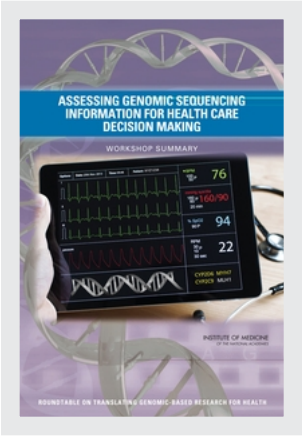

Assessing Genomic Sequencing Information for Health Care Decision Making: Workshop Summary

DETAILS

126 pages | 8.5 x 11 | PAPERBACK
ISBN 978-0-309-30494-8 | DOI 10.17226/18799

AUTHORS

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

ASSESSING GENOMIC SEQUENCING INFORMATION FOR HEALTH CARE DECISION MAKING

WORKSHOP SUMMARY

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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

THE NATIONAL ACADEMIES PRESS • 500 Fifth Street, NW • Washington, DC 20001

NOTICE: The workshop that is the subject of this workshop summary 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 Academy of Nursing (unnumbered contract); American College of Medical Genetics and Genomics (unnumbered contract); American Heart Association (unnumbered contract); American Medical Association (unnumbered contract); American Society of Human Genetics (unnumbered contract); Association for Molecular Pathology (unnumbered contract); Blue Cross and Blue Shield Association (unnumbered contract); College of American Pathologists (unnumbered contract); Department of Veterans Affairs (Contract No. VA248-P-1528); Eli Lilly and Company (unnumbered contract); Genetic Alliance (unnumbered contract); Health Resources and Services Administration (Contract No. HHSH250201100119P and Contract No. HHSH25034017T); International Society for Cardiovascular Translational Research (unnumbered contract); Kaiser Permanente Program Offices Community Benefit II at the East Bay Community Foundation (Contract No. 20121257); Life Technologies (unnumbered contract); Merck & Co., Inc. (CMO-140505-000393); National Cancer Institute (Contract No. HHSN263201200074I, TO#5); National Human Genome Research Institute (Contract No. HHSN263201200074I, TO#5); National Institute of Mental Health (Contract No. HHSN263201200074I, TO#5); National Institute of Nursing Research (Contract No. HHSN2632012000074I, TO#5); National Institute on Aging (Contract No. HHSN263201200074I, TO#5); National Society of Genetic Counselors (unnumbered contract); Northrop Grumman Health IT (unnumbered contract); Pfizer Inc. (unnumbered contract); and P*h*RMA (unnumbered contract). The views presented in this publication do not necessarily reflect the views of the organizations or agencies that provided support for the activity.

International Standard Book Number-13: 978-0-309-30494-8
International Standard Book Number-10: 0-309-30494-6

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Suggested citation: IOM (Institute of Medicine). 2014. *Assessing genomic sequencing information for health care decision making: Workshop summary.* Washington, DC: The National Academies Press.

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

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. C. D. Mote, Jr., is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Victor J. Dzau is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. C. D. Mote, Jr., are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

.

PLANNING COMMITTEE[1]

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

PAUL R. BILLINGS, former Chief Medical Officer, Life Technologies, Carlsbad, CA

PAMELA BRADLEY, Staff Fellow, Personalized Medicine Staff, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD

PHILIP J. BROOKS, Health Scientist Administrator, Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD

ANN CASHION, Scientific Director, National Institute of Nursing Research, National Institutes of Health, Bethesda, MD

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

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

DEBRA LEONARD, Representative of the College of American Pathologists; Professor and Chair of Pathology at the University of Vermont College of Medicine; Physician Leader of Pathology and Laboratory Medicine at Fletcher Allen Health Care, University of Vermont College of Medicine, University of Vermont, Burlington

ROBERT MCCORMACK, Head, Technology Innovation and Strategy, Veridex, LLC, Raritan, NJ

VICTORIA M. PRATT, Representative of the Association for Molecular Pathology; Associate Professor of Clinical Medical and Molecular Genetics and Director, Pharmacogenomics Diagnostic Laboratory, Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis

JANET K. WILLIAMS, Representative of the American Academy of Nursing; Professor of Nursing, University of Iowa, College of Nursing, Chair of Behavioral and Social Science, Iowa City

[1]Institute of Medicine planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published workshop summary rests with the workshop rapporteurs and the institution.

