institutional review board
IT	information technology
NCBI	National Center for Biotechnology Information
NIH	National Institutes of Health
PCPGM	Partners HealthCare Center for Personalized Genetic Medicine
PGRN	Pharmacogenomics Research Network
PHR	personal health record
SNP	single nucleotide polymorphism
TPMT	thiopurine S-methyltransferase
XLID	X-linked intellectual disability

1

Introduction[1]

The initial sequencing of the human genome, carried out by an international group of experts, took 13 years and $2.7 billion to complete. In the decade since that achievement, sequencing technology has evolved at such a rapid pace that today a consumer can have his or her entire genome sequenced by a single company in a matter of days for less than $10,000, though the addition of interpretation may extend this timeframe. With the next-generation sequencing technology currently being developed, the cost is projected to continue to decline significantly over the next few years, to the point that large-scale genome sequencing is expected to become comparable in cost to a single gene test or to a diagnostic imaging test such as a computed tomography (CT) scan (Mardis, 2006).

Given the rapid technological advances, the potential effect on the lives of patients, and the increasing use of genomic information in clinical care, it is important to address how genomics data can be integrated into the clinical setting. Genetic tests are already used to assess the risk of breast and ovarian cancers, to diagnose recessive diseases such as cystic fibrosis, to determine drug dosages based on individual patient metabolism, and to identify therapeutic options for treating lung and breast tumors, melanoma, and leukemia.

Recent studies have also demonstrated the usefulness of genomics for diagnosing disease and guiding treatment in the clinic. For example, genetic

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[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.

testing of the relatives of patients newly diagnosed with colon cancer has suggested a prevention strategy for identifying individuals with Lynch syndrome (Coates et al., 2011). Genomics data have been used to provide definitive diagnoses for patients with neuropathy, inflammatory bowel disease, and Proteus syndrome as well as to guide therapeutic care for patients with arterial calcifications, movement disorders, and Miller syndrome (Bainbridge et al., 2011; Lindhurst et al., 2011; Lupski et al., 2010; Ng et al., 2010; St. Hilaire et al., 2011; Worthey et al., 2011). Although applications of genomics technologies are currently limited in number, their number will only continue to increase. Thus, it is important to determine how genomic data can best be integrated with clinical practice so as to maximize patient benefit. As Bruce Blumberg from Kaiser Permanente observed in the workshop, "During the year in which we plan[ned] the workshop, the future became the present." It became increasingly clear, he said, that large-scale genomic information would be integrated more fully into clinical practice, which meant that issues related to implementing this change needed to be addressed.

Using DNA sequencing data on a large scale in a clinical setting will pose many difficult challenges. The storage, access, and portability of genetic data all raise significant issues. Questions exist about the need for confirmatory testing of results within a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory. Relevant information will need to be extracted and deposited into the appropriate medical records in a clinically comprehensible manner. The analysis of this information—and reanalysis as new findings emerge—will put further constraints and burdens on health care practitioners and laboratories, particularly as the current health care system lacks a mechanism to reimburse these activities. Ethical issues related to such things as informed consent and stewardship over this information will also need to be considered as integration moves forward. Complicating all of this is the fact that most patients and health care providers have not yet realized just how broad an effect genomic discoveries are likely to have on treatment course and health.

With these issues in mind and considering the potential impact that genomic information can have on the prevention, diagnosis, and treatment of disease, the Roundtable on Translating Genomic-Based Research for Health hosted a workshop on July 19, 2011, to highlight and identify the challenges and opportunities in integrating large-scale genomic information into clinical practice. The workshop was premised on the assumptions that sequencing technology will advance to the point that it can produce clinically meaningful results and that whole-genome sequencing will be cost-effective and comparable in cost to other diagnostic tests. There is little point in deliberating about these assumptions, Blumberg said, because "no matter what the outcome of our debate . . . this is going to happen. This is already happening."

The planning committee for the workshop decided early in its discussions that a single workshop would be insufficient to adequately address every issue, challenge, or opportunity related to clinical genomic medicine. Therefore, to begin a discussion about the use of genomic data in the clinic, the workshop committee decided to focus on several key topics, including the analysis, interpretation, and delivery of genomic information to health care providers plus workforce, ethical, and legal issues. This workshop report summarizes the speakers' presentations and the discussions that followed them. It begins by providing an overview of the current state of the field of genomic medicine, of how approaches to basic and clinical research are changing, and of areas in which steps can be taken immediately to build the necessary infrastructure (Chapter 2). The next two chapters describe the discussions that took place concerning the analysis and interpretation of genomic data (Chapters 3 and 4), while the following three chapters examine practical issues: the delivery of genomic information (Chapter 5), ethical and legal issues (Chapter 6), and developing the necessary workforce skills and knowledge (Chapter 7). The last chapter describes panel discussions on how to maintain curated databases, the role of the field in public health, and how each stakeholder could be involved in helping address the current challenges (Chapter 8).

The main objective of this workshop was to start a discussion of what needs to be done to prepare the necessary infrastructure and to address the various challenges so that patients will be able to benefit from genomics-based research. As Catherine Wicklund from Northwestern University said, the realization that genomics data can be useful in the clinic "is here and we really need to deal with this issue."

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The Realization of Genomic Medicine

Important Points Highlighted by the Speaker

- Genomics as a high-throughput, hypothesis-generating research method can complement traditional low-throughput, hypothesis-testing-based research to improve patient care.
- With demonstrated clinical utility, genomic medicine will, over time, be incorporated into clinical practice.
- Challenges for the field of large-scale genomic medicine include establishment of the infrastructure needed to generate, store, distribute, and interpret genomic data; increasing the sensitivity of sequencing; and assuring patient privacy.
- The study of rare diseases offers a way of implementing the tools and procedures that will later be used in more widespread applications of genomic medicine.

Leslie Biesecker of the National Human Genome Research Institute said that patients come into the health care system to get answers to three simple questions: What is wrong with me? What caused it? What can I do about it? Even if there are no known treatments for a disease or disorder, patients and physicians find significant value in having a diagnosis, Biesecker said. Genomic medicine can help shorten the diagnostic odyssey for patients, direct therapeutic intervention when available, and also build the knowledge base for developing treatments in the future.

SHIFTING RESEARCH PARADIGMS

Historically, Biesecker said, hypothesis testing in basic research, clinical research, and clinical practice research has relied on methods that produced relatively little data. This is changing, however. Biesecker said that in contrast to the low-throughput assays that have been employed to test a single hypothesis with a single assay and that are both expensive and time-consuming, genomics is emerging as a high-throughput, hypothesis-generating research[1] paradigm that can address these limitations. As a hypothesis-generating research tool, genomics will be used to narrow the focus to answer research questions with more classical, hypothesis-testing validation experiments.

CLINICAL APPLICATIONS OF GENOMICS-BASED MEDICINE

Biesecker described four clinical scenarios in which the hypothesis-generating paradigm could be applied to improve patient care. First, a newborn's genome could be tested for life-threatening congenital or metabolic disorders, and any genetic abnormality would be followed up with a specific test. Second, if an older patient presented with symptoms of a certain disorder, such as asthma, genomic data could be used to determine the disease subtype and to identify relevant pharmacogenomic information for treatment. Third, when two people are interested in conceiving a child, the genomes of both partners could be tested for recessive alleles for serious congenital disorders. Finally, during adulthood a patient may also be interested in learning about disease risk for particular cancers, such as breast or ovarian. These are lofty ideas about what a clinician could do with genomic data and a set of analytic tools to affect patient health, said Biesecker.

Altering the way that clinical medicine is conducted to include genomic analyses will take some work, Biesecker said. A major problem is that genomic analyses generate much more data than any clinician or patient can use, and clinicians are generally not likely to order tests that provide more data than they are seeking. Additionally, as more tests are performed, the likelihood of a false-positive signal increases. For example, many physicians resist doing a full panel of blood tests when only a specific test is needed. However, clinical laboratories routinely perform multiple tests when a single test is ordered because it is more cost-effective. If one of the non-requested tests on the resultant panel reaches a "panic" value, this is

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[1] Hypothesis-generating research is defined as an exploratory approach to science whereby an initial experiment, designed with a broad question in mind, produces a large amount of data or observations that can be used to formulate hypotheses that can be tested by directed experiments in the future.

reported to the clinician. Similarly, Beisecker said, a genetic "panic" value would indicate that action is needed.

Overcoming these obstacles is not a new challenge. Tandem mass spectrometry for newborn screening generates hundreds of peaks corresponding to metabolites, but much of this output can be filtered based on the analytes that are known to be useful. Clinicians and researchers always have the option of using data or not. Filtering or reserving genomic data for future use is not a radical change, Biesecker said.

Clinicians should not have to become geneticists, Biesecker said. Clinicians need to be able to use the majority of genomic data for routine clinical care and be able to recognize situations involving critical abnormalities that require the involvement of specialists, such as genetic counselors and clinical geneticists. But "most of the data in the genome should be eventually used by the general practicing physician, not by a clinical geneticist," Biesecker said.

The clinician's role will need to change from selecting tests based on clinical insight to integrating data from multiple sources in order to answer questions. Clinicians will have to adapt to large-scale, pre-differential testing. Clinicians will also become bioinformaticians. "This is a radical notion," Biesecker said, "but if you think about it, our lives are becoming much more information intensive in everything that we do. We are much more inclined to gather large amounts of information, mostly through the Internet, to make decisions in our everyday lives. There is no reason to presuppose that clinicians cannot do the same thing. And once it becomes clear to the clinician that the tools can work, they—like us when we are shopping or trying to answer a question on the Internet—will use large-scale information sources to answer those questions."

Clinicians are by nature conservative in their practice, Biesecker said, but once they are shown the utility of a new approach, many will quickly change their practices. Still, changes of this magnitude will take several years to be put into practice widely and effectively.

ADDRESSING OBSTACLES AND DEFINING A PATH FORWARD

As the clinical utility of genomic data increases, there will be practical considerations that need to be taken into account. Biesecker discussed four main areas that present significant challenges. First, the infrastructure necessary to generate, store, and distribute these kinds of large-scale data is not yet available. Second, although it may eventually be more cost-effective to regenerate genomic data when needed, at this point whole-genome analysis will probably be cost-effective only once a person's genomic information is evaluated on four or five different occasions. "You can generate it once and re-use it in multiple occasions," Biesecker said, "and the cost of that test is distributed over the lifetime of the patient." Third, data need to be securely stored and readily accessible, and patients need to be confident that their data will be used for their benefit. Biesecker discussed a system in which patients have access "keys" to their data so that the data cannot be shared without consent. (More patient privacy and other ethical and legal issues are discussed in Chapter 6.) Finally, the development of robust databases that correlate genetic variants with phenotypes will be a major challenge, Biesecker said. (This issue is discussed further in Chapter 8.)

Despite the challenges involved with bringing genomic medicine into the clinic, the tools to implement changes that will improve care with genomic data are available, Biesecker said. Using these tools to improve medicine will require gathering data, educating clinicians and patients, and developing the infrastructure. Biesecker said that additional clinical and translational research will be needed to move research results into the clinic and that information systems, such as analytic software, will need to become much more sophisticated and clinician-friendly. He added that clinical trials will need to compare the utility of sequence-driven algorithms to current practice. In particular, he said, the sensitivity of sequencing technologies needs to be improved. The sensitivity of current technologies ranges from 88 to 92 percent when examining all of the genes in the human genome; the sensitivity will need to exceed 95 percent to be useful for detecting specific diseases.

As a way of moving forward, Biesecker suggested using rare diseases as an entry point for genomic medicine. The many thousands of rare diseases and disorders result in a major expenditure of health care resources as patients go from provider to provider and test to test in what has been called the "diagnostic odyssey." A system that could efficiently diagnose patients with rare diseases would provide an opportunity to build infrastructure and also would provide experience in how to handle incidental findings. Sequences that reveal rare metabolic disorders would produce many other findings of interest, which clinicians could then use in routine care. Specialists applying informatics tools to sequence information in this context could in turn teach generalists and make the tools more user-friendly.

THE CLINSEQ PROJECT

As an example of an infrastructure-building project, Biesecker described a cohort study called ClinSeq, a large-scale pilot sequencing study involving about 1,000 participants that Biesecker and his colleagues began in 2006 to evaluate candidate genes associated with cardiovascular outcomes such as coronary artery calcification. The design of ClinSeq allowed for the evaluation of pilot technologies, assessment of challenges, and exploration of how best to interact with patients over the course of the study. ClinSeq was based on the assumption that common diseases consist, in substantial measure, of individually rare phenotypes. The many thousands of functional genes in the human genome provide pathways to similar phenotypic endpoints that are grouped together and interpreted as distinct diseases. According to this hypothesis, the underlying heterogeneity of common diseases explains the variation routinely seen in the disease progression, severity, therapeutic response, and side effects of therapies. By dividing the molecular pathophysiology into finer groups, it should be possible to understand this variation and predict the phenotypes.

Although the initial goal of ClinSeq was to study atherosclerosis, the patients in the study were asked to consent only if they agreed to return for additional tests if data from the genome sequence raised particular questions. This made it possible to perform hypothesis-generating research instead of studying only those phenotypes identified a priori. As a result, Biesecker and colleagues were able to use the ClinSeq cohort data to test for the presence of a mutated gene that, in a separate study, had been determined to cause combined malonic and methylmalonic aciduria (CMAMMA), a rare recessive metabolic disorder. With the ClinSeq data, Biesecker said, he was able to identify and diagnose a patient in the ClinSeq cohort with a homozygous mutation for CMAMMA who did not present clinically with the neurological manifestations and normal vitamin B_{12} levels found in typical adult patients. However, upon examination of frozen blood and urine samples, the patient had the characteristic pattern of elevated methylmalonic acid and malonic acid without a vitamin B_{12} deficiency (Sloan et al., 2011). "We thought we understood the spectrum of that disorder," he said, "but when you use a genomic approach, you dip into a database and you find a patient who has a phenotype that you didn't predict even existed. You identify that phenotype, and that expands your understanding of the disorder."

Biesecker also gave an example of how the ClinSeq study data aided in disease prevention. An analysis of the genome of a middle-aged man revealed a pathogenic mutation of BRCA2 (breast cancer 2, early onset), previously undiscovered in his family. In such a case, Biesecker said, it is more logical to test for breast and ovarian cancers proactively instead of waiting until multiple family members are affected by the disease. Thus, this is a situation in which the pilot study revealed important information that would not have ordinarily been discovered because the patient did not have classic risk factors of disease.

AN EVOLUTION OF MEDICINE

Biesecker said that he shies away from the idea that genomics is going to revolutionize medicine. “Revolutions aren’t terribly pleasant affairs to be involved with,” he said. “They are very disruptive. A lot of people get harmed by them, and they have manifold unanticipated consequences.” Instead, he said, he prefers to think of the changes going on today and anticipated for the future as evolutionary. “We take what works in medicine and evolve it toward [doing] what we already know how to do better.”

3

The Analysis of Genomic Data

Important Points Highlighted by Individual Speakers

- There needs to be agreement upon standards for both analytical and clinical validation.
- Clinical data will need to be linked to genomic databases in order to further understanding of the phenotypic effects of genetic variants.
- Genomic data should be put into meaningful formats in order to be most useful to health care providers.
- Clinical actions need to be determined through collaborative efforts involving physicians, patients, their families, and laboratories.

Technologies such as whole-genome sequencing generate a tremendous amount of data, and reducing those data down to clinically applicable information will require a robust analysis process. As Debra Leonard from Weill Cornell Medical Center introduced the speakers, she stated some of the key questions and challenges for analysis of genomic data: What standards will be applied to the analysis of genomic data? How will new knowledge be incorporated into previously analyzed data? Who will be responsible for re-contacting physicians and patients as new data are gathered and existing data are re-analyzed?

CHALLENGES FOR LABORATORIES

Federico Monzon from the Methodist Hospital Research Institute described how cancer screenings have evolved over time. For example, physicians who tested for breast cancer were originally limited to studying the morphology of the breast. Later, the science progressed to evaluating single biomarkers, such as analyzing estrogen receptors in tissue. Since that time, testing for breast cancer has advanced through biomarker panels, expression profiles, targeted sequencing of specific genes, exome sequencing, and, finally, to whole-genome sequencing. While this progression of tests has led to a greater understanding of disease morphology, it has also required laboratories and physicians to complete more complex analyses of the test results. As Monzon said, “This is an evolution of testing which is driven by our better understanding of disease, and with that better understanding of disease comes better clinical testing that we are doing in our laboratories.”

Based on his experience with the genomic testing of cancer tissues, Monzon offered several challenges that laboratories can expect to face when performing their analyses. Chief among them is demonstrating the analytical and clinical validity of the genetic test, no matter whether the test is for a single gene or for the whole genome. A laboratory is responsible for determining whether a test is able to detect all described variants—whether in sequences, transcripts, or some other biological indicator—as well as for validating that the data are correct when the test finds something new. Furthermore, patients and payers depend on the laboratory to determine whether a test identifies patients who have a disease or are at risk for a disease.

Today’s validation standards do not apply to multianalyte tests, much less to whole genomes. With millions of variants estimated to exist within a single genome, there are more potential backgrounds than individuals who can be used to validate the variants. It is thus a major question regarding how many patients or tumor types need to be identified for each variant detected; with the cross-genome differences among these patients, validating each variant in the same way that single-gene tests are handled is not possible, Monzon said.

No sequencing technology can validate every base pair, Monzon said, especially with variants that have never before been seen. Instead, laboratories will need to assess the concordance across results. Reference genomes will help in achieving analytically valid results. Laboratories will develop confidence in platforms based on experience, which will then generate confidence in results. Madhuri Hegde from the Emory University School of Medicine added that sequencing systems will inevitably introduce artifacts, and genomic analysis will need to separate those artifacts from real variants. As a result, some sort of confirmation, such as Sanger sequencing for the individual variant in question, will be necessary in many circumstances.