IOM Staff

ADAM C. BERGER, Project Director
SARAH H. BEACHY, Associate Program Officer
TONIA E. DICKERSON, Senior Program Assistant (*until January 2014*)
MEREDITH HACKMANN, Senior Program Assistant (*from January 2014*)

ROUNDTABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH[1]

GEOFFREY GINSBURG (*Co-Chair*), Director, Center for Genomic Medicine, Institute for Genomic Sciences and Policy, Duke University, Durham, NC
SHARON TERRY (*Co-Chair*), President and Chief Executive Officer, Genetic Alliance, Washington, DC
NAOMI ARONSON, Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association, Chicago, IL
EUAN ANGUS ASHLEY, Representative of the American Heart Association; Director, Center for Inherited Cardiovascular Disease, Stanford University School of Medicine, Palo Alto, CA
PAUL R. BILLINGS, former Chief Medical Officer, Life Technologies, Carlsbad, CA
BRUCE BLUMBERG, Institutional Director of Graduate Medical Education, Northern California Kaiser Permanente, Permanente Medical Group, Oakland, CA
PAMELA BRADLEY, Staff Fellow, Personalized Medicine Staff, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD
PHILIP J. BROOKS, Health Scientist Administrator, Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD
ANN CASHION, Scientific Director, National Institute of Nursing Research, National Institutes of Health, Bethesda, MD
C. THOMAS CASKEY, Professor, Baylor College of Medicine, Houston, TX
ROBERT B. DARNELL, President and Scientific Director, New York Genome Center; Investigator, Howard Hughes Medical Institute, Heilbrunn Cancer Professor and Senior Physician, Head, Laboratory of Molecular Neuro-Oncology, Rockefeller University, New York
MICHAEL J. DOUGHERTY, Director of Education, American Society of Human Genetics, Bethesda, MD

[1]Institute of Medicine forums and roundtables do not issue, review, or approve individual documents. The responsibility for the published workshop summary rests with the workshop rapporteurs and the institution.

VICTOR DZAU, former President and Chief Executive Officer, Duke University Health System; Chancellor for Health Affairs, Duke University, Durham, NC

W. GREGORY FEERO, Contributing Editor, *Journal of the American Medical Association*, Chicago, IL

ANDREW N. FREEDMAN, Branch Chief, Clinical and Translational Epidemiology Branch, Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD

JENNIFER L. HALL, Representative of the International Society for Cardiovascular Translational Research; Associate Professor of Medicine, University of Minnesota, Minneapolis

RICHARD J. HODES, Director, National Institute on Aging, Bethesda, MD

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

GABRIELA LAVEZZARI, Assistant Vice President, Scientific Affairs, P*h*RMA, Washington, DC

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

DEBRA LEONARD, Representative of the College of American Pathologists; Professor and Chair of Pathology at the University of Vermont College of Medicine; Physician Leader of Pathology and Laboratory Medicine at Fletcher Allen Health Care, University of Vermont College of Medicine, University of Vermont, Burlington

TERI A. MANOLIO, Director, Division of Genomic Medicine, National Human Genome Research Institute, Rockville, MD

OLUFUNMILAYO F. OLOPADE, Walter L. Palmer Distinguished Service Professor of Medicine; Director, Center for Clinical Cancer Genetics; Associate Dean for Global Health, University of Chicago, IL

MICHELLE A. PENNY, Senior Director, Translational Medicine Group, Eli Lilly and Company, Indianapolis, IN

AIDAN POWER, Vice President and Head, PharmaTx Precision Medicine, Pfizer Inc., Groton, CT

VICTORIA M. PRATT, Representative of the Association for Molecular Pathology; Associate Professor of Clinical Medical and Molecular Genetics and Director, Pharmacogenomics Diagnostic Laboratory, Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis

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

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

JOAN A. SCOTT, Chief, Genetic Services Branch, Division of Services for Children with Special Health Needs, Maternal and Child Health Bureau, Rockville, MD

SAM SHEKAR, Chief Medical Officer, Health Information Technology Program, Northrop Grumman Information Systems, McLean, VA

KATHERINE JOHANSEN TABER, Director, Personalized Medicine, American Medical Association, Chicago, IL

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

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

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

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

JANET K. WILLIAMS, Representative of the American Academy of Nursing; Professor of Nursing, University of Iowa, College of Nursing, Chair of Behavioral and Social Science, Iowa City

Fellow

SAMUEL G. JOHNSON, American Association of Colleges of Pharmacy/American College of Clinical Pharmacy Anniversary Fellow

IOM Staff

ADAM C. BERGER, Project Director
SARAH H. BEACHY, Associate Program Officer
TONIA E. DICKERSON, Senior Program Assistant (*until January 2014*)
MEREDITH HACKMANN, Senior Program Assistant (*from January 2014*)

Board on Health Sciences Policy Staff

ANDREW M. POPE, Director
DONNA RANDALL, Administrative Assistant

Reviewers

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

Jonathan S. Berg, University of North Carolina at Chapel Hill
Robert C. Green, Brigham and Women's Hospital and Harvard Medical School
Kenneth Offit, Memorial Sloan-Kettering Cancer Center
John Pfeifer, Washington University School of Medicine

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Melvin Worth.** Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the rapporteurs 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 Assessing Genomic Sequencing Information for Health Care Decision Making and for the development of the workshop summary report. Federal sponsors are the Department of Veterans Affairs; Health Resources and Services Administration; National Cancer Institute; National Human Genome Research Institute; National Institute of Mental Health; National Institute of Nursing Research; and National Institute on Aging. Nonfederal sponsorship was provided by the American Academy of Nursing; American College of Medical Genetics and Genomics; American Heart Association; American Medical Association; American Society of Human Genetics; Association for Molecular Pathology; Blue Cross and Blue Shield Association; College of American Pathologists; Eli Lilly and Company; Genetic Alliance; International Society for Cardiovascular Translational Research; Kaiser Permanente Program Offices Community Benefit II at the East Bay Community Foundation; Life Technologies; Merck & Co., Inc., National Society of Genetic Counselors; Northrop Grumman Health IT; Pfizer Inc.; and P*h*RMA.

The Roundtable wishes to express its gratitude to the expert speakers whose presentations helped outline the challenges in as well as the opportunities for assessing genomic information for decision making. 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.

Contents

Boxes, Figures, and Tables

BOXES

FIGURES

TABLES

Abbreviations and Acronyms

AAP	American Academy of Pediatrics
ACMG	American College of Medical Genetics and Genomics
ASCO	American Society of Clinical Oncology
CED	coverage with evidence development
CMS	Centers for Medicare & Medicaid Services
CMTP	Center for Medical Technology Policy
CPB	clinical policy bulletin
CSER	Clinical Sequencing Exploratory Research
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EGD	effectiveness guidance document
EHR	electronic health record
ENIGMA	Evidence-based Network for the Interpretation of Germline Mutant Alleles
FDA	U.S. Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IMPACT	Integrated Mutation Profiling of Actionable Cancer Targets
IOM	Institute of Medicine
IRB	institutional review board

MEDCAC	Medicare Evidence Development and Coverage Advisory Committee
NCCN	National Comprehensive Cancer Network
QOPI	Quality Oncology Practice Initiative

1

Introduction[1]

Rapid advances in technology have lowered the cost of sequencing an individual's genome from the several billion dollars that it cost a decade ago to just a few thousand dollars today and have correspondingly greatly expanded the use of genomic information in medicine (Hayden, 2014). This trend is anticipated to continue as technologies advance and as research increases the understanding of the basis of human disease.

The clinical use of DNA sequence information relies on the identification of linkages between diseases and genetic variants or groups of variants. Depending on the clinical setting, large-scale DNA sequencing may be used to identify germline/inherited or somatic/acquired mutations. More than 140,000 germline mutation entries have been submitted to the Human Gene Mutation Database, a collection of mutations in genes that have been linked with inherited human disease (Stenson et al., 2003, 2014). ClinVar[2] is another resource which contains information about genetic variants and related phenotypes (Landrum et al., 2014). Additionally, almost 12,000 single-nucleotide polymorphisms[3] have been associated with various diseases, including Alzheimer's and type 2 diabetes, but the majority of associations have not been rigorously confirmed and may play only a minor role in disease (Cruchaga et al., 2014).

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

[2]ClinVar, http://www.ncbi.nlm.nih.gov/clinvar (accessed June 12, 2014).

[3]For the most current numbers, see: *A Catalog of Published Genome-Wide Association Studies*, www.genome.gov/gwastudies (accessed April 10, 2014).

Because of the lack of evidence available for assessing variants, evaluation bodies have made only a few recommendations for the use of genetic tests in health care. For example, organizations, such as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group, have sought to set standards for the kinds of evaluations needed to make population-level health decisions (EGAPP, 2014a).[4] However, due to insufficient evidence, it has been challenging to recommend the use of a genetic test (EGAPP, 2009, 2010, 2014b).

An additional challenge to using large-scale sequencing in the clinic is that it may uncover "secondary," or "incidental," findings[5]—genetic variants that have been associated with a disease but that are not necessarily related to the conditions that led to the decision to use genomic testing (Berg et al., 2013; Kohane et al., 2006). Furthermore, as more genetic variants are associated with diseases, new information becomes available about genomic tests performed previously, which raises issues about how and whether to return this information to physicians and patients and also about who is responsible for the information.