Just as there is no agreed-upon method for validating all of the variations, there currently is a lack of regulatory guidance for whole-genome tests, and routine whole-genome sequencing will not be allowed to move into clinical settings without major changes in current regulations. In setting standards for whole-genome sequencing, Monzon said, it will be important to strike the proper balance between ensuring the quality of genomic testing and allowing innovation to proceed. Heidi Rehm from Partners HealthCare Center for Personalized Genetic Medicine (PCPGM) said that she expects more involvement from the U.S. Food and Drug Administration (FDA) and other regulatory bodies, which is generally a good thing, she said. The FDA has been trying to understand its role, and so far it has not been inhibitory. There are differences in the quality of testing, which the FDA should address. "I think we would benefit from some regulation," Rehm said. Monzon agreed that the FDA has been cautious about regulating such tests, partly because the vast majority of genetic tests have been developed by laboratories. Hegde said that different areas of testing will require different levels of oversight and that laboratories need to observe the guidelines and quality assurance documents that are currently in place.

The challenges stemming from the lack of guidance or regulation are also apparent in situations in which the physician needs to know whether test results direct clinical action. The laboratory has the responsibility of deciding which of its findings to report to the physician, but the meaning of most of what it finds is unknown. Monzon pointed out that this is especially true in cancer testing where there is an accumulation of mutations. There is no single repository for laboratory directors to find up-to-date standard-of-care guidelines. Current CLIA regulations specify that the responsibility for clinical validation rests with the medical director of the laboratory. "This is a heavy burden to have," Monzon said.

How Much Evidence Is Needed to Adopt a New Test?

As an example of many of the current regulatory and standardization issues, Monzon described a current standard-of-care test for chronic lymphocytic leukemia (CLL). Historically, fluorescent in situ hybridization (FISH) panels have been the only technique used to detect genetic aberrations in CLL that have a major impact on the behavior of the disease. These panels have many disadvantages, however. Commercial FISH panels do not detect all chromosomal deletions, cannot capture all relevant genomic lesions, and are limited in either their resolution or their breadth of coverage (Hagenkord et al., 2010). Cytogenomic arrays are beginning to gain acceptance as an alternative to the standard FISH panel for detecting these and other aberrations (Hagenkord et al., 2010). These new tests have the advantage that they can detect a condition known as genomic complexity, which describes a condition in which there are a large number of genetic changes. However, it is not clear that this is an actionable result that should be reported. The condition has been linked to adverse outcomes, but the combined literature is limited to data from only about 160 patients. Is this enough information to start using this test in the clinic? If so, how should it be reflected in the guidelines for treatment or management of these patients? What level of evidence is needed? Does the result provide prognostic information that can be used for decision making?

To answer these and other questions, Monzon said, guidelines, regulations, and standards are needed that allow such tests to be validated. Validation is needed for technologies and platforms, not just individual tests. Furthermore, laboratories need tools to define the clinical relevance of a result and link this information to therapeutic agents.

Meeting the Demands for Actionable Results

Monzon emphasized that in the near term it will be important to accumulate data regarding which mutations drive diseases such as cancer and which mutations are passenger variants. Actionable results need to be distinguished from results that are not relevant, and this distinction may change as research progresses. Laboratory directors need to be thoroughly familiar with current research, and sophisticated laboratory information systems are essential.

Laboratories currently "do not have the resources to deal with genomic medicine," Monzon concluded. "Access to curated information is fragmented, and there is no . . . sole source of information that we can go through." Furthermore, reimbursement for these activities is virtually nonexistent today, especially when the activity involves reviewing past results in light of recent research.

LABORATORY-BASED SOLUTIONS

The Emory Genetics Laboratory is a not-for-profit clinical testing laboratory that focuses on rare genetic disorders, Hegde said. It is a comprehensive laboratory that performs biochemical, cytogenetic, nutritional, and clinical testing. Its DNA laboratory uses a variety of technologies to conduct tests on a wide variety of genes and inherited disorders. It has been doing next-generation sequencing for more than a year and has accrued considerable experience with clinical applications. It is certified and accredited through CLIA, the College of American Pathologists (CAP), and New York State.

There is a typical life cycle for the development and use of a single-gene test, Hegde said (Figure 3-1). After a gene is reported in the literature,

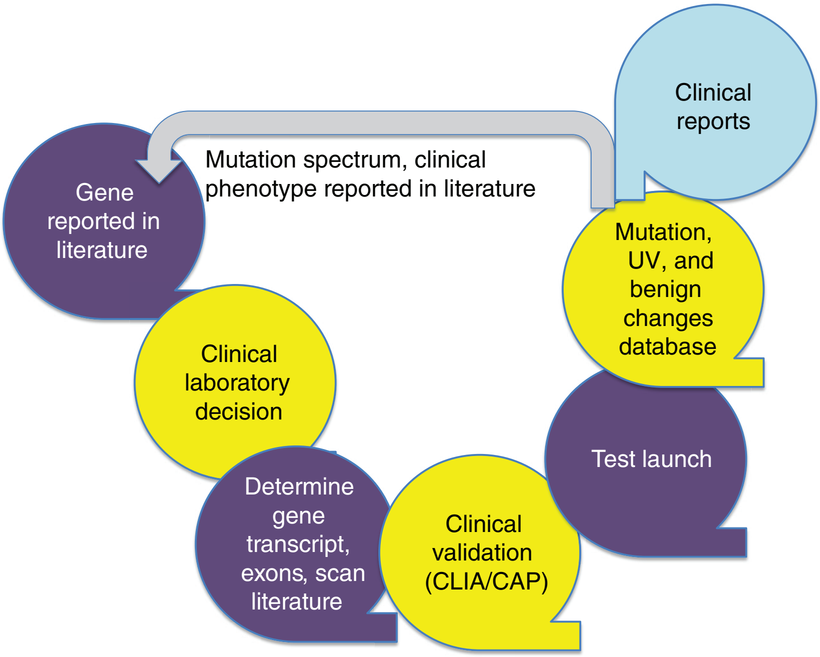

FIGURE 3-1 Genetic tests undergo a characteristic progression from gene discovery to test application.
NOTE: CAP = College of American Pathologists; CLIA = Clinical Laboratory Improvement Amendments; UV = unclassified variants.
SOURCE: Hegde, IOM workshop presentation, July 19, 2011.

a clinical laboratory decides whether to investigate and test for that gene based on requests from clinicians or others. The laboratory determines the gene transcript, including such information as the number of exons contained, and the laboratory scans the literature to extract all relevant information. A clinical validation step is performed that meets CLIA and CAP standards, and then the laboratory makes the test available. Once the test is being used, the laboratory has to report its findings in a way that is understandable to a clinician. The current policy of the Emory Genetics Laboratory is to report only the data that have been requested, an approach that allows the laboratory to avoid many of the interpretation issues that Monzon described.

From the data collected from the tests it runs, the laboratory constructs databases of mutations, unclassified variants, and benign changes. These restricted-use databases can be used to determine whether a variant or group of variants is clinically actionable. In the past not many clinical laboratories have put mutation and phenotype databases into the open literature, Hegde said, but the Emory Genetics Laboratory has produced many such reports.

Detecting Variance with Genome Test Results

The Emory Genetics Laboratory has been moving from single-gene testing to multigene panels using next-generation sequencing. The laboratory is now testing for three disorders: X-linked intellectual disability (XLID), congenital disorders of glycosylation (CDG), and congenital muscular dystrophy (CMD). The XLID panel examines 92 genes that segregate with the disease, including both genes that are syndromic and those that are non-syndromic (Nelson and Gibbs, 2009). The CDG panel tests for a group of metabolic disorders caused by a deficiency in some or all parts of the glycosylation pathways that results in an abnormal glycosylation of oligosaccharides. Just as there are many different organelles that could be affected, there is a wide range of phenotypic symptoms for this disease, ranging from death in infancy to mild involvement in adults (Jaeken, 2011). The CMD panel surveys a collection of gene mutations that result in muscle disorders that are defined by a combination of early-onset hypotonia and weakness, contractures, variable progression, normal or elevated serum creatine kinase (CK), and myopathic changes on an electromyogram and that are usually associated with a dystrophic muscle biopsy. The gene mutations considered on the CMD panel result in muscle weakness soon after birth (Peat et al., 2008).

Because of limitations in sequencing technology, some of the laboratory's tests detect more gene variants than others. The CMD panel detects an average of 39 variants in just 13 genes, for example, while the XLID panel detects an average of 31 variants in 92 genes.

Sequencing detects many genetic changes that cannot be interpreted, Hegde noted. In response, the laboratory uses its database of known variants as an initial screening tool for determining which changes may be real and which may be artifacts. It can then continuously re-classify variants and re-contact physicians to tell them if a variant that had been detected previously but that had been considered non-actionable at the time has been re-classified. In order to help determine which panel of genes to test, the laboratory has developed a tool to allow the physician to link phenotypic symptoms with genes that are known to be related to those symptoms.

Reimbursement and Collaboration Challenges

The experience with next-generation sequencing at the Emory Genetics Laboratory has identified a number of challenges with important implications for whole-exome or whole-genome sequencing, Hegde said. The amount of reimbursement available compared with the amount of time a comprehensive analysis requires is a concern. "The reality of the situation is that the cost of the tests is not the cost of the reagents. There are lab directors. There are technicians. There are a lot of other factors that need to be accounted for when you are costing out a test."

Whole-exome and whole-genome analysis will require a team composed of clinical and laboratory geneticists, genetic counselors, and other health care specialists, Hegde said. It will be important to get as much data as possible into databases, including the clinical presentation, in order to aid in the interpretation of the data. Futhermore, curating the variant databases will be very important in making the transition from sequencing gene panels to sequencing the whole genome.

MEANINGFUL USE OF TEST RESULTS

For genetic test results to be used in clinical settings, Rehm said, the data need to be put into useful and meaningful formats for physicians. In particular, she identified four issues for consideration: (1) structuring genomic data; (2) providing accurate and readily accessible data interpretation resources; (3) supporting the generation of high-quality, clinically relevant reports; and (4) creating systems to support re-analysis and independent interpretations of genomic data.

Structured Genomic Data

The standards group at the Laboratory for Molecular Medicine within PCPGM has been working to define a system for reporting genetic variation and test content in well-structured ways. The system includes such information as allele state, nucleotide changes, amino acid changes, and clinical classification. At Partners HealthCare this information goes into an electronic medical record (EMR) and into a research repository as structured data.

Structured data make it possible to use clinical support tools that can leverage genetic data even as algorithms and use cases change over time. Whole-genome sequence records can be accessed in EMRs as clinical symptoms arise or as adverse-event warnings are received, and proactive alerts can be generated as new clinically actionable knowledge is learned. It is important, Rehm said, that regulatory partners, including the FDA and Centers for Medicare and Medicaid Services, be engaged in order for laboratory systems and health care systems to be sure of the validation of this information.

Data Interpretation Resources

A basic challenge in using genomic data, Rehm said, is that the terminology is not standardized. Genetic variants can be referred to as mutations, polymorphisms, or SNPs (single nucleotide polymorphisms); their effects might be called pathogenic, deleterious, or disease-associated; and harmful effects can be possible, probable, or likely.

Another challenge is that most variants are rare, with the association linked in only a small population. For example, of the more than 1,400 mutations in the hypertrophic cardiomyopathy (HCM) database, two-thirds have been seen in only one family. In addition to the challenges presented by the rarity of variants, other challenges arise from the fact that new clinically significant mutations continue to be identified at a substantial rate. For example, even though more than 150,000 patients already have been tested for BRCA1 (breast cancer 1, early onset) variants, tests continue to detect 10 to 20 new missense variants each week. Thus, once standards for reporting and clinical action have been created, they will need to be re-evaluated and updated continually.

As our understanding of associations is refined, it will become possible to use new models and algorithms to evaluate actions based not only on genetic variants but also on lifestyle, environmental influences, and other factors. This will require extensive information technology support to search databases for variants, and a centralized and standardized open-access variant database with standardized nomenclature and careful curation, Rehm said. Steps in that direction have already been taken by the MutaDATABASE Project and the ClinVar Project, both of which are attempting to create a single place for genetic variations to be housed and curated in standardized ways. ClinVar, for example, is seeking to build rich datasets that are updated on an ongoing basis. Another model is the work done by the International Standards for Cytogenomic Arrays consortium, which is seeking to create a single place in which data generated by clinical laboratories can be deposited. “We are going to have to continue to learn from the datasets even though we are at a limited level of understanding today,” Rehm said.

Rehm noted that many current databases contain much incorrect data. Discussions among the groups mentioned above have centered on developing quality thresholds that set standards for data, but even with thresholds there will be questions about whether data are correct or not.

Most clinical laboratories have been willing to submit their data to public databases, which Rehm said she found surprising. Their willingness demonstrates, she said, “that we all recognize, as we move to whole-genome sequencing, that none of us can interpret the entire genome in an effective way, and we will all need to rely upon everybody’s data.”

High-Quality Clinically Relevant Reports

Clinically relevant reporting of genetic data must do four things, Rehm said. It must:

- accurately interpret the impact of each variant on a gene or protein;
- accurately interpret a set of variants relevant to a single phenotype;
- accurately relay the relevance of the identified variants in the patient's presentation; and
- determine how to apply the genetic information to the care of the patient (and the patient's family members).

Interpreting the impact of a variant or set of variants is clearly the role of the laboratory, Rehm said. But as the complexity of an interpretation increases, this role becomes more diffuse. For example, secondary variants can modify the effects of a primary variant, and some laboratories do not analyze these data fully. Furthermore, laboratories often do not get clinical data, so putting variants into the context of a patient's presentation can be difficult.

As interpretation becomes more complex, few laboratories will have the infrastructure needed to provide interpretations of results, especially in smaller laboratories. Rehm predicted that some entities will be good at analysis while others will be good at interpretation and that questions about interpretation will go to those with the greatest expertise. "There needs to be better recognition that not the same entity has to do both," she said. Regardless of how the specialization of laboratories happens, interpretation will have to be a team effort because most physicians are not currently capable of determining how to apply genetic information to care, Rehm said. Hegde observed that actions need to be determined through a collaborative effort. Clinicians, patients and their families, and laboratories all need to work with each other to make optimal decisions. Furthermore, responses may be tiered, with primary care physicians dealing with certain things and other professionals being called in to deal with other findings. Hegde added that the role of genetic counselors as intermediaries between the laboratory and the clinician is very important.

PCPGM has been planning a genetic consulting service that would enlist cardiologists with genetics expertise who could combine information about a patient's phenotype and family history with the results from the genetic report in order to generate patient and family care packages. The group has also been developing software to help laboratories generate customized reports that would allow cardiologists to integrate genomic data into patient care.

Re-analysis and Independent Interpretations

Guidelines issued by the American College of Medical Genetics is 2007 state that "the testing laboratory . . . should make an effort to contact physicians of previously tested patients in the event that new information changes the initial clinical interpretation of their sequence variant" (Richards et al., 2008). However, Rehm said, no effective method of updating information currently exists. For example, over the past 5 years about 300 HCM variants have been moved from one to another of the five risk categories (benign, likely benign, unknown significance, likely pathogenic, and pathogenic), and more than half of those moves represented significant changes.

PCPGM has developed an extension of its laboratory software called GeneInsight Interface that reports new results in a structured form to clinicians. When a variant is changed in the mutation database, patient reports are automatically updated. Clinicians see that a previously reported category is crossed out and a new category has been inserted. The clinician can click on the variant to read the evidence for why the classification of the variant was changed. The clinician also receives an e-mail alert that links to any patients who have the variant for which the new information is relevant. PCPGM, which has a grant to evaluate the system, has found that, for the most part, physicians have found it extremely useful.

In order to address other problems with re-contacting health care providers and patients, the health care system needs methods that will ease the laboratory's efforts, Rehm said. She suggested developing a system that allows patients to access their genetic data when appropriate and makes patients responsible for updating their current health care providers so that updated information can be delivered to medical professionals when appropriate. This is necessary since the laboratory often does not have reliable methods for determining who is currently caring for a patient or how to reach a patient or physician.

The GeneInsight Interface can also be used to direct researchers to patients who have certain genetic variants so that they can be notified of relevant clinical trials. PCPGM is also considering ways to allow multiple knowledge sources to feed information into genetic databases. "The bigger the network, the more information can be generated and shared across it," Rehm concluded.

GENOMIC MEDICINE IN PRACTICE

In a 2008 interview, Francis Collins, who is now the National Institutes of Health (NIH) director, said, "We desperately need, in this country, a large-scale, prospective, population-based cohort study. And we need to enroll at a minimum half a million people. We would need to have their environmental exposures carefully monitored and recorded, their DNA information recorded, their electronic medical records included, and have them consented for all sort of other follow-ups" (Collins, 2008).

The Coriell Institute for Medical Research, a large biorepository located in New Jersey, is conducting, in partnership with several medical centers, a smaller version of such a study through its Coriell Personalized Medicine Collaborative (CPMC). The goals of this collaborative are to study the use of genome-informed medicine in a real-world clinical setting to determine the best mechanisms for providing information to providers and patients, as well as to find correlations in observational data. "There are not enough resources out there to do randomized clinical trials on every bit of genome information or other quantitative information that is emerging that may be clinically relevant," said Michael Christman of the Coriell Institute. A large observational database will be essential.

More than 5,000 people are currently enrolled in the collaborative study. In order to enter the study, participants are required to fill out extensive medical and family history and lifestyle questionnaires, which are used to report quantitative risks based on environmental or family history information. Extensive genomic analysis—although not yet whole-genome sequencing—is conducted on DNA extracted from each participant's saliva. Only results that are deemed clinically relevant by an expert panel are reported to the patient and, depending on the arm of the study in which the patient is enrolled, also to his or her physician. Much of that information is pharmacogenomic, which is currently the most clinically actionable information and applies to the largest number of people.