The value of genetic sequence information will depend on how it is used in the clinic, said David Veenstra, professor in the pharmaceutical outcomes research and policy program in the Department of Pharmacy at the University of Washington and chair of the workshop. Evidence is a driver of key health care decisions, and it is used to determine whether a treatment or procedure is reimbursed. "The focus of this meeting is to understand the processes that are being used to evaluate evidence" and to suggest pragmatic approaches that would address the challenges encountered during this process, Veenstra emphasized, but "not to identify a single process as the best [or] to try to establish what level of evidence is needed or what specific recommendations should be made."

Until better evidence becomes available, best practices could allow for making genomic-based clinical decisions in the context of abundant information but limited evidence. Exploring these best practices requires an understanding of how stakeholders gather and evaluate existing genomic evidence to make clinical decisions, to develop practice guidelines, and to decide whether to cover and reimburse the generation and use of genomic information. To help develop a better understanding of

[4]For more information, see Evaluation of Genomic Applications in Practice and Prevention, http://www.egappreviews.org/default.htm (accessed April 10, 2014).

[5]Presidential Commission for the Study of Bioethical Issues. Anticipate and Communicate. http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf. See Table 1.2 (accessed June 25, 2014).

how genomic information is used for health care decision making, the Roundtable on Translating Genomic-Based Research for Health of the Institute of Medicine (IOM) held a workshop in Washington, DC, on February 3, 2014.[6] Stakeholders, including clinicians, researchers, patients, and government officials, discussed the issues related to the use of genomic information in medical practice. The objectives for the workshop are outlined in Box 1-1.

ORGANIZATION OF THE REPORT

Chapter 2 summarizes the presentations of several representatives of research and clinical organizations who described how they gather evidence and how that evidence is assessed, graded, and evaluated for both inherited and acquired diseases. A particular focus of these presenters was the "actionability" of specific genetic variants—that is, whether these variants warrant clinical action—and how it is determined whether a specific genetic variant is actionable. In short, this chapter examines the foundations upon which clinical decisions involving genomic evidence are made; the details of how these decisions are made are discussed in the three chapters that follow Chapter 2.

BOX 1-1
Workshop Objectives

- Provide a forum for diverse stakeholders to present approaches for assessing genome sequencing information for clinical use.
- Compare and contrast evidence evaluation processes for different clinical indications and across stakeholders.
- Discuss key challenges in the evidence evaluation process.
- Elicit pragmatic approaches to facilitate the effective translation of genomics into the clinic by improving evidence-based policy development.

[6]The workshop agenda, speaker biographical sketches, full statement of task, and registered attendees can be found in Appendixes A–D. For more information about the workshop, see http://www.iom.edu/Activities/Research/GenomicBasedResearch/2014-FEB-03.aspx (accessed July 11, 2014).

The use of genomic information to make patient care and health decisions is examined in Chapter 3. The specific issues covered in this chapter include what evidence is used to make the decision whether to use large-scale sequencing or a more targeted (e.g., gene panel) approach, the role of patient preferences in deciding on testing, and what information is disclosed to the patient.

Chapter 4 focuses on the process of developing clinical guidelines. In addition to describing how the guidelines process is being applied to next-generation sequencing, the chapter also covers challenges to developing guidelines and the use of recommendations for developing practice guidelines.

Decisions made about the coverage and reimbursement of genomic tests are examined in Chapter 5. Private and government payers explained their perspectives on the process used to evaluate genomic or multi-panel sequencing for reimbursement as well as on the criteria used for deciding on coverage.

The final chapter of this workshop summary reviews the major themes that developed over the course of the workshop, as identified by individual speakers. These themes include consistency of gathering, analyzing, grading, and reimbursing the collection of genomic data; developing collaborations for generating and applying genomic data; and considering patient preferences when using genomic information in the clinic. Other topics were also addressed by a panel of discussants, including the challenges for genomic medicine; two such challenges that individual workshop participants identified are a lack of evidence and a lack of sequencing standards.

2

How Evidence Is Gathered and Evaluated

Important Points Highlighted by the Individual Speakers

- While targeted mutation and gene panel testing are more technically complete than exome sequencing, exome information can be useful for carrier screening, disease diagnosis, and pharmacogenomic testing.
- Rare variant databases and other databases that include both genotype and phenotype information can be valuable shared resources for clinicians and researchers to aid in disease diagnosis, gene–phenotype associations, and drug development.
- A transparent, reproducible, evidence-based method for determining variant actionability is helpful when individual experts have different opinions about what variant information should be returned to patients.
- The actionability of genomic findings depends on the clinical context, such as whether testing is done before conception, prenatally, for newborn screening, during childhood, or for screening, diagnostic, or monitoring reasons.
- "Binning" the genome on the basis of clinical validity and clinical utility and other staged approaches can facilitate pre-test informed consent, analysis, and post-test return of results.
- Given how resource-intensive the process of evaluating variant evidence is, a collective effort using a standardized assessment approach and shared variant databases would be helpful in leading to more efficient variant curation.
- Improving the communication between testing laboratories and clinics would make it possible to update genotype–phenotype information as new data are collected.
- Technical issues—from gene coverage during data collection to bioinformatics interpretation of the data—vary and can impose limits on the information that can be derived from whole-exome or whole-genome sequencing unless they are standardized by the genomics community.

During the workshop a variety of experts in academia and the private sector described current research and clinical perspectives concerning the ways in which genomic data are being generated and linked to human diseases and applied to the practice of medicine. The topics covered during the presentations and discussions included the sources of genomic data, various processes such as "binning" genomic findings into categories with different degrees of actionability, systematic approaches to evaluating gene–phenotype associations, and a collaboration to create a curated resource that can help standardize the interpretation of genetic variation. Other topics addressed were the gathering, assessment, and evaluation of evidence for use in next-generation sequencing in cancer genomics; how new information is reviewed in the context of existing information; and how variant information can be shared more widely.

GATHERING DATA

In recent years, many gene panels have been introduced into the clinical setting, noted Madhuri Hegde, professor of human genetics and executive director of the Emory Genetics Laboratory. The targeted mutation and gene sequencing panels are technically complete in that they cover all the exons of a gene and the entire mutation spectrum of a gene, including point mutations, insertions–deletions, copy number variability, and deep intronic pathogenic changes. By contrast, while exome sequencing covers more overall genes, the majority of the genes covered by exome sequencing are not clinically relevant, and for those genes that are clinically relevant, exome sequencing may not have complete coverage of all exons and may not cover the full spectrum of mutations, Hegde said. Despite this incompleteness, however, exome sequencing can still collect evidence important in assigning genes to a disorder, and it can be useful in yielding information relevant to carrier screening and pharmacogenetic markers.

There is a "critical need in our community to establish what is the [essential] amount of data [for including] a gene in a genetic test," said Heidi Rehm, director of the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine and assistant professor of pathology at Harvard Medical School.

Many of the gene panels being offered today have a highly variable number of genes for the same indication, partly because of different evaluations of the evidence for a gene–phenotype association (Rehm, 2013).

Even in the case of a targeted panel where phenotypic information can be gained from the results, complementary assays often need to be included with the gene panel, Hegde noted. For example, with the gene panel for short stature, methylation-based assays are necessary. Whether a gene panel works in a clinical setting therefore "depends on which disorder you are looking at," Hegde said.

Exome sequencing can be used for either clinical or research purposes, though recently the boundaries between the two have been blurring. In Hegde's laboratory, exome data are divided according to why the sequencing is being done. For new disease presentations the diagnostic yield, or likelihood that the test will provide enough information to make an appropriate diagnosis, ranges roughly from 30 percent to 40 percent, depending on which laboratory is reporting and what kinds of cases are considered, Hegde said. When writing clinical reports, she said, it is critical to sorting the data into categories of what can be interpreted in the clinic and what is clinically actionable (see Box 2-1).

BOX 2-1
Contextual Usage of Clinical Actionability, Validity, and Utility

- **Clinical actionability:** in the context of incidental findings or in an asymptomatic individual, the degree to which an intervention exists that can mitigate harm before a clinical diagnosis is made.
- **Clinical validity:** the accuracy and reliability of a variant for identifying or predicting an event with biological or medical significance in an asymptomatic individual.
- **Clinical utility:** the usefulness of information in clinical decision making and in improving health outcomes.

Genomic Sequencing in Oncology

In the past, oncologists have based treatment largely on traditional immunochemistry, pathology, and, more generally, anatomical staging, said Mark Robson, attending physician of the clinical genetics and breast cancer medicine services in the Department of Medicine at Memorial Sloan–Kettering Cancer Center. Now next-generation sequencing is creating a massive experiment in whether knowing the pattern of genomic aberrations will allow therapies to be targeted more effectively. "Although everybody is very enthusiastic about it," Robson said, "whether or not we are going to be able to achieve better outcomes on a global scale throughout the cancer population still remains to be seen."