Participants and physicians can view the information through a secure Web portal. When only participants get the information, they are encouraged to present it to their physicians. The collaborative study offers genetic counseling and access to pharmacists at no cost since it is a research study. The Web portal allows for continual follow-up with participants on such issues as the actions they take, their perceptions of risks and benefits, and their participation in ancillary studies. The collaborative is fully compliant with the Health Insurance Portability and Accountability Act. But Christman also said that we should not claim to provide complete security for genetic data because "we have to assume that [the data are] going to get out there. If Google can get hacked, then anyone can get hacked." People worried about their privacy when Internet shopping was first getting under way, but the system used for such shopping generally works well, even though some people abuse it, and some people go to jail as a result. "With genetics, it would be largely the same way," Christman concluded.

The collaborative study currently has three arms. The largest arm is a community study of otherwise healthy individuals. Participants have to be at least 18 years old and be able to use the Internet. The other two arms focus on heart disease and cancer and use EMRs and other clinical information. For example, in a partnership with The Ohio State University the collaborative is enrolling 2,000 people with congestive heart failure or hypertension.

The Informed Cohort Oversight Board

One innovation with relevance to whole-genome sequencing was the development of the Informed Cohort Oversight Board (ICOB) (Kohane et al., 2007). CPMC uses the ICOB concept to determine which genomic data should be considered clinically relevant and thus reportable to participants. The ICOB is composed of geneticists, statisticians, ethicists, and a community member. Researchers at Coriell curate the scientific and medical literature and present evidence to the board to determine which genetic information is actionable. The board meets twice a year and approves or disapproves proposals in much the same way as a study section for NIH would.

Consent is obtained from each participant in the study cohort. New results are reported to all participants, and each participant then decides whether or not to view information about his or her genome. The information is presented as a relative risk, taking into account family history and environmental factors. "This is a dynamic group," said Christman. "They know that they will find out new information, but they don't know exactly what."

Potentially actionable conditions that are currently approved to be reported by the CPMC study include several drug metabolism variants and the following complex diseases:

- Age-related macular degeneration
- Bladder cancer
- Breast cancer
- Chronic obstructive pulmonary disease
- Colon cancer
- Coronary artery disease
- Diabetes, types 1 and 2
- Hemochromatosis
- Inflammatory bowel disease
- Lupus
- Melanoma
- Obesity
- Prostate cancer
- Rheumatoid arthritis
- Testicular cancer

At this time, Christman acknowledged, groups of variants explain very little of the risk of complex diseases, but, he said, "with the advent of whole-genome sequencing and the appreciation of rare variants, we are going to be there sooner rather than later, and we have to figure out the system."

A different ICOB advises on testing for pharmacogenomic variants. The project has developed a strength-of-evidence code for these variants that gives greater importance to variants that will affect clinical decisions. The strongest evidence code is reserved for situations in which the reference drug has shown actual clinical outcomes in a randomized clinical trial.

Study Parameters

In order to put together a representative sample, the project is trying to match the demographics of the Delaware Valley, which is about 15 percent African American and 15 percent Hispanic. Follow-up surveys conducted 3 months and 12 months after a result is reported to participants ask them what actions they have taken. For example, the collaborative study keeps track of which medical tests the participants or their physicians choose to do. It has found that the number of tests or procedures taken correlate strongly with age and with the completeness of family history information. The participants' actions are not significantly related to the number of genetic risk variants that they have for that disease. This is good news, Christman said. "People in the study tend to understand that these are risk factors and not determinative."

Another investigation is looking at what participants in the study perceive as the risks and benefits of participation (Gollust et al., 2011). One alarming result is that 13 percent of participants think that they will be able to change their risk with gene therapy if testing is done. "This shows the level of misunderstanding that can be out there," Christman said. Furthermore, about one-third of participants are worried that they will find out something that they do not want to know.

The study of patients with congestive heart failure or hypertension will track physicians' actions in addition to the patients' actions when they receive genetic information. In this arm of the study patients have been randomized for either receiving genetic counseling or not receiving genetic counseling, although everyone in the latter group has access to counseling if requested. Anyone who wants to withdraw from the study can do so at any time and have his or her sample destroyed as well, which some have chosen to do.

Many ethical, legal, and social issues remain to be resolved, Christman said, including various genetics-related privacy issues, the anxiety associated with genetic prognoses, education of various stakeholder groups, and the fact that payers are likely to drive clinical application. But work is ongoing in each of these areas.

4

The Interpretation of Genomic Data

Important Points Highlighted by Individual Speakers

- For genomic testing to be accepted, it should have not only analytical validity but also clinical and social utility.
- Genomic testing should be used as a tool that is integrated with traditional tests for making a disease diagnosis and guiding therapy.
- Human genetic diversity and genetic differences between maternally and paternally derived chromosomes need to be considered when interpreting genomic data.

The interpretation of genomic data is even more difficult than generating and curating the data, said Muin Khoury of the Centers for Disease Control and Prevention (CDC), who moderated the workshop session on interpretation of genomic data. The genome does not mean the same thing to each person at every point in time. The significance of particular variants can depend on age, health status, and other contextual factors during different life stages. The interpretation of genomic data also raises many difficult questions: Will different vendors use the same data to offer different interpretations? How will the results be verified? Who will generate second opinions? How will non-genomic information such as epigenetic data be incorporated into interpretations? And how will interpretation services be regulated?

DATA INTEPRETATION FROM A CLINICIAN'S PERSPECTIVE

A genetic test can have different types of utility, including clinical utility and social utility, according to Robert Nussbaum of the University of California, San Francisco. Clinical utility is a measure of how valuable a test result is to a patient and a clinician in making decisions about whether to do further diagnostic testing or end the "diagnostic odyssey" as well as in deciding how treatment is managed or how lifestyle should be altered. A test that leads to a diagnosis may have tremendous utility for a patient and clinician, but a third-party payer wants the test to result in an action that makes a measurable difference in health. Individual patients may have the option to pay for a test out of pocket if third-party payers refuse to provide reimbursement, but in that case, Nussbaum observed, many people will be excluded because they cannot afford to pay for the test.

In addition to clinical utility, a test must have social utility if private and government insurers are to be willing to pay for it. The insurers need to be convinced that a new test, when compared with current standards of care, would lead to improved health by reducing the need for less successful therapy and would decrease costs by preventing more costly outcomes. "You have to convince them that it is worth their paying for it as opposed to paying for other things," Nussbaum said.

Critical Assessments of Genomic Testing for Prevention

Nussbaum outlined six areas in which whole-genome sequencing could be used in a clinical setting and described the common criticisms that arose during discussions with his colleagues. First, whole-genome testing could have clinical use for the identification of carriers of Mendelian disorders prior to conception. At this point it is far less expensive to test for most of the common autosomal recessive conditions than to perform complete genome sequencing. Although the sequencing coverage is not complete for the tests currently used to detect autosomal recessive genes, current standard practice probably continues to be cost-effective compared to the use of whole-genome sequencing for the same indication, Nussbaum said.

A second area, the use of genomics in prenatal and pre-implantation testing, raises many issues, Nussbaum said. "A very serious decision has to be made under severe time pressure with unclear genotype and phenotype correlation." Pre-implantation testing has advantages over prenatal testing, but it is often limited by the amount of tissue available. This could change with the development of epiblast biopsies to take the place of single-cell testing.

Identification of personal risk for Mendelian disorders is a third area that also raises unanswered questions, especially with regard to clinical validity. This application of genomics raises a variety of questions, including which variants are responsible for a particular phenotype, what mutations are pathogenic, and what the penetrance is of a known pathogenic mutation. "There is a real gap in being able to tie the genotype to the phenotype," Nussbaum said, and progress needs to be made in that regard.

A fourth area in which genomics can be used in the clinic is pharmacogenetic testing. In some cases it already has clear clinical validity and proven clinical and social utility. One well-established application, for example, is human leukocyte antigen typing to prevent idiosyncratic adverse reactions for drugs such as abacavir, an antiviral for treatment of human immunodeficiency virus (HIV) infection (Hughes et al., 2008). But the clinical and social utility of tests for common variants that affect the pharmacokinetics or dynamics for drugs such as warfarin, clopidogrel, irinotecan, codeine, and 6-thiopurine is still unclear (EGAPP, 2009; Gong et al., 2011; Ned, 2010; Teml et al., 2007; Zhou, 2009). Part of the reason for the lack of clarity, Nussbaum said, is that there may be replacement drugs used instead, such as dabigatran and rivaroxaban for warfarin or prasugrel instead of clopidogrel (Brandt et al., 2007). Furthermore, Nussbaum said, it is too late to perform a complete sequencing when a drug is about to be prescribed; the information generated by the sequencing needs to be available in advance.

The fifth area is direct tissue typing for transplantation. This technique is, at the moment, still less costly to conduct than whole-genome sequencing, although delays in receiving the results may affect transplantation for some indications. A possible advantage of whole-genome sequencing in this case is that it may be possible for tissue typing information to be incorporated into networks for organ sharing, which would provide better and more rapid identification of donor–recipient matches.

The sixth area is the identification of alleles, whether rare or common, that increase the risk for common disorders. Such identification, at the present, has very limited clinical validity and utility, Nussbaum said, suggesting that this use of genetic testing currently "is more in the realm of entertainment than medicine." The few people who make the effort to have their genomes tested do not necessarily consider it an essential component of their medical care. Furthermore, this information generally cannot clearly distinguish people who will suffer from a disease from those who will not. For example, results from a panel of 13 SNPs show that people in the top quintile of risk for coronary artery disease have a risk that is 1.7-fold higher than those in the lowest quintile (Ripatti et al., 2010). But the distributions of people at different levels of risk overlap extensively, Nussbaum said, and the test offers "very little discrimination between those who have coronary artery disease and those who do not."

Genomic Testing for Diagnosis

"Could whole-genome sequencing be a cost-effective replacement for candidate gene panels?" Nussbaum asked. It now costs more than $3,000 to have two genes tested, so in the future, sequencing the entire genome could be reasonable by comparison, but, he said, "I don't think we are anywhere near there yet." Discovery of the genetic reasons for undiagnosed hereditary diseases has yielded some remarkable success stories, but in other cases extensive searches have not been successful. It remains to be seen whether the genes that have been uncovered in the recent past, such as those for Miller syndrome (Ng et al., 2010), are exceptions or the rule, Nussbaum said. As technology is applied to larger pools of patients and families, the success rate will go down.

With cancer genomes, sequencing is revealing a tremendous amount of information about the variants that can be used for classification, prognosis, and therapeutic management. Thus, it is reasonable to ask whether in the future the most cost-effective and efficient assay with the most predictive power will be whole-tumor-genome sequencing or simply sequencing a few key variants. An important research question will be whether every cancer is different, which, if true, would make it necessary to scan large amounts of genomic data to understand each person's disease.

Identifying a Path Forward

Nussbaum stressed that he was not trying to discourage the discussion with his criticisms. "The analytical validity of whole-genome sequencing is improving, the costs are coming down, and the poor state of genotype–phenotype correlation is a recognized problem."

Several points need to be emphasized in moving forward, he said. First, the potential advantages of having complete sequences need to be recognized. "Knowing this element or that element is not the same as knowing the periodic table." Because of the huge amounts of data involved, bioinformatics will be essential in building a genomic basis for clinical work. Second, a few demonstration projects are needed as part of an overall health assessment throughout all stages of life that would integrate genomic data into ongoing health care. A good candidate organization to carry out such a project would be a large health plan that is also a provider and is willing to establish a partnership. Third, interpretation should be ongoing, with genome sequencing becoming more like a subscription service in which technologies, software, and information constantly improve and knowledge is exchanged. Patients expect their health care providers to be talking with each other. Furthermore, a subscription implies a continuing relationship among bioinformaticists, providers, and patients and their families in interpreting genomic data. Nussbaum added that efforts to standardize nomenclature are under way, which should enhance collaboration. "As the databases grow and become more and more useful," he said, "there is going to be constraint on the way people report things, and they will come to a common reporting. I am actually fairly optimistic about it."

Finally, it will be important to develop software to interpret variants and provide decision support. In part, this will require establishing partnerships among laboratories, clinics, and the institutions that create and maintain electronic medical records that are functional and allow for interpretation but not necessarily storage of genomic data. "It is useless to think about dumping all the sequence data into an electronic medical record," said Nussbaum. "It has to live someplace else in a way that makes sense, and the interpretation and the re-interpretation have to come into the medical record in a way that is valuable."

INTEGRATING GENOMIC DATA WITH PATHOLOGY

In 2009 Mark Boguski of Harvard Medical School and two colleagues published a paper that laid out a futuristic scenario for cancer care in the year 2020 (Boguski et al., 2009). The process they described begins when a patient presents with symptoms and needs to rely on the involvement of a clinical laboratory for care (Figure 4-1). In addition to conventional analyses of formalin-fixed, paraffin-embedded tissues, such as hematoxylin and eosin and immunohistochemical staining, genome sequencing is also performed. In this situation the pathology report is not just a textual description of what is seen through a microscope and a diagnostic code. It is a dataset and a collection of therapeutic recommendations that includes the parameters under which the modeling was conducted. The oncologist and the rest of the clinical care team then can accept the report's simulations or develop their own to administer precision targeted therapy. This is a model in which advances in sequencing, systems biology, and other areas make it possible to reverse engineer disease pathways, to annotate disease networks and drug targets, and to simulate therapeutic interventions with virtual drugs or combinations of virtual drugs.

In 2009 this seemed improbable, Boguski said. A year later, however, a paper published in *Genome Biology* demonstrated as a proof of concept every conceptual step in the scenario (Jones et al., 2010).

Integration of Genomic Data and Cancer Pathology

Boguski described a case study from the paper that demonstrates what is possible. A 78-year-old man with no prior history of cancer presented with a sore throat. A biopsy of a lump on the back of his tongue revealed

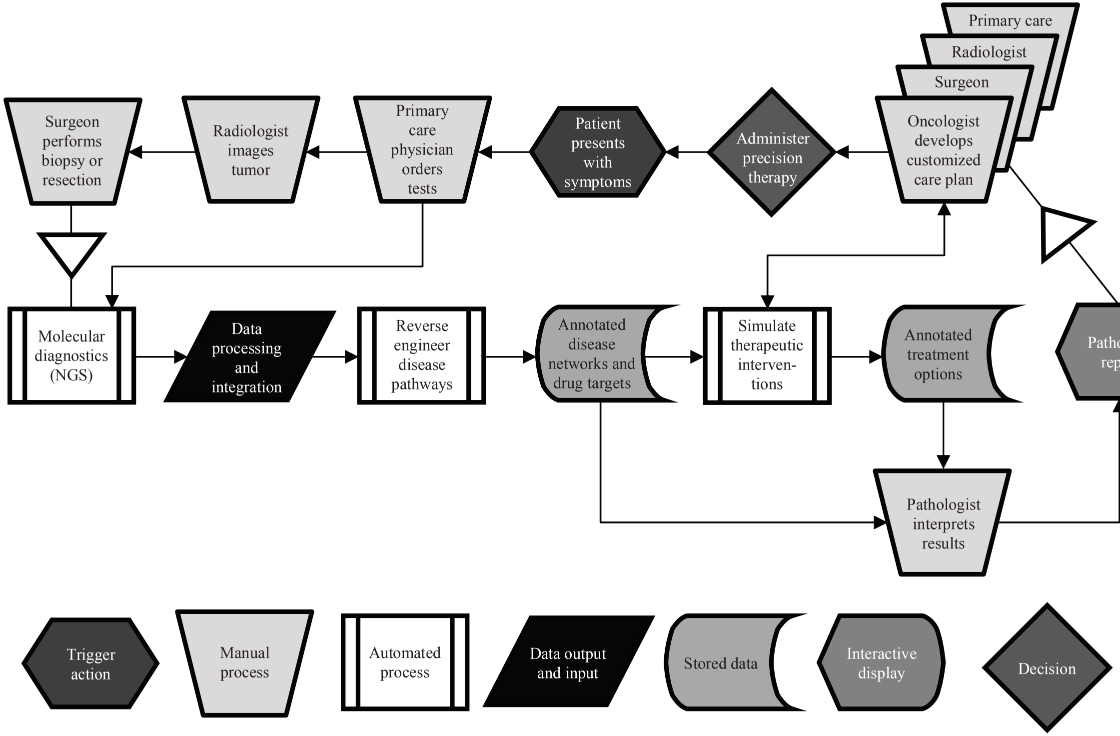

FIGURE 4-1 A model for future cancer care demonstrates how genomic sequencing and network biology will enable personalized medicine.
NOTE: NGS = next-generation sequencing.
SOURCE: Adapted from Boguski et al., 2009.

a papillary adenocarcinoma, which probably originated in a minor salivary gland. A lymph node dissection revealed that the tumor had spread beyond his tongue and was present in 3 of 21 lymph nodes in his neck. In response, he was given adjuvant radiation therapy.

Four months later he returned for a follow-up visit, and a scan revealed that the tumor had metastasized to both of his lungs. Because this was a relatively rare tumor, no standard chemotherapy was available. A pathology review indicated that the tumor was positive for epidermal growth factor receptor (EGFR), and the man was started on targeted therapy with erlotinib. However, the tumor continued to grow.

Both genome and transcriptome sequencing analyses were performed on the patient's tissue sample as a part of his clinical care. In this case the transcriptome analysis was more important than the genome analysis, as it showed an absence of EGFR expression. This finding indicated that treatment with a different chemotherapeutic agent, sunitinib, might be beneficial. After switching the patient to the new treatment, the disease progression stabilized for 4 to 6 months.

Boguski described a second case in which genomic data was used to guide therapy. A 60-year-old man with a long history of alcohol and tobacco abuse presented with difficulty breathing and heart palpitations. Physical examination of the patient revealed palpable right supraclavicular lymph nodes, and a biopsy revealed metastatic squamous cell carcinoma originating in his esophagus. Standard cytotoxic chemotherapy was initiated. The patient's tumor genome was then sequenced along with DNA from his peripheral blood cells. Following genomic analysis, cytotoxic chemotherapy was discontinued, and the patient was started on imatinib, a targeted therapy that disrupts tyrosine kinase signaling, and the tumor responded.

Cancers can continue to mutate after treatment has begun, Boguski noted, and this makes them difficult to treat. In the first case above, the patient eventually became resistant to sunitinib, and a second genomic and transcriptome analysis was done, and the drug was changed. Again the patient stabilized, and today the patient is still alive. "Had the genome analysis not been done, I doubt that would have been the outcome," Boguski said, "but this is one of those stories that . . . is quite dramatic when you see potentially what kind of cost avoidance and precision diagnosis can be achieved with genome and transcriptome analysis."

A lesson drawn from the first case study is that whole-genome analysis will consist of a variable package of genome or exome sequencing with or without transcriptome analysis, depending on the clinical indication and diagnostic goals. In the future, such analyses could also include epigenetic measurements or other data. It is still unclear, Boguski said, "whether the genome or transcriptome or some combination of both is going to be most efficacious for certain kinds of cancers."

Another conclusion drawn by Boguski's paper is that whole-genome characterization will become a routine part of cancer pathology. Furthermore, it will be done not once but multiple times during the course of the disease for tumor subtyping, monitoring response to therapy, and diagnosing the reasons for recurrence and therapeutic failures. "2020 is here," Boguski said. "This will become [the] standard of care for certain cancers sooner than we think. I am absolutely convinced of that. . . . If I had that choice as a patient, I would certainly [have my genome sequenced]."

Increased integration of genomic medicine in routine care also opens up the potential for increased disparities in health care access and services. Nicholas Schork from the Scripps Translational Science Institute suggested that disparities could well be exacerbated in the short term. But when sequencing becomes routine, he added, disparities will not be as severe. Boguski made the same point, observing that in the first part of the 20th century a major source of health care costs was hospitalization because of infectious diseases, whereas today such diseases are mostly treated with generic drugs. Similarly, a major therapy for gastric ulcers in the 1960s was removal of part of the stomach, but the realization that ulcers are caused by an infectious agent has led to the disease being managed with a 10-day course of antibiotics. "This is the history of medicine," Boguski said. "[Genomic medicine] will eventually become democratized and available to a larger portion of people."

Overcoming Obstacles

Genomics is the pathologist's new microscope, Boguski said. A torrent of data will emerge from high-technology platforms. To pathologists these technologies will largely be black boxes. The important factors will be cost, accuracy, and turnaround time.

Interpretation of whole-genome analysis could be costly, Boguski said, noting that some have talked of the $1,000 genome and a $1 million interpretation. But technologies will likely drive down the cost of interpretation. In particular, data annotation will increasingly be outsourced and automated. What is ultimately needed, Boguski said, is a clinically actionable knowledge base that any pathologist, genetic counselor, or medical geneticist can rely on to make a decision.

Workforce issues could be a more severe constraint, Boguski said. Today the United States has about 1,000 medical geneticists, 3,000 genetic counselors, and 17,000 pathologists. Many more people in these specialties will be needed in the relatively near-term future if the potential of genomic medicine is to be realized.

A paper focused on workforce issues that emerged from an October 2010 meeting (Green and Guyer, 2011) called for several "Blue Dot" pilot projects within 2 to 20 months that would establish a nationwide program for residency training by July 2012, define the concept of the "primary care pathologist" in genomic-era medicine, and establish by December 2011 a prototype "clinical-grade" disease variant database for one disease area. The other projects are to compile and analyze current genetic, newborn, and molecular pathology tests and create a whole-genome analysis "replacement map," to identify and validate operations models for whole-genome analysis, to formulate the regulatory guidelines to conduct whole-genome analysis test accreditation, and to address reimbursement issues.

Progress has been made on several of the Blue Dot projects, including the development of a program called Training Residents in Genomics, which is a collaborative project of pathology organizations, the National Society for Genetic Counselors, and the National Coalition for Health Professional Education in Genetics. The group is creating a modular transportable curriculum for training pathology residents in personalized genomic medicine that will be introduced into a third of U.S. pathology residency programs on a pilot basis by 2012.

Boguski concluded by saying that the current cost of a genome sequence has decreased significantly from the initial cost of sequencing the first human genome, which exceeded $2 billion. With the cost of genome sequencing nearing that of routine clinical tests, the implications of such a capability are going to be revolutionary, not evolutionary, Boguski said. "Next-generation sequencing and whole-genome analysis is a disruptive technology."

USING A BIOINFORMATICS MODEL FOR INTERPRETATION

Individual genomes contain about 4 million variants that are not in reference genomes, with 50,000 to perhaps 150,000 that have not been seen before, Schork said. Many of these variants influence phenotypic expression, but the question is which ones. If a variant is in an exon or an intron, it can be studied to determine if it is likely to disrupt the functioning of the gene, but this is not a useful approach for novel variants because they have not previously been examined by a functional assay. Instead, determining the likely functional effect of those variants requires bioinformatics.

One bioinformatics approach to determining the functionality of a variant relies on evolutionary conservation. If a nucleotide or nucleotide sequence is conserved across species, a variant in that sequence or at that position in humans is likely to be functional because otherwise it would have been seen in other species. Analogous strategies for identifying functionally important sites can also be used for determining variants that disrupt regulatory elements in exons, introns, silencers, and promoters (Torkamani and Schork, 2008). But there are problems with just using sequence conservation for determining the functional effects of variants, Schork observed, as a recent analysis showed that structural information about a protein is more effective than conservation information for determining which variants are functional (Torkamani et al., 2008).

A recent paper described a program called Variant Annotation, Analysis, and Search Tool, which uses bioinformatic techniques to identify variants that are likely to be correlated with idiopathic conditions (Rope et al., 2011). The program compares a patient's genome with reference genomes to rule out variants seen in other individuals who do not have the disease. Any novel variants that are identified in functional elements are then considered as potential causative candidates for the idiopathic condition. Annotations and predicted functional effects then can help prioritize variants.

Schork and his colleagues have applied this approach to every variant in public domain databases, including those from the 1000 Genomes Project, dbSNP, and the Online Mendelian Inheritance in Man variants. Many novel variants in each individual's genome were predicted to be functional. Not all of these variants cause disease, however, even where the coding variants that affect the proteins are predicted to be damaging, which makes interpretation difficult.

Commenting about using these types of bioinformatics tools, Schork said that students need to become more computer savvy. Even among students at the Scripps Translational Science Institute, he said, many could improve their knowledge about how to conduct basic BLAST searches or annotate variants against dbSNP. Exposure to such tools is absolutely critical, even if they are not used on a day-to-day basis. Furthermore, exposure to concepts in systems biology is important to build understanding of how genes work in concert rather than separately.

Genomic Diversity

In a clinical context it will be essential to take into account the genomic diversity of the human population, Schork said. This will be important, for example, in comparing individuals with a disease from one part of the world with individuals without the disease from another part of the world. Some variants would appear to be more frequent in the diseased individuals than in the non-diseased individuals, but these would reflect false-positive results because of population stratification. Similarly, if a reference panel from one population were to be used to draw inferences about the novelty of variants from a patient from a different population, the resulting conclusions could be highly misleading (Bustamante et al., 2011).

Human genetic diversity is greater in Africa than elsewhere in the world because only a subset of the variation present in Africa made its way through the Middle East into Asia, Europe, and the Americas as modern humans migrated out of Africa. As a result of this bottleneck, particular genomic positions might have greater homozygosity in European populations than in African populations (Lohmueller et al., 2008). Using the bioinformatics tools described earlier, Schork's group found more functional variation in African genomes than in European, Asian, or Native American genomes because of the increased diversity in Africa. Similarly, African genomes have more novel functional variants. However, the standard human "reference" genome is made up largely of contemporary European DNA, which presents a misleading view of global variation in the genome. Reference panels need to be larger, Schork said, in order to determine what is novel and what is not.

Considering the Complexity of the Diploid Genome

The DNA sequencing community often ignores the fact that humans are diploid. Yet variants that differ between the maternally and paternally derived chromosomes can have a critical effect on health (Tewhey et al., 2011). If the maternally derived homolog can compensate for mutations in a paternally derived chromosome, for example, gene function can be normal. If it cannot, the result is haploinsufficiency. Similarly, the presence of different mutations or polymorphisms within the same gene but on separate alleles, such as in the coding region of the maternal homolog and in the regulatory region of the paternal homolog, can yield a phenotype unique to a diploid organism called compound heterozygosity. "Merely knowing that this individual was heterozygous at these two sites wouldn't be enough," Schork said. "You would have to know that one damaging variant [which impairs protein function] was on the paternal homolog and [a separate function-impairing] variant was on the maternal homolog." Copy number variations and other insertions and deletions also can have different effects depending on parental origins.

In order to identify maternally and paternally derived homologs, it is necessary to sequence families to determine which variant was inherited from whom, or the assembly of DNA sequences can be used to recover the two chromosomes that an individual inherited. Collecting phase information, however, is not a simple matter, especially with new sequencing technologies, since the short stretches of DNA that they generate make assembly of different genomes difficult.

Another way to generate phase information is to use chemical or molecular tweezers to pull apart chromosomes during metaphase and sequence them separately (Bansal et al., 2011). This approach probably could not be routinely adopted in clinics, Schork said, but other approaches may be able to distinguish between maternally and paternally derived homologs and deal with issues like compound heterozygosity.

Risk Predictions and Perceptions

Schork concluded his remarks by talking about the utility of genomic information compared with other measures that clinicians use. For example, to predict diabetes, an individual could be typed at all known diabetes susceptibility loci, or else a family history, body mass index, glucose and insulin responses, and other indicators could be collected. Comparisons of these two approaches reveal that genetic information does not provide a benefit over clinical information, Schork said (Lyssenko et al., 2008). However, genotyping did prove to be better at making long-term predictions, as compared with the clinical predictors, which were better at predicting who would become diabetic within 1 or 2 years. Thus, if long-term predictions were of interest, “there might be utility in using genetic information over and above clinical information,” Schork said.

Schork has been involved in an investigation to study the behavior of 3,000 individuals who received genetic information after undergoing consumer-oriented genome-wide testing (Bloss et al., 2011). The study found that such testing did not result in any measurable short-term changes in physiological health (e.g., anxiety), diet or exercise behavior, or the use of screening tests. Furthermore, other studies have shown that people respond best when they are involved in social networks or have some other kind of support to change their behaviors.

ENVISIONING CLINICAL GENOMICS IN 2020

Each of the three speakers commented on how genomic data will be interpreted in the year 2020 if research and development continue to progress on their current trajectory. Interpretation will focus on patterns in a genome that point to biological pathways subject to perturbation rather than on single mutations that might explain a particular disease, Schork predicted. It will be necessary to integrate information from many parts of the genome using a greater understanding of systems biology in order to derive actionable conclusions, he said.

Boguski emphasized the role of empowered patients and participatory medicine in making actionable conclusions. When a patient comes into an emergency room with a stroke, the emergency room personnel will probably not ask the patient for the password to a commercial genome testing website to check on warfarin sensitivity, but they may check a patient’s status on an online site where such information is routinely posted. “In some cases it is going to be easier to get medical information out of a person’s Facebook profile than legacy EMR systems,” Boguski said. For example, the Association of Cancer Online Resources has about 18,000 cancer patients who share information on diagnoses and therapeutic interventions. "If the medical profession is not going to be capable of doing this, it will be crowd sourced. That is my prediction for 2020."

Nussbaum predicted that instead of a single solution there will be multiple solutions based on partnerships. Patient empowerment is important, he said, "but at the same time I firmly believe that this has to be embedded in traditional medical care in some way." Research into genomic interpretation is now progressing on a broad front, but clinical and family information still will be needed to understand the effects of genetic variants. Furthermore, this information needs to be in the public domain so that people can use it.

How Clinical Trials Will Be Affected by Genomics

Each participant in this section also commented on how the realization of genomic medicine will change the role of clinical trials. Nussbaum suggested that the era of randomized controlled trials is fading. Cohort sizes are too small for such trials, because every cancer patient has a unique set of genetic variants, making large-scale trials impractical. Instead, clinical trial designs will need to be adaptive and engage patients during Phase IV[1] of the clinical trial. "Once a drug is out there, we have to be collecting information from [patients] about efficacy and side effects." Furthermore, genomic information will need to be re-interpreted throughout a patient's life. Physicians will gather clinical information and write an order for updated interpretation of the genome based on the validated information that has accrued since the patient's last encounter with the health care system.

Boguski added that clinical trials may still exist, but they will not be organized by drug companies. Instead, they will be organized by other organizations once a new drug becomes available. Patients will be much more active in contributing observations to organizations that collect and act on their data. "We have to expand our notion of what a clinical trial is, and I think it is going to involve post-marketing surveillance and so-called Phase IV use of those drugs."

Schork emphasized that trials for individual patients can be done as a part of the standard of care. "If you can show that treating each patient based on the genomic profile is the way to go rather than standard care, then despite the fact that you are treating each patient individually, you vetted the whole concept." This becomes more complicated with rare diseases, however, as a surrogate endpoint is needed to measure the efficacy of treatments.

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[1] During Phase I clinical trials, researchers evaluate the safety of a drug or treatment, establish a dosage range, and identify side effects. In Phase II, efficacy of the drug or treatment is evaluated. In Phase III, drug or treatment effectiveness is confirmed, side effects are further observed, comparisons to current treatments are performed, and safe-use information is obtained. In Phase IV, post-marketing studies are performed to gather additional evidence of benefits and risks of a drug or treatment.

5

The Delivery of Genomic Data

Important Points Highlighted by Individual Speakers

- Pharmacogenetic results can be important for patient care, but data need to be carefully integrated into patient records and care processes.
- If patients are empowered to make their privacy preferences available to caregivers and researchers, the delivery of care and the use of patient data for research could both be enhanced.

Genomic data are of no value unless they can be communicated in an effective way to people who can act on that information. Understanding what the message needs to be is only part of the challenge, said Greg Feero of the National Human Genome Research Institute, who moderated the workshop session on communicating genomic data. The actual delivery of that information to both the health care professional and the consumer is essential to improving outcomes. Will such information be delivered at the point of care or in some other setting? What infrastructure is needed to deliver genomic information? Who has the responsibility for delivering the information and ensuring that it is understood?

IMPLEMENTING PHARMACOGENETICS IN CLINICAL PRACTICE

St. Jude Children's Research Hospital, in association with the Pharmacogenomics of Anticancer Agents Research 4Kids program under the Pharmacogenomics Research Network (PGRN) at the NIH, has been using well-known genetic polymorphisms to adjust drug therapy in patients in real time. St. Jude has the advantage of being able to overcome (or ignore) many obstacles to preemptive genotyping, said Mary Relling of St. Jude. The hospital covers all patient care costs and provides all medications for 5,000 unique, high-risk patients per year, 80 percent of whom have cancer and 20 percent of whom have sickle cell disease, HIV infection, or other life-threatening diseases. St. Jude has a collaborative approach to patient care, in which pharmacists are integrated into the team that delivers care and are responsible for signing off on every consult associated with a pharmacogenetic test result. St. Jude also maintains comprehensive EMRs that fully integrate every aspect of outpatient and inpatient care, which Relling said was a large motivating factor for St. Jude to incorporate genetic testing into the patient record.

For pharmacogenomic testing, St. Jude is now using the Affymetrix DMET-plus array, which tests for more than 1,900 polymorphisms in 225 genes that are likely to be important for pharmacogenetics. Previously it had been screening for only two of the genes included on that panel and doing so at a higher cost. The medical staff would rather not have the medical record populated with genomic information of uncertain clinical utility, Relling said. As a result, the hospital obtains consent from patients to withhold results that are not clinically interpretable, though it also discusses with patients the possibility that these findings may in the future have implications for disease risk.

A new program known as PG4KDS has the goal of migrating a larger number of pharmacogenetic tests from the laboratory into routine patient care so that results are available for preemptive use. The primary program objective is to estimate the proportion of patients who have high-risk or actionable pharmacogenetic results entered in their EMR with decision support (automated information alerts generated to assist health care providers in making decisions about a patient's care). The secondary objectives are to use systematic procedures for prioritizing and migrating pharmacogenomic test results to the EMR, to incorporate clinical decision-support tools linking test results to medication use, and to assess the attitudes and concerns of research participants and clinicians.

An educational video made with the hospital's Family Advisory Council is available to provide information for families. Information is also available on the program's website (www.stjude.org/pg4kds) which lists which genes are tested for and which genes are reportable, along with links to more detailed information for clinicians.

After patients are enrolled, their DNA is genotyped, and the results that pass quality control thresholds are posted in the research database. Only the small portion that meets the clinical threshold is migrated to the EMR. A limited number of the clinical results that are based on high-risk genotypes and high-risk drugs have decision-support rules that send automatic alerts to clinicians. The study investigators, with the input of an oversight committee, decide how to update the information that is entered into the chart, including the addition of new clinically actionable variants and which results are designated to receive decision support, starting with widely accepted results for high-risk genotypes. "We won't tackle the most controversial ones until later, or maybe never. We do a big disservice to implementing clinical genomics by trying to implement stuff too fast. We should concentrate on the home runs first," Relling said.