Most cancer centers are using targeted assays rather than whole-exome or whole-genome sequencing to look at a variable number of genes that have been selected according to an a priori rationale for involvement in the oncogenetic or oncologic process. For example, the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) panel probes for biologically or clinically relevant cancer genes (Wagle et al., 2012). Many of the genes are linked to cancer only through somatic mutations, but most of the germline predisposition syndrome genes are included on these panels as well, because many of them are also involved in carcinogenesis in nonhereditary contexts, Robson said.

In the clinical context, mutational profiling is used for variants that are clearly linked to response to a U.S. Food and Drug Administration (FDA)-approved drug, that define clinical trial eligibility, or that are plausibly predictive of response to an approved drug which might not otherwise have been chosen. Variants linked to response to an approved drug have already been defined through the companion diagnostic mechanism, though the companion diagnostic development process can be extremely complicated (IOM, 2014; McCormack et al., 2014). Similarly, variants used to define clinical trial eligibility have generally already been defined.

The more challenging area involves variants that are potentially predictive of response to an already approved drug. "In other words," Robson said, "you send the test off to [a] commercial entity, get back a series of variations, and now you pull [a drug] off the shelf and use it." This determination depends on such factors as whether the variant is germline or somatic, whether the link is biologically plausible, the prevalence of the allele for somatic mutations, whether the primary tumor or metastatic

disease has been analyzed, and whether a drug or a combination of drugs is available to use.

The optimal interpretation of a somatic sequence requires the sequencing of normal tissues, Robson said. Sorting out driver and passenger mutations can be very difficult, but finding that something is present in a tumor and not present in the germline is at least an initial piece of evidence that could be relevant to the cancer process. However, if there is a germline alteration, it may not be seen when comparing the two sequences, as many algorithms subtract germline from somatic variants found during sequencing (Bombard et al., 2013). Using next-generation sequencing techniques to generate data and compare germline and somatic mutations has also shown promise for identifying variants that are associated with susceptibility to cancer (Stadler et al., 2014).

SOURCES OF DATA

Databases for Genomic Case Reports

Databases could be useful repositories for finding information about genes with weak disease associations or with unknown significance. For example, Rehm told of how a patient with the rare disease distal arthrogryposis type 5, a condition related to congenital joint contracture, underwent genome sequencing even though at the time the disorder had no known genetic etiology. Because this patient had unaffected parents, a de novo cause of disease was suspected, Rehm said.

Sequencing the genomes of the patient and the parents revealed two such de novo variants, one of which was quickly ruled out as a common loss-of-function mutation in that population. The remaining variant was a candidate, but there was no evidence to indicate it was causative of the disease, because everyone has de novo variants that are not necessarily related to a phenotype. Rehm and her colleagues contacted a researcher who studied the PIEZO2 protein, the product of the gene in which the variant appeared, and in this way they learned about a second family with a mutation in the same gene who had the same phenotype. The interaction "gave us enough evidence to claim a true causal association with this gene and that phenotype," Rehm said (Coste et al., 2013).

One cannot expect serendipity to produce such findings too often, so Rehm and her colleagues are working to establish a database to house genomic cases. Various groups have contributed exome and genome data

along with phenotype information to a database that Rehm has developed. The data will be searchable and structured in a way that will allow for the identification of genetic commonalities among phenotypes. This is, she said, "a more robust, international approach to solving these very rare cases in both a clinical testing arena as well as a research context."

ClinVar and ClinGen

The ClinVar variant database is designed to provide a freely accessible, public archive of reports of the relationships between human genetic variations and phenotypes (Landrum et al., 2014). All of the information being generated in Rehm's laboratory is also being submitted to ClinVar so that the community can benefit from that information. "By putting a lot of this data that we come across [from] clinical testing and research testing into a common environment," Rehm said, "that then provides a list of variants that either a researcher or a pharmaceutical company could . . . study. If they don't know what variants are out there, there is no project to be done." The individual efforts of institutions to gather and evaluate evidence can be scaled to benefit the larger genomics community through databases such as ClinVar, Rehm said. Data, including benign variant assessments, are deposited here for sharing it more broadly.

The Clinical Genome Resource, or ClinGen, is a collaboration among research groups dedicated to combining research data with data from clinical tests as well as expert curation to determine which genetic variants are most relevant to patient care (NIH, 2013). As part of this effort, the research groups are examining the standards and processes for evaluating genes and variants and genetic disorders in order to move toward more standardized procedures, said Jonathan Berg, assistant professor in the Department of Genetics at the University of North Carolina at Chapel Hill.