When it is decided to put a new gene into the EMR, the results for that gene are inserted into the medical record for all past and future patients, with participants having the choice of getting a letter for each new gene that is posted. "So far every single patient has asked for that information," Relling said, "and of course that could be converted to something electronic in the future."

To facilitate access to information, the EMR at St. Jude Children's Research Hospital has been customized with a pharmacogenetics tab, where genotypes are entered along with a detailed laboratory report of how the test was performed and clinically relevant gene-specific information explained. These are lifetime results, Relling said, and physicians should not have to search for them by date or order a test on a gene that has already been interrogated.

When the decision to prescribe a high-risk drug conflicts with the presence of a high-risk or high-priority genotype, a decision-support alert is sent to the clinician. For example, the EMR will automatically generate a warning if codeine is prescribed for the 10 percent of patients who are poor metabolizers based on their CYP2D6 profile. There are two types of warnings. The first is a post-pharmacogenetic test result: If the patient already has a high-risk genotype in the EMR, the clinician will get an alert. The second is a pre-genetic test warning: If thiopurine is ordered for a patient and the patient has not had thiopurine S-methyltransferase (TPMT) tested, an alert is issued. Alerts are also being linked to an explanation of why a high-risk drug–gene pair exists for use by clinicians who are interested in learning more.

Challenges in Implementation

Implementing this system has revealed several challenges that future genomic medicine initiatives will likely face, Relling said. First, she said, there is a lack of consensus or guidelines on which drug–gene diplotypes are most important, although she acknowledged that "it is better to have experts review the evidence and come up with some recommendations" even if they are not in agreement than to make each individual clinician have to synthesize his or her entire knowledge and medical practice experience. The PG4KDS program is addressing this issue through the PGRN. Specifically, a subgroup called the Clinical Pharmacogenetics Implementation Consortium has been formed to evaluate drug–gene pairs using standard grading systems, the peer-reviewed literature, and other information. Severity of disease, therapeutic alternatives, consequences of giving the wrong drug, and consequence of giving the right dose all have to be taken into account when making these decisions.

Another complication is that once a gene test is in the EMR, clinicians are obligated to use those results for all drugs affected by the test. Even rarely prescribed drugs need decision support. "It is going to take a lot of work to go through and make rules that we are all comfortable with," Relling said.

Diplotypes are sometimes ambiguous because of the nature of the testing. For example, the DMET array often produces ambiguous calls, Relling said. "We have to look very carefully at the reasons for those ambiguous diplotype assignments. Is it the fact that you can't phase haplotypes, so we can't always distinguish between a heterozygous- and a homozygous-deficient patient? Or is it because of a simple no call of a probe for a rarely involved SNP? Someone has to decide whether those [ambiguous assignments are actually important] or not, and again that takes a high level of knowledge of the genes and the drugs."

Using a software program called PHASE, a much higher percentage of diplotype assignments can be made non-ambiguous, but it is a judgment call as to whether to deliver that information to the clinician. Interpretation is complex and time consuming, and it changes over time, Relling observed. For example, even with the relatively simple TPMT diplotypes, about 8 percent of patients have an ambiguous diplotype. Some patients are homozygous deficient, and if they get a normal dose of thiopurine, there is a high probability they will die of toxicity, whereas other patients can tolerate doses for a much longer time period. "Basically, we have to write very specific [reports] to say what the caveat is in interpreting these kinds of results."

Multiple testing of the same gene over the lifetime of the patient requires that someone check to see whether the results contain discrepancies. One must also check other details such as whether the race of a patient in the EMR agrees with the patient's self-declared race or whether the sex in the EMR agrees with the self-declared sex. "Flagging some of those genotypes and eventually manually approving them to move from the research laboratory into the EMR takes a lot of steps," Relling said.

Another critical issue is who will pay for preemptive genotyping. Array-based genotyping can be cheaper, easier, and more effective than testing one gene at a time even when no drug is being contemplated for treatment, but it may not be easy to get reimbursement for such tests. Finally, Relling said, until patients have universal lifetime EMRs, the fragmentation that affects all of health care is going to affect genomic medicine.

GRANTING ACCESS TO PERSONAL HEALTH INFORMATION

"Remember when using an ATM was a mysterious and improbable experience?" asked Robert Shelton of Private Access, Inc. "That's about where health care data sharing is today."

The first automated teller machines (ATMs) were introduced in 1967, but their use was limited until networks of ATMs enabled people to withdraw money from almost any machine. Over time ATMs also developed a compelling business justification because they saved money spent on human tellers and generated revenue from ATM fees. Today there are 2.2 million ATMs around the world, with a new one being added every 4 minutes.

Using a search engine also used to be a mysterious and improbable experience, Shelton observed. In 1990 a search engine called Archie offered access to a directory of directories. In July 2008 Google announced that it had indexed 1 trillion pages and was adding several billion new pages per day. As with ATMs, several intermediate technologies and changes made this massive growth possible, including natural language search of contents, analytics-assisted search that helped a user find the desired Web page despite the terms entered, and compelling business models.

"What if people could search for health information as easily as we do public documents?" Shelton asked. In that case physicians or patients could call up any information contained in an EMR as easily as they access information on the Web. But privacy needs to be protected. Thus, access provisions need to be interposed between a search query and a result to determine whether the searcher has the right to see the results of the search.

The tipping point for integrating privacy protections is occurring now, Shelton said. In December 2010, the President's Council of Advisors on Science and Technology released a report that called for a "universal exchange language for health care information that enables health IT [information technology] data to be shared across institutions, along with network infrastructure that enables a patient's data to be located and accessed across institutional boundaries subject to strong, persistent, privacy preferences" (PCAST, 2010). Even before the release of the report, the company Shelton directs had built and tested such a system. The centerpiece of the system is that patients log onto a secure website and set their own privacy preferences, after which researchers can search for information. For example, Shelton said, if a researcher is looking for subjects for a clinical trial, patients "need to have their hand raised for interest in clinical trials already."

Private Access does not actually hold patient data. Instead it holds the patient index and search capability, with the privacy directives acting as the switch for searches. For example, if a researcher logs in and searches for potentially relevant subjects through the search index, the system filters the results based on patients' preferences. If a patient has indicated interest in being part of a trial, the researcher gets contact information and can make an offer.

The system has been tested in patient populations, and the lessons learned have been applied in successive generations of the system. First, patients need to be educated and empowered, not coerced. Consumers are more likely to engage in an environment of trust if they are referred by a trusted intermediary, a friend, a health care provider, or peers, Shelton said. Patients should control the use of their personal information for expressed purposes, they need guide-based assistance to help make informed choices, and the consent tools should be dynamic and granular. To make sure that patients have the information needed to set preferences, links should be available to more detailed educational sites.

On the searcher's side, the system needs to be fast, easy to use, and powerful. It should use familiar Web-based search conventions such as bookmarks and automated alerts. And, Shelton said, researchers should be able to receive pre-authorized access to personal health data.

Implementation

When using such a system, a patient who is undergoing the registration process at a hospital would also convey privacy preferences to the hospital, perhaps through a smartphone application. The patient would be asked if information could be deposited in a personal health record (PHR), whether or not the patient has established one previously. If the patient agrees, information from the hospital would be moved beyond the hospital's firewall to a PHR where it could be searched through a search index.

Other data, such as pharmacy histories, laboratory results, or the results of genetic tests, can also be moved into the PHR. Data can also be moved into other repositories, such as EMRs or searchable databases in each institution visited.

Patients have heterogeneous preferences, Shelton said. Attitudes range from "It is okay for researchers to use my data without my consent at all" to "I am willing to give general consent in advance for the use of my data without being consented" to "Consent is not needed if my identity will never be revealed and the study is supervised by an IRB [institutional review board]" to "I want each study seeking to use my data to contact me in advance and get my specific consent each time" to "I would not want researchers to contact me or use my data under any circumstances." Most patients fall in the middle of this distribution of preferences, but it used to be logistically impossible to satisfy their wishes. New technologies have now made it possible, Shelton said. Furthermore, he added, "It is empowering, and it creates the data liquidity that we all are looking for."

In one example cited by Shelton, a researcher at the University of California, Los Angeles, looking for lupus patients found six within 25 miles of campus in under a minute. "Why? Because he was using a search engine to find them."

Many resources are currently flowing to the basic science of genomic medicine, Shelton said, but resources also need to be expended on sociological research directed at how the science will be applied. This research in turn could inform the business models that will drive adoption.

The patient is the key, Shelton concluded. "We have to give them the tools, and we have to give them the chance."

ADVANCING THE UTILIZATION OF GENOMIC INFORMATION

Increasing the use of genomic information by providers and consumers will be a slow process. Many people may be able to understand genetic data if they are provided with information, Relling said, but people who are old or poor or who can barely read will have much more difficulty. "There are a lot of people in this country who need us to be a little paternalistic," she said. If highly trained physicians sometimes cannot understand the information linking genetic variation with clinical recommendations, creating such understanding among others may not be feasible in the short term. "We have to crawl before we walk," she said. "We have to get this to work in health care institutions where we have highly trained people and get it understood and adopted, and then we can maybe start pushing it out more to consumers."

Shelton added that he did not expect consumers to have the ability to understand the data that they are receiving. "What I am advocating is that a consumer knows that I don't want Aunt Betty to see my data. 'If you tell me that Aunt Betty can't see it, then I am fine with anybody else who is a researcher seeing it.' Consumers understand their privacy wishes. That is one thing they do understand and the law doesn't." Patients should be empowered to sign up for a personal genome project if they wish, just as they should be empowered to forbid the use of any of their genetic data. "We don't use sushi-grade data in the medical establishment. We use chum. It is deidentified and it is all ground up because we have to in order to come under the IRB requirements and in order to avoid a lot of the challenges of asking for permission. If we ask for permission, empower it, and make it easy, it will happen."

BUILDING A BUSINESS CASE FOR GENETIC TESTING

Given the limited associations between genetic test results and most diseases, Shelton suggested that the business case for using health IT systems that incorporate genetic results rests on two motivations. The first is recruiting subjects for clinical trials. The second is the reduction of duplicate tests. In the future an advertising model may evolve as well, he added, as patients become willing to have their medical information used to make them aware of offers that are custom tailored to them.

More generally, he said, the most important piece of health care in the future will be data, which will make the IT department the profit center of health organizations. "The IT department in health care gets a very small fraction of what IT departments get in other industries," he said. "The reason is because it is a cost center. It is not a profit center. Make it into a profit center, and budgets will go up."

6

Ethical and Legal Issues

Important Points Highlighted by the Speaker

- Sequencing devices, interpretation software packages, and testing laboratories will all need to meet stricter proficiency standards as genomic medicine progresses.
- Patients' genomic information should always be obtained within the confines of a doctor–patient relationship.
- Health care providers have a responsibility to provide patients with clinically significant genomic information but not necessarily other less clearly actionable information.
- Patients' concerns about confidentiality cannot be completely resolved with technological approaches.

The ethical and legal issues associated with integrating large-scale genomic information into clinical practice differ somewhat depending on the developmental stage of the technology, said Henry Greely of Stanford University. In the initial stage the technology has been used largely by researchers and by early adopters who are curious about genetic testing, with some overlap between the two groups in the case of research subjects interested in genetic findings. In a second stage, which is now under way, clinicians have been using genetic tests as a tool to discover the causes of otherwise mysterious ailments.

In a third stage, which Greely predicted will start once the price of whole-genome sequencing nears $1,000, sequencing a person's entire genome will be nearly as inexpensive as a single genetic test, in which case insurance companies may prefer to pay for a whole-genome analysis rather than for multiple genetic tests. Finally, when the price drops below $1,000, whole-genome sequencing will be routine. "Everyone who has decent health coverage . . . will be fully sequenced," Greely said, and that information will be stored. "Within the next 10 to 20 years that is probably where we are headed," he added, and the ethical issues will differ slightly depending on the stage.

REGULATORY ISSUES

Greely described three major regulatory issues that will be important as the technology progresses through these three developmental stages. First, he said, sequencing machines will need to become Class III medical devices. They will need to be regulated by the FDA and will require proof of safety and efficacy. Before the instruments can be used for clinical purposes, their developers will need to demonstrate their sensitivity and their specificity, and the machines will need to be assessed for their ability to phase chromosomes and sequence areas of high GC content.

Second, the laboratories that do the sequencing will need to meet stricter proficiency standards. These facilities will need to be certified under CLIA and should additionally be certified by CAP. The CLIA certification process will need to establish clear proficiency standards before the sequencing of patient genomes is allowed for clinical purposes. Laboratories will need to demonstrate the kinds of quality control systems they have in place, the kinds of procedures they have for repeating unclear or unexpected results, and how they will make sure that important positive results are not false-positives. Meeting these standards will require "effective regulatory attention to clinical laboratories," Greely said.

The most difficult regulatory issues will involve the interpretation of genomic data. When whole-genome analysis is used in the clinic, interpretation will need to be largely automated because, Greely said, "with 6.8 billion base pairs in a diploid genome, you are not going to get a human brain looking at all of those." Software packages will sort findings into different categories for action, and where information belongs will depend partly on the medical needs and characteristics of the patient. These software packages will presumably allow for sequence validation and updates, Greely said, and as such will be considered medical devices that should also be regulated by the FDA for safety and efficacy.

ETHICAL ISSUES: THE DOCTOR–PATIENT RELATIONSHIP

Greely discussed four ethical issues, all of which revolve around the doctor–patient relationship. First, genomic information should be disseminated to a patient within the confines of medical care. Already many companies offer results directly to consumers, and many consumers argue for their right to access such information outside of a medical relationship. Greely argued, however, that as is the case with a patient obtaining a tissue biopsy or imaging scan, sequencing data should not be acquirable without the assistance of a physician. Many health care providers may know relatively little about genetics, Greely said, but "they know something about tests and they know something about patients." They can listen to patients, tell them when they do not need to take a result too seriously, and determine when a patient is confused or worried about something. They have skills and information that an e-mail from a direct-to-consumer company will not provide. Health information is "powerful and important and likely to be misinterpreted by people to their own harm," Greely said.

The second aspect of the doctor–patient relationship involves which information a doctor needs to provide to a patient. The answer is fairly straightforward, Greely said. Under normal circumstances, the health professional should provide the patient with any information that is clinically important but not necessarily with information that is not clinically significant. For example, a patient might have a whole-genome sequence to test for BRCA1 or BRCA2 mutations with negative results. However, if the test revealed mutations related to Lynch syndrome, which confers a very high probability of getting colorectal cancer during a lifetime, a physician should have to reveal this information to a patient. "You are in a clinical relationship with the physician," Greely said. "If the physician orders an X-ray on you because he is worried about your liver and sees a big growth on your kidney, he is not going to say your liver is fine and not mention anything about the kidney." Genomic information can be just as clinically significant as information from a medical imaging test, and physicians are responsible for the information that genetic testing reveals. On the other hand, physicians do not need to tell patients about things that are not clinically significant, Greely said, although he admitted that this is a difficult phrase to define clearly. Still, health care providers do not need to convey information about variants of unknown significance that might cause undue anxiety.

The third issue—consent—also involves the information that doctors need to convey to their patients. Physicians need to let patients know that they will tell them about clinically significant results from genomic testing, and they need to explain that they will not tell patients about results that are not clinically significant unless specifically requested. Physicians should ask their patients if they want to know more, in which case access to additional information can be provided. "Having them consent to the fact that you are not going to tell them about absolutely everything that is in those 6.8 billion base pairs is, I think, both ethically a good idea and maybe legally a good idea," Greely said. "The goal of the medical profession shouldn't be to eliminate possibilities that it will get sued but to do a good job in taking care of its patients, which in turn will limit the number of times it loses lawsuits."

The fourth category is the most challenging, Greely said: How can health care providers tell patients about all of the genetic results that are clinically significant? Based on early experiences with whole-genome analysis, an average patient might have roughly 100 clinically significant genetic variants, with 5 to 10 things that are quite important and 90 to 100 that deserve mention. Even if a genetic counselor spent just 3 minutes talking about each thing, discussing 100 results would require 5 hours. "Who is going to give that counseling? Who is going to listen to that counseling? And most important, who is going to pay for that counseling? We are going to have a real challenge trying to educate patients about what this means."

Research projects are needed to look at how best to convey information to patients about their genetics, Greely said. The solution will probably involve presentations using various media combined with some face-to-face discussions, especially for the most important results. "You don't want them just reading it on the Web," he said. And doctors should be careful that patients understand the implications of the information, he said: "'Yes, your BRCA1 and BRCA2 genes are normal, but no, that doesn't mean you should stop getting mammograms,' which is the kind of mistake I am afraid patients will likely make that could be fatal."

PRIVACY ISSUES

Greely also discussed five privacy-related issues. First, where should information be stored? Options mentioned at the workshop include re-sequencing as needed, giving it to the patient, inserting it into the EMR, or putting it in the cloud. "My own sense right now is the right answer is, yes, all of the above," Greely said. On one end of the spectrum, the information is always available for re-sequencing since it cannot be removed from the nucleus. On the other end, if a patient changes doctors or health plans, as most Americans do, having the information in the cloud will enable the information to be retrieved by a new health care system.

Second, a germline sequence will not change over time, but interpretations will change continually as research progresses and as a patient goes through life. Standards will be needed for how often data need to be requeried with software interpretation tools and how to pass new information on to doctors, said Greely.

The third category involves children. Today, children are generally not tested for health conditions that are not important during their minority. But if all children are tested neonatally, how will those data be treated? Should the data be stored in a lockbox and given to them when they are 18? Should the data be given to their parents or pediatricians? "I don't know the answer to this one," Greely said. "It is a tricky one, but it is one where we are going to have to come up with an answer."

Fourth, the huge amount of genomic information that will soon be stored in EMRs and in the cloud could be enormously valuable for the understanding of disease. How much pressure should society exert on individuals to encourage them to let those data be used for research? Perhaps we should consider that patients could be compensated in some manner when they allow their information to be used for research purposes. This is another issue that will be difficult to resolve, Greely said.

Finally, technological approaches cannot completely resolve confidentiality problems. "The good news of genetic data is it will be protected as much as other health data," Greely said. "The bad news is it will be protected as much as other health data." There will always be some security risk involved with storing the data since it, like any other data, can be compromised illegally or through poor oversight by the user, such as losing a password or a laptop. Even if data are anonymized, people can be re-identified if phenotype and genotype data are combined. "Confidentiality cannot be guaranteed, and we need to be honest with people about that," Greely said. "We need to tell them there is some privacy risk."

OTHER ISSUES

Greely concluded by briefly mentioning several other issues that will loom large in an era of genomic medicine. Parents will more easily be able to make decisions about the genetic traits of their children. The information will be available for governments to construct universal forensic databases. People will make invalid and discriminatory connections between genetic data and personal or group attributes.

As the cost of sequencing continues to plummet, genome sequencing will become ubiquitous, Greely said. "We can manage the transition in ways that make it less painful, or we can manage it or fail to manage it in ways that make it more painful," he said. "I applaud the Institute [of Medicine] for this workshop, because it is really important for us to try to figure out how to use this in ways that maximize its benefits and try to minimize its harms."

7

Workforce Development

Important Points Highlighted by the Speaker

- Education and training should focus on competencies more than on knowledge. For a non-specialist health care provider, these competencies may include recognizing when a genomic diagnostic test is needed or how pharmacogenomic testing can guide decisions about therapy.
- Genetics and genomics should be integrated into health professional education from undergraduate study through to maintenance of certification.
- Collaborative efforts among health professionals will be essential in implementing genomic medicine.

The preparation of the health care workforce to deal with genomic information will be vital, and the precise details of that development will depend on how the genomic information will be used, said Bruce Korf of the University of Alabama at Birmingham. This use in turn will hinge on two questions: What can be learned from whole-genome sequencing that will contribute to medical care? How will this information be incorporated into the workflow of the clinician?

KNOWLEDGE, SKILL SETS, AND TRAINING OPPORTUNITIES

What are the necessary knowledge and skill sets required for analyzing, interpreting, and using genomic information? The first principle Korf posited was that education and training should focus on competencies, not knowledge. The important issue should be what clinicians are able to do, not necessarily what they know.

Much of the accumulated knowledge concerning health care will be embedded into point-of-care decision-analysis tools associated with electronic medical records, Korf said. When pharmacogenetic testing is routine, clinicians will not order pharmacogenetic tests and wait for the results to decide on a drug and dosage. Instead, some sort of electronic prescribing system will search a database, find a patient's pharmacogenetic results, and recommend the proper drug and dosage to use. Clinicians will still need to know about pharmacogenetics, but the skills they will need will be different. For example, they might need to explain to a patient why he or she is taking a drug and dosage that differ from what someone else is taking.

Given this background, the kinds of competencies that a non-specialist health provider might be expected to have will include the ability to explain the concept of carrier status and to provide a referral to a genetic counselor for additional information. He or she would also need to recognize and order tests when there are indications that the diagnosis would benefit from the use of genomic sequencing and be able to use pharmacogenetic data for guiding therapies. Other necessary competencies will include using sequencing data to formulate an individualized disease management plan and improving differential diagnoses.

Laboratory geneticists would need a somewhat different set of competencies, Korf said. These will include proficiency in the use of bioinformatics tools and databases to interpret whole-genome sequencing results and the ability to annotate genomic data in the context of phenotypic information. The laboratory scientist would also need to provide clinicians with tools and genomic data interpretation that would guide clinical decision making. These lists, Korf said, provide a starting point for thinking about the competencies that different health care providers should have.

Health care competencies for genomic medicine will need to extend from pre-health professionals to the health professions. Undergraduates will need to be attracted to the field and be better prepared for their chosen health care careers by learning about subjects that they will need in the future, said Korf. In addition, genetics and genomics should be integrated into health professional education, residencies, and maintenance of certification, Korf said.

Korf described a recent effort organized by the Howard Hughes Medical Institute and the American Association of Medical Colleges in 2009 to develop descriptions of competencies for medical education. The competency for genetics was: "Use the principles of genetic transformation, molecular biology of the human genome, and population genetics to infer and calculate risk of disease, to institute an action plan to mitigate this risk, to obtain and interpret family history and ancestry data, to order genetic tests, to guide therapeutic decision making, and to assess patient risk." Even this competency, Korf noted, has become somewhat outdated over the course of several years because of rapid advances in genomics, but it makes the point that competencies and learning objectives can be defined.

Korf also described the Summer Genetics Scholars Program, which is sponsored by the American College of Medical Genetics Foundation and is designed to attract more students into the discipline. "Students . . . have a huge interest in this area, and it has not been difficult to motivate medical students to be thinking about genetics whether as a primary career or as a critical [area] that will integrate into their careers."

The University of Alabama at Birmingham has been pursuing a personalized health care competencies project, which is divided into the areas of genomics, pharmacogenetics, informatics, and culture and the environment. Competencies have been defined for undergraduates with the goals of helping them make better health care decisions and attracting some of them into health care careers. These same competencies can be re-purposed for other audiences, such as business, law, or engineering students. For example, a business student could learn how to make the case for using genomic data in a medical practice.

A GENERATION OF EFFORT

At the University of Alabama at Birmingham, Korf's department runs a laboratory that performs diagnostic testing for neurofibromatosis type 1. Even after testing more than 5,000 people over the course of 8 years, the laboratory frequently identifies previously unseen mutations. The clinical impact of many of these mutations is uncertain and would require a considerable amount of investigation to determine. Yet this is just one gene. "We are going to need a lot more work before we can define phenotypes just by looking at genotypes," Korf said. It will take "a generation of effort" to understand the many nuances written into the human genome.

Collaborative partnerships will be essential, Korf said, but many of these will not be straightforward. For example, questions of referral can be complex and difficult. Pediatricians, for example, will soon be learning of conditions diagnosed in newborns that they have never heard of before. They will need point-of-care decision support, which eventually will need to be fully integrated into electronic records.

Korf argued that the model of one health professional sitting in a room talking with a patient about one gene will be disrupted by advances in sequencing technologies. Though consumer-driven genetic testing is not very powerful now, it could become a disruptive technology (Christensen, 1997). As the data improve, such testing could become much more mainstream. "I don't know that consumer genomics is the answer," Korf said, "but I think there has to be an answer that is going to make it possible to provide the information, and it is going to have to be more than just looking something up on a website."

Creative thinking will be essential as health care is transformed by technology. As computer scientist Alan Kay once said, the best way to predict the future is to invent it. Whether the future is evolutionary or revolutionary, Korf said, "this is . . . the opportunity that we all have before us right now."

8

Envisioning the Future

MAINTAINING CURATED DATABASES

Establishing a curated genomic-variant database is essential for bringing genomic medicine to fruition, a number of speakers said. However, many existing databases contain frequent errors, conventions are often different across databases, and funding for databases can be difficult to acquire. Madhuri Hegde of Emory University said that one approach would be to encourage individual laboratories to take responsibility for curating the data on particular genes. In that case, laboratories could develop and apply expertise to curation rather than simply dumping data into databases. However, such laboratories will need to have lines of communication with other laboratories and groups developing databases in order to convey information about important variants. They will also need funding, said Hegde, to carry out the responsibilities of curating and communicating the data.

Mark Boguski of Harvard Medical School countered that individual grant-supported databases do not constitute a sustainable business model and will not be able to achieve the kind of long-term quality and oversight needed for clinical applications. Henry Greely of Stanford University agreed and asked if, instead, a non-profit organization could examine genetic information, publicly disseminate a proposed interpretation, and then welcome comments from experts. It would be, he suggested, "almost like a continuous consensus conference that is always looking at the genome but in a transparent way, so that experts from around the world can see what they recommended, why, and try to change their minds." Such an organization could be funded both through grants, perhaps from a private funder, and through a small fee for the use of curated data at a national or an international level, Greely said.

Heidi Rehm of Partners HealthCare pointed out that the way to reduce errors in databases and in interpretations is to generate much more data so that results are more statistically significant. Furthermore, different kinds of models may exist simultaneously. There may be a role for databases with limited access for a small group of contributors who are willing to curate data at a much higher level, for example, or different levels of curation could be performed on an individual, an expert panel, or a professional guidelines level. "There are a lot of ideas we have to work through to figure out how to do this," Rehm said.

Boguski recommended that the field move away from literature-based curation efforts because of the large number of errors and bias in publications. Instead, he suggested carrying out a large-scale sequencing effort that would re-compute all gene–disease associations from scratch once sequencing costs are low enough to do so.

Several of the panelists discussed whether the National Center for Biotechnology Information (NCBI) is an appropriate organization to maintain a genomic database. Rehm observed that NCBI has not had much experience with clinically curated environments, but she said that it "has done an amazing job at providing resources in real time to the community, and we should leverage that." Boguski countered by noting that NCBI is not a health care delivery organization but rather a library that stores archival data that people use infrequently. "Working in a place where you see patients being wheeled past you on gurneys everyday is different than sitting at a data center somewhere and making decisions" about what is clinically relevant data, he said. Michael Christman of the Coriell Institute for Medical Research said that the data likely will end up residing in multiple places. What is important, he said, is that data have the equivalent of an audit trail so that it is possible to keep track of who sees data when and for what purpose. People may be reluctant to have a for-profit entity house their data, he said, although as Hegde pointed out, many clinical laboratories would be willing to pay a fee to get access to it. The problem is not who houses the database but rather who is going to curate it and whether the database is clinically validated.

Greely observed that an international organization that is not funded or run by any one country may have advantages, especially since countries like China are making significant investments in genomic research. Rehm added, however, that international projects often struggle with differing laws concerning what data may be put in a public environment. Bruce Korf of the University of Alabama at Birmingham asked whether a collaboration of professional societies could play a role, since that is where many of the consensus discussions take place. But Federico Monzon of the Methodist Hospital observed that the size of the task for professional societies is "daunting," especially since most of the work done for professional societies is performed by volunteers.

"We are talking about millions and millions of variants," Rehm said. "I spend hours every day, every week, curating individual patient reports with individual variants to try and read through data and figure out what they mean. It is a difficult model to scale." The only way to proceed, she said, is to start with the most common variants and gradually work toward the less common variants.

Hegde said that the development of databases should be carried out via a unified, rather than a fragmented, effort.

Funding will be a huge challenge, Rehm said. Many laboratories do not have the resources to place their data in the public domain even though they have agreed to do so. Grant support may be necessary to move data into the public domain so that experts can be engaged to curate it.

Building and curating a clinical variant database will be a long, multistep process, Debra Leonard of Weill Cornell Medical Center said. A clinical-grade genome sequence and phenotype repository is needed first, and the curation at that point will revolve around collecting the proper information about the data being deposited. A clinical variant database can then be derived from those data by grading and assessing the sets of sequence and phenotype information in order to build decision-support tools. Breaking down the process into these steps may provide a way forward in developing this resource since groups may be willing to collaborate to create and maintain the repository, she suggested.

DATABASES FOR GENETIC VARIANTS INVOLVED IN CANCER

Maintaining databases for cancer variants raises somewhat different issues than maintaining databases for germline variants. As Monzon observed, sequencing cancer genomes also uncovers germline sequence information, but in sequencing cancer genomes there tends to be a much more direct link between acquired mutations and the disease. "There are intrinsic differences in the data that you are generating about somatic mutations . . . that would warrant having a separate database that you could interrogate very specifically for interactions with drugs, the ability to treat [the cancer], or even to prevent the development of tumors," Monzon said. Boguski observed that including cancer genomes in a master database could create difficulties. People with Stage IV melanoma who have a life expectancy of 6 months are not going to be worried about a hypothetical risk of Alzheimer's disease in 20 years. "To comingle presymptomatic genetic test databases with things that are directed at solving an acute clinical problem, I think, is a mistake," he said.

Rehm countered that variants can be important in both acute clinical problems and long-term problems, which would argue for putting all the data in one place. But the data should be annotated to specify whether a variant has somatic effects, germline effects, or both. If that were done, everything that people would want to know about genetic variation would be available in one place. Furthermore, Korf said, other diseases are likely to involve variants in somatic cells, which will increase linkages to germline variants.

A PUBLIC HEALTH APPROACH TO GENOMIC MEDICINE

Muin Khoury of the CDC asked how genomic medicine can progress from clinical validity to clinical utility. How will it be possible to document the value added and the social benefits of genomic information in large populations? Will there be a protracted period during which researchers and clinicians may not know enough to offer useful advice? (See Box 8-1.)

Nicholas Schork of the Scripps Translational Science Institute responded that there are probably just a handful of common diseases where enough is known to predict who is more likely to develop the disease, such as type 1 diabetes. But type 2 diabetes and other common diseases remain difficult to predict from genomic tests alone, partly because the increased risks demonstrated by tests today are not sizable enough to convince most people to change their behaviors. Still, Schork said, there may be various other advantages to having such genomic information. For some patients, having this information is empowering, even if very little can be done to change that risk. “There may be individuals out there who would like that information and capitalize on it in whatever way that they see fit.”

Christman argued that it will be a major development when sequencing costs are lowered to the point that the technology is widely used. Even if the clinical utility is limited at present, it will grow as extensive databases are developed from much larger cohorts.

Robert Nussbaum of the University of California, San Francisco Medical School argued for pilot projects “because I don’t expect to actually find something in every person.” Nevertheless, enough is known to move forward even if most people do not have actionable findings. Furthermore, genomic findings are complete and enduring, so a person’s genomic data can be useful whenever something changes in a person’s life.

Monzon pointed out that the experience with cancer, where conditions that once seemed to be the same can now be divided into molecular subtypes that call for different treatments, may be extended to many other diseases. In that case, genomic medicine should be used on a population-wide basis to spread its benefits as widely as possible.

BOX 8-1
Goals to Realize the Vision of Genomic Medicine

- The genomics field should take a systems approach[a] to whole-genome sequencing, which will require important changes by government, health care providers, and patients. (Greely)
- There should be more collaboration between clinical entities and laboratories, a greater emphasis on the fact that some parts of the genome will remain refractory to analysis, and NIH funding to laboratories to establish databases that can be used to refine and deliver genomic medicine. (Hegde)
- Informatics capabilities should be leveraged to create clinical genotype–phenotype databases, education should be improved, and reimbursement should be set at levels that make it possible for the health care system to do analytical thinking about how best to serve patients. (Monzon)
- There should be greater interoperability of medical records systems so that information relevant to care follows people throughout life and so that genomic information can act as an incubator for innovation. (Korf)
- A public–private partnership should be established to test the full introduction of genomic information into health care to demonstrate its feasibility. (Nussbaum)
- A universal health care information technology system should be established that includes both genetic and clinical information, and barriers to data sharing should be reduced. (Rehm)
- There should be funding for education, novel research to explore gene–phenotype relationships, and improved sequencing technologies. (Schork)
- More emphasis should be placed on genetics and genomics in medical schools. (Christman)
- A study should be carried out to determine whether patients can be encouraged to use genomic information in productive ways. (Shelton)
- Intellectual property issues surrounding gene patents should be resolved, whether through licensing, litigation, or legislation. (Boguski)

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[a] Systems approach is defined as an interdisciplinary method of study that involves consideration of all the components involved in a process and their interactions with each other.

Greely agreed that genomic medicine may not be cost-effective today but said that it may become cost-effective soon as costs go down and efficacy goes up. Furthermore, people are interested in the technology. The best approach for scientists and clinicians, he said, may be to figure out how the technology can be used in ways that are the most helpful and least harmful.

Rehm observed that many cancer patients are involved in a research study even as they are being treated. This is "one of the reasons that cancer has made much more progress," she said. "It is because we are doing so much research in real time." If information can be gathered from clinical care in low-cost ways, it should be, she said. The focus needs to be on what is clinically useful, "especially from the standpoint of what payers will reimburse and where to distribute limited funds."

Nussbaum said that a quality improvement research model may be the most appropriate approach for genomic medicine. "Educate, implement, assess, and then go back and do it again. It is an ongoing, iterative process." The databases and informatics tools are necessary complements to this process and their development will require usage data.

"For rare Mendelian disorders, genomics is here and it can help," Schork said. "For cancer, I think there is no question [that genomics is useful]. For pharmacogenomics, there is [also] no question. For prevention of common chronic conditions . . . there has to be more research in that area."

RETURN OF RESULTS

One workshop participant noted that some patients may not want to know the results of genetic tests. Rehm added that patients with late-onset diseases for which there are no treatments have good reasons not to want to know the results of genetic tests. Patients should be able to decide what information they want or do not want, she said. However, as information becomes more actionable, the health care provider may have to take a more active role in disseminating that information. Greely agreed that physicians will be less comfortable letting their patients refuse to learn information that may save their lives, although he also observed that they often do not have much success getting patients to change behaviors that are harmful to health.

GETTING HEALTH CARE PROVIDERS INTERESTED

Increasing physician interest in genomic tests when their own work may not be closely linked with such tests is a challenge, some participants noted. Korf suggested that it is necessary to provide some motivation to learn about these technologies while the field is still forming. For example, a surgeon who will be performing an anterior cruciate ligament repair may be interested in how genetic variants may affect wound healing, recovery from traumatic events, or response to pain medications. The challenge is to test these factors and demonstrate their clinical utility. "I don't think any kind of physician or health provider is looking for more work to do unless they can be shown that it is going to somehow make outcomes better or make their jobs easier," Korf said. Boguski added that in some cases it may be necessary for patients to help educate health care providers about the utility of genetic tests.