ClinGen starts with the variants, Berg said, so the first step in the effort has been to encourage laboratories to submit data to the project. The next step is to gather phenotypic information about patients in whom the variants are found, along with evidence from the laboratory indicating whether a variant is pathogenic or benign or if there is not enough evidence to be certain. The final step is to understand the clinical validity of gene–phenotype associations, which will provide a standardized framework for curating these associations. "If we can bring that information all together with standardized language and using the same vocabularies to describe what we're talking about, then we will have a computational

resource that can be mined for clinical validity and the associations of these variants to disease," he said.

ClinVar is part of the ClinGen collaboration, and together these resources will have a number of valuable uses, Rehm said. For example, they could enable the community to define what the best assays are for assessing a particular gene or disease model. "When you come up with a variant, you can turn toward the appropriate assay . . . and know where you could get it done," she said.

THE ELEMENTS OF ACTIONABILITY

Clinical actionability (see Box 2-1) requires both technical accuracy and interpretive accuracy, which together produce high specificity in terms of predictive value. It is important, Berg said, that such an intervention not impose undue hazards to an individual, whether psychosocial, medical, or financial.

Because individual expert opinions vary considerably, there is a need for a transparent, reproducible, evidence-based method for determining whether an identified variant is clinically relevant, Berg said. Thus Berg and his colleagues have divided the concept of actionability into several specific elements that give a semi-quantitative assessment of actionability for every gene–phenotype pair:

- *Severity of a disease*, which is typically the most severe possible outcome
- *Likelihood of a severe outcome*
- *Effectiveness of an intervention* to mitigate the severe outcome
- *Acceptability of the intervention*, with consideration given to all the hazards of the intervention
- *State of the knowledge base*, including knowledge about the gene–phenotype association, disease manifestations, and interventions

Each of the 5 elements receives a score from 0 to 3, for a total score of between 0 and 15. Thresholds can be set for dividing variants into bins indicating whether the variants have clinical utility or clinical validity or the clinical implications are unknown (Berg et al., 2011). (More details are provided later in this chapter in the subsection labeled "Binning the Genome.") Different users could set the thresholds in different places, which provides the system with a measure of flexibility. "It balances the

benefits of the information versus the harms of the information, the paternalism of the physician's duty to warn versus not doing any harm, and patient preferences for their right to know and not to know," Berg said.

In addition to being flexible, the advantages of this system are that it is transparent and less subjective than expert opinion, with a clearly defined evidence base, Berg said. Furthermore, some of the workload can be crowd sourced—for example, in the analysis of the consistency or variability of scores. Different end users can use the information in various ways, weighing the parameters depending on the scenario of interest to the particular user (for example, research, diagnostic testing, healthy adults, or newborn screening). Finally, scoring can be revisited as new information becomes available.

This system could be useful in the context of other efforts, such as the return of incidental findings. For example, when Berg and colleagues used Berg's system to compare 200 genes sorted into bins with a recent list of variants in 56 genes for which the American College of Medical Genetics and Genomics (ACMG) recommends returning information to individuals,[1] they found variability in what different groups consider actionable (Green et al., 2013) (see Figure 2-1). The spectrum of actionability raises the question of whether the threshold has been set too low for the ACMG list because, for example, a number of genes on that list score only between 7 and 10 using Berg's methodology.

As Robert Green, director of the Genomes to People Research Program in Translational Genomics and Health Outcomes in the Division of Genetics at Brigham and Women's Hospital and Harvard Medical School, observed, thousands of genomes were being sequenced, and physicians were becoming uncomfortable with the idea that potentially lifesaving information discovered in sequencing data was not being reported. The ACMG recommendations were crafted to address this issue. The recommendations propose reporting specific mutations found in those 56 genes to physicians regardless of the indication for which the clinical sequencing was ordered.

With the information in hand, physicians are able to decide what to do with it while taking patient preferences into account. "You can have a

[1]Following much discussion over the ACMG Genome Sequencing Return of Results guidelines issued in March 2013, ACMG has since updated their recommendations to include an "opt-out" option for patients undergoing whole exome or whole genome sequencing. For more information, see ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results, https://www.acmg.net.docs/Release_ACMGUpdates Recommendations_final.pdf (accessed June 11, 2014).