REIMBURSEMENT FOR INTERPRETATIVE SERVICES

While cardiologists and radiologists receive ample reimbursement for reading an electrocardiogram, interpreting an echocardiogram, or reading a CT scan, the same is not true for laboratory testing. The challenge in this is the laboratory coding system, Rehm said. "It is like trying to reimburse for how many times you picked up a scalpel [instead] of the actual surgical procedure." Monzon added that some interpretative services are reimbursed, but reimbursement decisions depend on the service and on the payer. "There is no consistency in the system." Rehm noted that this issue is not specific to laboratory reimbursement and that the fee-for-service, as opposed to an outcome-based, reimbursement system is "a universal problem that every specialty needs to address."

THE ROLE OF INDUSTRY

Private-sector companies, such as sequencing technology manufacturers and pharmaceutical companies, are integral players in genomic medicine, Rehm said, but those companies must recognize the differences between operating in a clinical environment and a research environment. For example, changes in technologies can undermine extensive validation that has been done with specific platforms. Having regulations in place that would establish standards for raw reagents and software systems could be helpful in this regard, Rehm said.

Hegde added that private companies are very interested in the establishment of genomic databases and that perhaps it would be possible for them to create a common fund that would support this work. Schork said that many possible business models could work and that private-sector interpretation of genomic information is likely to grow.

FINAL WORDS

Bruce Blumberg of Kaiser Permanente concluded the workshop by saying that "this is going to happen. . . . It is not a matter of whether it should. This [workshop] was an effort to begin to flesh out some of the issues that clearly need to be solved. . . . It was a very good start."

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Appendix A

Workshop Agenda

Integrating Large-Scale Genomic Information into Clinical Practice

July 19, 2011

The Keck Center of the National Academies
500 Fifth Street, N.W.
Washington, DC 20001

MEETING OBJECTIVE

To highlight and identify the challenges and opportunities in integrating large-scale genomic information into clinical practice.

Workshop Assumptions:

- Sequencing technology will advance enough to produce clinically meaningful results.
- Whole-genome sequencing (WGS) will be cost-effective and comparable to other diagnostic tests.

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**

Bruce Blumberg, *Workshop Cochair*
Institutional Director of Graduate Medical Education, Northern California Kaiser Permanente, The Permanente Medical Group

Catherine A. Wicklund, *Workshop Cochair*
Past President, National Society of Genetic Counselors; Director, Graduate Program in Genetic Counseling; Associate Professor, Department of Obstetrics and Gynecology, Northwestern University

8:45–9:15 A.M. **KEYNOTE ADDRESS: THE REALIZATION OF GENOMIC MEDICINE**

Leslie G. Biesecker
Chief and Senior Investigator, Genetic Disease Research Branch, National Human Genome Research Institute

9:15–9:45 A.M. **WORKFORCE**

Session Moderator: Michael S. Watson, American College of Medical Genetics

9:15–9:45 A.M. **Requisite Knowledge and Skill Sets for Large-Scale Genomic Data Utilization**

Bruce R. Korf
Wayne H. and Sara Crews Finley Chair in Medical Genetics; Professor and Chair, Department of Genetics; Director, Heflin Center for Genomic Sciences, University of Alabama at Birmingham

9:45–11:50 A.M **ANALYSIS**

Session Moderator: Debra G. Leonard, Weill Cornell Medical Center

9:45–10:25 A.M. **Defining Actionable Novel Discoveries, Annotating Genomes, and Re-analysis—A Laboratory Perspective**

Federico A. Monzon
Associate Professor of Pathology, Weill Cornell Medical College/The Methodist Hospital; Director, Research Pathology and Molecular Diagnostics Cores, The Methodist Hospital Research Institute

Madhuri Hegde
Associate Professor, Department of Human Genetics; Scientific Director, Emory Genetics Laboratory, Emory University School of Medicine

10:25–11:05 A.M. **Defining Actionable Novel Discoveries, Annotating Genomes, and Re-analysis—A Clinical Perspective**

Heidi L. Rehm
Assistant Professor of Pathology, Brigham and Women's Hospital and Harvard Medical School; Chief Laboratory Director, Laboratory for Molecular Medicine, Partners HealthCare Center for Personalized Genetic Medicine

Michael F. Christman
President and Chief Executive Officer, Coriell Institute for Medical Research

11:05–11:50 A.M. **Discussion with Speakers and Attendees**

11:50 A.M. **WORKING LUNCH BREAK**

12:05–2:15 P.M. **INTERPRETATION**

Session Moderator: Muin Khoury, Centers for Disease Control and Prevention

12:05–1:20 P.M. **Interpretation Models and Context**

Medical Practice

Robert L. Nussbaum
Holly Smith Chair and Professor of Medicine; Chief, Division of Medical Genetics; Member, Institute of Human Genetics; Professor of Neurology, University of California, San Francisco School of Medicine

Pathology

Mark S. Boguski
Associate Professor, Center for Biomedical Informatics, Harvard Medical School

Bioinformatics

Nicholas J. Schork
Director of Bioinformatics and Biostatistics; Professor, Molecular and Experimental Medicine, The Scripps Translational Science Institute

1:20–2:15 P.M. **Discussion with Speakers and Attendees**

2:15–3:40 P.M. **DELIVERY OF INFORMATION**

Session Moderator: W. Gregory Feero, National Human Genome Research Institute

2:15–2:55 P.M. **Innovative Mechanisms for Delivery**

Integral Delivery Systems and Active Monitoring of Data

Mary V. Relling
Chair, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital

Granting Access to Personal Health Information

Robert H. Shelton
Founder and Chief Executive Officer, Private Access, Inc.

2:55–3:40 P.M. **Discussion with Speakers and Attendees**

3:40 P.M. **BREAK**

3:55–4:25 P.M **ETHICAL AND LEGAL ISSUES**

Session Moderator: Martha Turner, American Nurses Association

Ethical and Legal Implications for Integrating Large-Scale Genomic Data into Clinical Practice

Henry T. Greely
Deane F. and Kate Edelman Johnson Professor of Law; Professor, by courtesy, of Genetics; Director, Center for Law and the Biosciences, Stanford University

4:25–5:55 P.M **PANEL DISCUSSION: ENVISIONING THE FUTURE**

Session Moderators: Bruce Blumberg, Northern California Kaiser Permanente

Catherine A. Wicklund, National Society of Genetic Counselors

Panelists:

Mark S. Boguski, Harvard Medical School
Michael F. Christman, Coriell Institute for Medical Research
Henry T. Greely, Stanford University
Madhuri Hegde, Emory University
Bruce R. Korf, University of Alabama at Birmingham
Federico A. Monzon, Weill Cornell Medical College/The Methodist Hospital

Robert L. Nussbaum, University of California, San Francisco School of Medicine
Heidi L. Rehm, Harvard Medical School
Nicholas J. Schork, The Scripps Translational Science Institute
Robert H. Shelton, Private Access, Inc.

5:55–6:10 P.M. **CONCLUDING REMARKS**

Bruce Blumberg, *Workshop Cochair*
Northern California Kaiser Permanente

Catherine A. Wicklund, *Workshop Cochair*
National Society of Genetic Counselors

6:10 P.M. **ADJOURN**

Appendix B

Speaker Biographical Sketches

Leslie G. Biesecker, M.D., received his undergraduate education at the University of California, Riverside, and his medical training at the University of Illinois, and he served his residency in pediatrics at the University of Wisconsin. He trained as a medical genetics fellow at the University of Michigan. He is certified by the American Board of Pediatrics and the American Board of Medical Genetics. He is currently senior investigator and chief of the Genetic Disease Research Branch, National Human Genome Research Institute. He is a member of the American Society of Clinical Investigators, the Association of American Physicians, and the American Society of Human Genetics (ASHG). He has served as a member of the ASHG subcommittee on the use of stored DNA samples, the David Smith meeting organizing committee, the National Cancer Institute Institutional Review Board, the National Institute of Child Health and Human Development strategic planning committee, the World Trade Center Kinship and Data Analysis Panel, the ASHG program committee, and the ASHG board of directors. He serves on the editorial boards of *Clinical Dysmorphology*, *BMC Medicine*, and the *American Journal of Medical Genetics*. He serves as medical advisor to the Proteus Syndrome Foundations of the United States and the United Kingdom. His research interests include applications of genomic technology to human disease and clinical and genetic delineation of human heritable disorders.

Bruce D. Blumberg, M.D., is director of graduate medical education (the resident physician training programs) for Northern California Kaiser Permanente. He currently maintains small clinical practices at both his

Oakland and San Francisco facilities. He believes in a team-based approach to medical care with patients and their families as key members of the team. Since he practices at multiple sites, genetic counselors are a crucial and consistent communication link between him and his patients. Also, he is a clinical professor of pediatrics at the University of California, San Francisco, and an adjunct clinical professor of pediatrics at Stanford University School of Medicine. His clinical interests within genetics are broad, and he has a subspecialty interest in inherited disorders of skeletal and connective tissue development. His research interest is in the area of the psychosocial and emotional aspects of prenatal diagnosis. Dr. Blumberg holds a medical degree from the Yale University School of Medicine, completed his residency in pediatrics at both Stanford University Hospital and UCLA Center for the Health Sciences, and held a specialty fellowship in medical genetics at Harbor-UCLA Medical Center. He also received a B.A. from Dartmouth College.

Mark S. Boguski, M.D., Ph.D., FCAP, is on the faculty of Harvard Medical School at the Center for Biomedical Informatics and the Department of Pathology at Beth Israel Deaconess Medical Center in Boston. He previously held positions at the Johns Hopkins University School of Medicine, the National Institutes of Health, and the National Library of Medicine and served as an executive in the biotechnology and pharmaceutical industries. Dr. Boguski is a former vice president of Novartis and was honored as a visionary and influencer by the Personalized Medicine Coalition in 2006. He was elected to the Institute of Medicine of the National Academy of Sciences and the American College of Medical Informatics in 2001. Dr. Boguski is a graduate of the Medical Scientist Training Program at Washington University in St. Louis.

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 was 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, an NHGRI Center of Excellence in Ethical, Legal, and Social Implications research, and codirector of the Northwest-Alaska Pharmacogenomic Research Network.

Michael F. Christman, Ph.D., is president and chief executive officer of the Coriell Institute for Medical Research. With an entrepreneurial spirit, he is guiding Coriell on new ventures in emerging science that will both further the institute's research and add to the breadth of services it provides to scientists worldwide. In 2007 he initiated the Coriell Personalized Medicine Collaborative, a research study evaluating the utility of using the knowledge of genetics in medicine. As a leader in the exploration of genomics, Coriell is paving the way toward the development of personalized medicine. Under his leadership, Coriell has also established a federally funded induced pluripotent stem cell lab. This remarkable technology allows a skin or blood cell to be coaxed into becoming nearly any cell type in the body, opening new avenues for research, drug discovery, and, eventually, therapy. He recently collaborated with Dr. Charles Rotimi of the National Institutes of Health (NIH) to perform one of the first genome-wide association studies on an African American cohort—the Howard University Family Study. He is an expert in genetics and genomics, with a focus on the integration of genomic information into the delivery of clinical care. Prior to joining Coriell, he served as professor and founding chair of the Department of Genetics and Genomics at the Boston University School of Medicine. There he led an international team of scientists in one of the first genome-wide association studies using the Framingham Heart Study cohort, published in *Science* magazine in 2006. He received his bachelor's degree in chemistry with honors from the University of North Carolina at Chapel Hill; his doctorate in biochemistry from the University of California, Berkeley; and was a Jane Coffin Childs postdoctoral fellow at the Massachusetts Institute of Technology. He serves on the New Jersey Technology Council Board of Directors, the NIH Drug Discovery and Experimental Pharmacology Study Section, and the WHYY Scientific Advisory Committee.

W. Gregory Feero, M.D., Ph.D., is special advisor to the director for genomic medicine at the National Human Genome Research Institute. Dr. Feero obtained his M.D./Ph.D. from the University of Pittsburgh School of Medicine with a Ph.D. in human genetics. He then completed his residency in family medicine at the Maine–Dartmouth Family Medicine Residency Program in Augusta, Maine. Dr. Feero sees patients at the Maine–Dartmouth Family Practice Residency Program, a residency site where he is an associate professor in the Department of Community and Family Medicine at Dartmouth Medical School. Dr. Feero is board certified in family medicine and holds licenses in Maine and West Virginia. He has authored numerous peer-reviewed and invited publications.

Henry (Hank) T. Greely, J.D., is the Deane F. and Kate Edelman Johnson Professor of Law and professor, by courtesy, of genetics at Stanford University. He specializes in ethical, legal, and social issues arising from advances in the biosciences, including genetics, neuroscience, and human stem cell research, among other things. He chairs the California Advisory Committee on Human Stem Cell Research and the steering committee of the Stanford University Center for Biomedical Ethics and directs the Stanford Center for Law and the Biosciences. From 2007 to 2010 he was a codirector of the Law and Neuroscience Project. In 2006 he was elected a fellow of the American Association for Advancement of Science. He graduated from Stanford in 1974 and from Yale Law School in 1977. He served as a law clerk for Judge John Minor Wisdom on the U.S. Court of Appeals and for Justice Potter Stewart of the U.S. Supreme Court. After working during the Carter Administration in the departments of defense and energy, he entered private practice in Los Angeles in 1981 as a litigator with the law firm of Tuttle & Taylor, Inc. He began teaching at Stanford in 1985.

Madhuri Hegde, Ph.D., FACMG, is an associate professor and scientific director at the Emory Genetics Laboratory and senior director of the Molecular Laboratory at the Emory University School of Medicine. Her areas of specialty and interest are muscular dystrophy, mental retardation, and novel and high-throughput methodologies to detect sequence variation. The focus of her laboratory is to develop and perform comprehensive mutation analysis and interpretation for complex or challenging genetic disorders using multiple approaches. The primary focus of her clinical work is the development of high-throughput sequencing strategies for rare disorders using sequence-capture technologies, robotics, next-generation sequencing, oligonucleotide array platforms, predictive analysis tools, and biological testing. Her research is focused on the functional analysis of sequence variants in disease-associated genes, specifically mental retardation and muscular dystrophy, and translating what is learned in the basic research laboratory to clinical practice. The ultimate goal is to create an algorithm that will be clinically useful for interpretation of novel sequence variants. She is also interested in identifying novel genes in these diseases using next-generation tools and a laboratory-developed bridged approach to whole-exome sequencing. An understanding of the important changes will eventually provide an opportunity to improve early detection of disease and to target more effective treatment. She received a B.Sc. and a M.Sc. from the University of Bombay, India, and a Ph.D. from the University of Auckland, New Zealand. She did postdoctoral studies at the Baylor College of Medicine and is board certified in clinical molecular genetics.

Muin Khoury, M.D., Ph.D., is the first director of the National Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC). The office was formed in 1997 to assess the impact of advances in human genetics and the Human Genome Project on public health and disease prevention. CDC's National Office of Public Health Genomics serves as the national focus for integrating genomics into public health research and programs for disease prevention and health promotion. Dr. Khoury joined the CDC as an epidemic intelligence service officer in 1980 in the Birth Defects and Genetic Diseases Branch and served as a medical epidemiologist in 1987. In 1990 he became deputy chief of the same branch. In 1996 Dr. Khoury chaired a CDC-wide Task Force on Genetics and Disease Prevention and provided important leadership in outlining a plan delineating the future direction that the CDC should take in this important area. Dr. Khoury received his B.S. degree in biology/chemistry from the American University of Beirut, Lebanon, and his medical degree and pediatrics training from the same institution. He received a Ph.D. in human genetics/genetic epidemiology and training in medical genetics from Johns Hopkins University. Dr. Khoury is board certified in medical genetics. Dr. Khoury has published extensively in the fields of genetic epidemiology and public health genetics and is a member of many professional societies and serves on the editorial boards of several journals. He is an adjunct professor of epidemiology at Emory University's School of Public Health and an associate in the Department of Epidemiology at Johns Hopkins University Bloomberg School of Public Health.

Bruce R. Korf, M.D., Ph.D., received his M.D. degree from Cornell University Medical College and his Ph.D. degree in genetics and cell biology from Rockefeller University. He then completed training in pediatrics, pediatric neurology, and genetics at Children's Hospital, Boston. He served as clinical director in the Division of Genetics at Children's Hospital from 1986 to 1999 and as medical director of the Harvard-Partners Center for Genetics and Genomics from 1999 to 2002. Currently he holds the Wayne H. and Sara Crews Finley Chair in Medical Genetics and is professor and chair, Department of Genetics, and director, Heflin Center for Genomic Sciences, at the University of Alabama at Birmingham. He is the author of *Human Genetics: A Problem-Based Approach*, published by Blackwell Science and currently in its third edition. He is also coauthor of *Medical Genetics at a*

Glance, coeditor of the fifth edition of *Emery and Rimoins Principles and Practice of Medical Genetics*, and coeditor of *Current Protocols in Human Genetics*. He is immediate past president of the American College of Medical Genetics and a member of the Board of Scientific Counselors of the National Human Genome Research Institute. He has served as president of the Association of Professors of Human and Medical Genetics, as a member of the boards of directors of the American College of Medical Genetics and the American Society of Human Genetics, as a member of the Liaison Committee on Medical Education, and as a member of the National Cancer Institute Board of Scientific Counselors.

Debra Leonard, M.D., Ph.D., received her M.D. and Ph.D. from the New York University School of Medicine and is currently professor and vice chair for laboratory medicine in the Department of Pathology and Laboratory Medicine as well as director of the clinical laboratories for New York–Presbyterian Hospital's Cornell campus (NYPH–WCMC). She is also director of the Pathology Residency Training Program at NYPH–WCMC. Dr. Leonard was previously director of molecular pathology at the University of Pennsylvania School of Medicine and is a nationally recognized expert in molecular pathology. She has served on several national committees that develop policy for the use of genetic and genomic technologies and information, including most recently the Secretary's Advisory Committee on Genetics, Health, and Society that advises the Secretary of Health and Human Services. Dr. Leonard is editor of two molecular pathology textbooks and has spoken widely on various molecular pathology test services, the future of molecular pathology, and the impact of gene patents on molecular pathology practice. Dr. Leonard is interested in the use of genomic technologies in the practice of medicine to improve patient outcomes.

Federico A. Monzon, M.D., is an associate professor of pathology at Weill Cornell Medical College and a molecular pathologist at the Department of Pathology and Laboratory Medicine in the Methodist Hospital. He is director of the research pathology and molecular diagnostics cores at the Methodist Hospital Research Institute. He is a board-certified AP/CP pathologist with subspecialty training in molecular diagnostics. He received his M.D. from the National University in Mexico City and spent several years conducting basic research at the Instituto Nacional de Cancerología in Mexico City and at the University of Pennsylvania in Philadelphia. He completed his AP/CP residency training at Thomas Jefferson University Hospital in Philadelphia and his molecular genetic pathology subspecialty training at the University of Pittsburgh. He has a broad background in molecular diagnostics and pathology informatics and significant experience in the translation of novel technologies into clinical genomic tests such as a microarray-based clinical assay for the diagnosis of tumors of unknown origin and array-based karyotyping for solid tumors. He is engaged in research projects that involve the application of genomic knowledge as a clinical tool. His main research focus is the translation of genomic information into clinical tools for the molecular classification of human tumors in general and, in particular, in renal cell carcinoma.

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

Heidi L. Rehm, Ph.D., FACMG, is a board-certified clinical molecular geneticist at Partners HealthCare and an assistant professor of pathology at Harvard Medical School. Her graduate degree in genetics is from Harvard University, and her postdoctoral and fellowship training was at Harvard Medical School. She was recruited in 2001 to build the CLIA-certified Laboratory for Molecular Medicine at the Partners HealthCare Center for Personalized Genetic Medicine and now serves as the lab's director. The lab focuses on the rapid translation of new genetic discoveries into clinical tests that can be used to improve patient outcomes, supporting the model of personalized medicine. The lab also focuses on bringing novel technologies and software systems into molecular diagnostics to support the integration of genetics into clinical use. Dr. Rehm also directs the clinical molecular genetics training program at Harvard Medical School and conducts research in hearing loss, Usher syndrome, and cardiomyopathy.

Mary V. Relling, Pharm.D., earned her B.S. degree from the University of Arizona College of Pharmacy and her doctoral degree from the University of Utah College of Pharmacy. She came to St. Jude Children's Research Hospital in 1985 as a research fellow and in 2003 was named chair of the

Department of Pharmaceutical Sciences. She is also a professor at the University of Tennessee in the Colleges of Medicine and Pharmacy and an active member of the children's oncology group at the National Cancer Institute (NCI). Her primary interests are in anti-neoplastic pharmacokinetics and pharmacodynamics in children, pharmacogenetics of anti-leukemic therapy, and host- and treatment-related risk factors for adverse effects and secondary malignancies. Dr. Relling is one of the principal investigators within the Pharmacogenomics Research Network. The impetus for her research is the need to improve drug therapy of childhood leukemia by better understanding the contributions of and mechanisms underlying interindividual differences in pharmacokinetics and pharmacodynamics. Using currently available medications, acute lymphoblastic leukemia (ALL) is cured in the great majority of children. Her objectives are to increase the cure rate for ALL while decreasing the risk of serious adverse effects of therapy. Her pharmacogenetic, pharmacokinetic, and pharmacodynamic research is tightly integrated into clinical protocols for ALL and involves collaborations with several laboratory, translational, and clinical investigators at St. Jude and within the NCI children's oncology group. She has published over 200 original scientific manuscripts. She is a frequent national and international guest lecturer and has served and chaired national committees for such prestigious organizations as the American Association for Cancer Research, the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration, and the National Institutes of Health. She was elected to the Institute of Medicine in 2009.

Nicholas J. Schork, Ph.D., is director of bioinformatics and biostatistics at the Scripps Translational Science Institute, director of research at Scripps Genomic Medicine, and a professor in the Department of Molecular and Experimental Medicine at the Scripps Research Institute. His interest and expertise are in quantitative human genetics and genomics, especially the design and implementation of methodologies to dissect the genetic basis of complex traits and diseases. He has published over 250 scientific articles and book chapters on the analysis of complex multifactorial traits and diseases. Prior to joining Scripps in 2007, he served for 7 years as a professor of biostatistics and psychiatry and as codirector of the Center for Human Genetics and Genomics at the University of California, San Diego. From 1994 to 2000 he was an associate professor of epidemiology and biostatistics at Case Western Reserve University in Cleveland, Ohio, and an associate professor of biostatistics at Harvard University. During 1999 and 2000 he took a leave of absence to conduct research as the vice president of statistical genomics at the French biotechnology company Genset, where he helped guide efforts to construct the first high-density map of the human genome. A member of several scientific journal editorial boards, Dr. Schork is a frequent participant in National Institutes of Health–related steering committees and review boards and has served on the advisory board of five companies. In addition, he is currently director of the Bioinformatics and Biostatistics Core of the National Institute on Aging–sponsored Longevity Consortium and a member of the Genetic Association Information Network data analysis committee of the National Human Genome Research Institute. Dr. Schork earned a B.A. in philosophy, an M.A. in philosophy, an M.A. in statistics, and a Ph.D. in epidemiology, all at the University of Michigan in Ann Arbor.

Robert H. Shelton, M.B.A., is chairman and chief executive officer of Private Access, Inc. Drawing on his varied experiences in heading a national non-profit disease advocacy group and in health care information systems, as an inventor, serial entrepreneur, and parent of a child who was prenatally diagnosed with a rare genetic condition, Mr. Shelton founded Private Access in late 2006 based on a unique vision for how to simultaneously improve patient privacy while making it possible to achieve better accessibility to sensitive and confidential information. In 2009 Private Access won the Hot Product Award from the Towards an Electronic Patient Record trade show and was selected by Forbes as No. 12 on the list of America's Most Promising Companies. Mr. Shelton was named by Healthspottr as No. 86 on its list of the top 100 persons in health care. He has testified on cutting-edge technologies for consumer choice before numerous public and private groups, including the the Privacy & Security Tiger Team appointed by the Office of the National Coordinator for Health Information Technology; the Secretary's Advisory Committee on Genetics, Health, and Society and the International Association of Privacy Professionals regarding how enabling patients with the appropriate technology to control who can and cannot access their confidential information will build greater trust in the system and result in accelerating important medical research; and the Present and Future of Personalized Medicine Policy Forum hosted by 23andMe, Inc. In addition to Private Access, Mr. Shelton is a director and for 7 years formerly served as chairman of KS&A, a national 501(c)(3) group serving several genetics-based conditions. He holds an undergraduate degree in public and international affairs from George Washington University and an M.B.A. from the University of Texas at Austin. Mr. Shelton has been awarded four U.S. patents and is a named inventor on numerous other pending patent applications.

Martha Turner, Ph.D., R.N., B.C., C.N.A.A., is currently assistant director of the American Nurses Association (ANA) Center for Ethics and Human Rights and an adjunct professor in the Department of Preventive Medicine and Biometrics, School of Medicine, Uniformed Services University (USU). She is codirector and lecturer for the public health ethics course (PMO 991). A recently retired Air Force colonel, Dr. Turner was the consultant for health care ethics to the Air Force Surgeon General from 1998 until 2006. She represented the U.S. Department of Defense as an ex-officio member of the Secretary's Advisory Committee for Genetics, Health, and Society (SACGHS). During her 3 years with SACGHS, she became familiar with challenges associated with the development of new technologies and other scientific advances in genetics and genomics. On behalf of the ANA, she reviewed and submitted comments on drafts of the reports, *Policy Issues Associated with Undertaking a Large U.S. Population Cohort Project on Genes, Environment, and Disease* (2006) and *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges* (2007). Her understanding of the challenges and opportunities for health professionals is demonstrated by her experience at the USU, where she teaches applied ethics courses in the M.P.H. and Ph.D./Dr.P.H. programs. Additional activities have included membership on the TriService Nursing Research Program Advisory Council, various scientific review panels, the editorial board for the *Journal of Nursing Staff Development*, and the USU Institutional Review Board. Her research, projects, and policy work have addressed pain management, end-of-life care, air evacuation of patients, care of those imprisoned, and other topics related to health care delivery in diverse environments. Dr. Turner has been participating on behalf of ANA at ASBH, NCHPEG, and International Society of Nurses in Genetics meetings. Additionally, she has been collaborating with a national work group in planning and strategizing on implementation of the nursing core competencies approved and endorsed by the national nursing community.

Michael S. Watson, Ph.D., received his Ph.D. in physiology and biophysics from the University of Alabama at Birmingham while focusing on human medical genetics and received his postdoctoral training in the Medical Genetics Training Program at Yale University School of Medicine, where he was the associate director of clinical cytogenetics. He was director of clinical and molecular cytogenetics at Washington University School of Medicine in St. Louis and professor of pediatrics and genetics from 1986 to 2001 and is certified by the American Board of Medical Genetics (ABMG) in clinical cytogenetics and as a Ph.D. medical geneticist. He served on the board of directors of the American College of Medical Genetics (ACMG) (1992–1998) and was vice president for laboratory affairs, chair of the Laboratory Practice Committee, and cochair of the Test and Technology Transfer Committee. He chaired the ACMG Economics Committee and the Intellectual Property Subcommittee. He was cochair of the NIH/Department of Energy Task Force on Genetic Testing from 1995 through 1997. He cochaired the Rare Diseases Subcommittee of the Secretary's

Advisory Committee on Genetic Testing of HHS from 2000 to 2002. He directed the HRSA-funded project "Newborn Screening: Toward a Uniform Screening Panel and System" from 2002 through 2005. He is director of the National Coordinating Center for Regional Genetics and Newborn Screening Collaborative Groups. As of 2001 he became an adjunct professor of pediatrics at Washington University School of Medicine and executive director of both ACMG and the ACMG Foundation.

Catherine A. Wicklund, M.S., CGC, is director of the Graduate Program in Genetic Counseling at Northwestern University and an associate professor in the Department of Obstetrics and Gynecology. She received her master's in genetic counseling from the University of Texas Graduate School of Biomedical Sciences. She has 15 years of experience in clinical genetic counseling and has provided prenatal and pediatric genetic services. She codirected the Graduate Program in Genetic Counseling at the University of Texas before she joined Northwestern. While she was at the University of Texas, she was also director of Genetic Counseling Services in the Department of Obstetrics, Gynecology and Reproductive Medicine. She served on the board of directors of the National Society of Genetic Counselors (NSGC) first as Region V Representative, then as secretary, and then as president in 2008. As a leader in NSGC she has represented the organization at several national committees, including the Secretary's Advisory Committee on Genetics, Health, and Society. She is also active on a state level and is working with the Illinois Department of Public Health on genetics education and finance and reimbursement issues and is on the Genetic and Metabolic Diseases Advisory Committee.

Appendix C

Registered Attendees

Marc Allard
U.S. Food and Drug Administration

James Allred
American Cancer Society Cancer Action Network

George Annas
Boston University

Leposava Antonovic
U.S. Food and Drug Administration

Eric Assaraf
Washington Research Group

Igor Astsaturov
Fox Chase Cancer Center

Marian Ault
Mediatech/Cellgro

Nazneen Aziz
College of American Pathologists

LeeAnn Bailey
Deloitte Consulting

Sarah Beachy
National Cancer Institute

Elise Bendik
University of Miami

Judith Benkendorf
American College of Medical Genetics

Courtney Berrios
Johns Hopkins University

Leslie Biesecker
National Human Genome Research Institute

Paul Billings
Life Technologies

Susan Blanton
University of Miami

Bruce Blumberg
Kaiser Permanente

Mark Boguski
Center for Biomedical Informatics, Harvard Medical School

Denise Bonds
National Heart, Lung, and Blood Institute

Wylie Burke
University of Washington

Kathryn Camp
National Institutes of Health

Grant Campany
X Prize Foundation

Michael Cantor
Pfizer Inc.

Julie Cantor-Weinberg
College of American Pathologists

Alexis Carter
Emory University

C. Thomas Caskey
Baylor College of Medicine

Chia-Chien Chiang
Human Genome Sciences

Michael Christman
Coriell Institute for Medical Research

George Chrousos
Library of Congress

Emily Clements
Jones Public Affairs

Nadine Cohen
Johnson & Johnson

Sarah Comley
Independent

Sara Copeland
Health Resources and Services Administration

Maria DeTolve Donoghue
G&M Consulting

Helena Duncan
College of American Pathologists

Sherman Elias
Northwestern University

Raj Emmadi
University of Illinois at Chicago

W. Andrew Faucett
Geisinger Health System

W. Gregory Feero
National Human Genome Research Institute

Suzanne Feetham
University of Wisconsin, Milwaukee

Amanda Field
Children's National Medical Center

Louis Fiore
Department of Veterans Affaris

Natalie Flechsig
FasterCures

Ron Galloway
Method Content, LLC

John Gardenier
Independent

Rosalynn Gill
Rosalynn Gill Consulting, LLC

Geoffrey Ginsburg
Duke University

Jonathan Gitlin
National Human Genome Research Institute

Mark Gorman
National Coalition for Cancer Survivorship

Henry T. Greely
Stanford University

Ramachandra Gullapalli
University of Pittsburgh Medical Center

Susanne Haga
Duke University

Pauliana Hall
PCH Integrated Regulatory Services, Inc.

Heather Halvorson
U.S. Air Force

Madhuri Hegde
Emory University

Gerald Higgins
GenomeQuest, Inc.

C. J. Hoban
Southwest Oncology Group and University of Michigan

India Hook-Barnard
National Academy of Sciences

Ekopimo Ibia
Merck & Co., Inc.

Naoko Ishibe
National Institutes of Health

Justin Johnson
EdgeBio

Nicole Johnson
Johns Hopkins Medical Institute

Sam Joseph
University of Maryland, College Park

Jeffrey Kant
University of Pittsburgh Medical Center

Sharon Kardia
University of Michigan

Jill Kaufman
College of American Pathologists

James Kelly
Roche Molecular Systems

Mohamed Khan
Vancouver Cancer Centre

Muin Khoury
Centers for Disease Control and Prevention

Roger Klein
Blood Center of Wisconsin/Medical College of Wisconsin

Bruce Korf
University of Alabama at Birmingham

Alla Lapidus
Fox Chase Cancer Center

Jennifer Leib
HealthFutures, LLC

Debra Leonard
Weill Cornell Medical Center

Dane Leone
Macquarie

Xueying Liang
U.S. Food and Drug Administration

Paul Lipkin
Robert Woods Johnson Foundation Health Policy Fellow

Tracy Lively
Cancer Diagnosis Program, National Institutes of Health

Michele Lloyd-Puryear
Health Resources and Services Administration

Juliana Macri
The Urban Institute

Teri Manolio
National Human Genome Research Institute

Elizabeth Mansfield
U.S. Food and Drug Administration

Denise Toyer McKan
AstraZeneca

Kathryn McLaughlin
Health Resources and Services Administration

Christine Micheel
Institute of Medicine

Ronald Miller
Air Force Medical Support Agency

C. Douglas Monroe
Kaiser Permanente Drug Information Services

Federico Monzon
The Methodist Hospital

Anne Mueller
AstraZeneca

Amy Muhlberg
Life Technologies

Nancy Munoz
Genesis HealthCare

Jessica Nadler
Deloitte Consulting

Marc Newman
Telecenter, LLC

Ginger Norris
Independent

Robert Nussbaum
University of California, San Francisco School of Medicine

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

Brad Ozenberger
National Human Genome Research Institute

June Peters
National Cancer Institute

Margaret Piper
Blue Cross/Blue Shield Association

Aidan Power
Pfizer Inc.

Victoria Pratt
Quest Diagnostics Nichols Institute

Ronald Przygodzki
Department of Veterans Affairs

Michael Raff
MultiCare Health System

Kate Reed
National Coalition for Health Professional Education in Genetics

Heidi Rehm
Partners HealthCare and Harvard Medical School

Naved Rehman
Brother

Mary Relling
St. Jude Children's Research Hospital

Ronald Rerko
Cleveland Clinic

Ann Rose
ViCro

Mary Rubino
Health Affairs

Nicholas Schork
Scripps Translational Science Institute

Beverlyn Settles-Reaves
Howard University

Robert Shelton
Private Access, Inc.

Andy Shih
Autism Speaks

Dee Simons
Biogen Idec

Jennifer Skornik
Independent

Scott Steele
University of Rochester

Errol Strain
U.S. Food and Drug Administration

Katherine Johansen Taber
American Medical Association

Cara Tenenbaum
Ovarian Cancer National Alliance

Sharon Terry
Genetic Alliance

Umesh Thakkar
Department of Veterans Affairs

Barry Thompson
American College of Medical Genetics

Bernadette Toner
GenomeWeb LLC

Lois Tully
National Institute of Nursing Research

Martha Turner
American Nurses Association

Lisa Vasquez
Health Resources and Services Administration

Natalia Volfovsky
SAIC–Frederick

Robert Wassman
Life Designs Ventures

Michael S. Watson
American College of Medical Genetics

Daniel Wattendorf
Department of the Air Force

Angele White
Fair Chance, Inc.

Catherine A. Wicklund
Northwestern University

Kelly Wilkicki
U.S. Food and Drug Administration

Hui-Lee Wong
U.S. Food and Drug Administration

Robert Yates
Social & Scientific Systems, Inc.

Melanie Young
Independent

Wenqi Zeng
Ambry Genetics