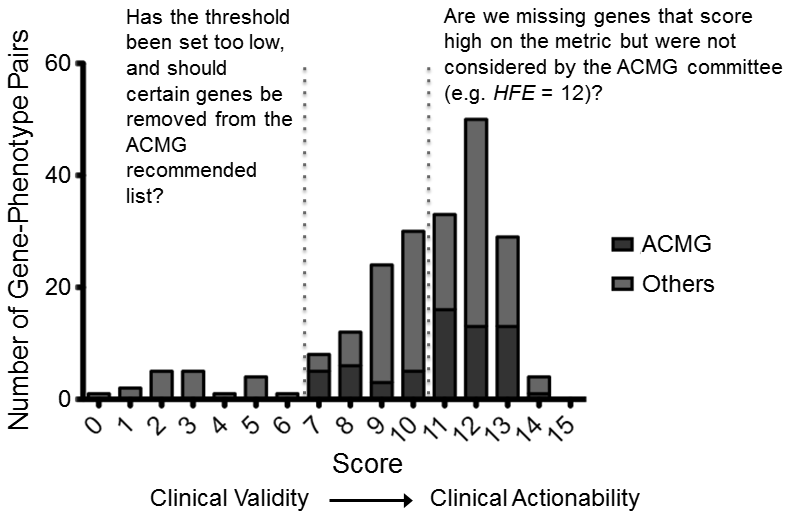

FIGURE 2-1 Application of Berg's binning metric to genetic variants demonstrates variability in which variants different groups would consider actionable.
NOTE: ACMG = American College of Medical Genetics and Genomics; *HFE* = hemochromatosis gene
SOURCE: Jonathan Berg, IOM workshop presentation, February 3, 2014.

very clear conversation with a patient about what they do not want to hear about, and you can respect that," Green said. Berg asked whether some genes not included in the ACMG list, such as those involved in hemochromatosis, for example, should be considered for addition because of their high scores on the metric he developed.

The Medical Exome Project

Hegde's group has taken an approach to qualifying evidence that is different from Berg's. The production of a *medical exome*—the subset of a human genome consisting of the more than 4,000 genes that have been identified as clinically relevant and that can be adequately covered—will require evidence about each gene and a technically complete assay, Hegde said. To do this, Hegde's laboratory has collaborated with the Children's Hospital of Philadelphia and Partners HealthCare Laboratory

for Molecular Medicine to create the Medical Exome Project, a "highly curated gene resource and a technically optimized assay to provide a stepping stone for standardizing the interpretation of genetic variation." The goal of the project is to develop a "medically enhanced exome" capture kit that covers all clinically significant genes so that when physicians are trying to diagnose a patient, they will have confidence that the known clinically relevant genes have complete coverage. Achievements to date have included increasing the coverage of known relevant cardiomyopathy genes from 85 percent to close to 99 percent.

The members of the project have defined the medical exome, Hegde said, by starting with all genes that have possible or proven disease associations, then curating to eliminate false-positive disease association claims, and doing iterative curation to remain current. The Medical Exome Project has worked closely with the ClinGen project to set up a four-tier classification scheme for genes (see Table 2-1). It also went through a pilot curation phase that found many incorrect gene–phenotype associations.

This is a time-consuming process; it takes about 5 hours per gene with at least 2 people researching and curating the gene data. With approximately 4,000 clinically relevant genes, Hegde said, "it is going to take a tremendous amount of [curation] time," with many of the genes eventually being discarded because of a lack of evidence.

TABLE 2-1 Proposed Gene Classification Criteria

Evidence Level	Description	Criteria
0	Gene of undetermined (no studies available) or unlikely significance	**Undetermined:** No reported evidence **Unlikely:** Evidence arguing against role in disease
1	Gene of "uncertain significance" (studies available but insufficient to draw conclusions)	Single or few studies, variants, and families reported **AND** segregation not established **OR** no human studies reported but strong animal model data with relevance to human disease
2	Probably disease associated	Single or few studies, variants, and families reported **AND** limited segregation observed
3	Definitely an established disease gene	Multiple studies, variants, and families reported **AND** significant segregation and or strong functional evidence

SOURCE: Madhuri Hegde, IOM workshop presentation on February 3, 2014.

The Medical Exome Project is working on standardizing assays that will be publicly available for assessing variants, Hegde said. Through the Jain Foundation,[2] Hegde and her colleagues have been assessing the biological significance of the variants of unknown significance of dysferlin, a protein involved in muscular dystrophies. By working with the Jain Foundation to acquire clinical data from patients, Hegde's group is generating information about the variants, which will be submitted to ClinVar, Hegde said.

ACTIONABILITY DETERMINATION

Actionability depends on the clinical context in which a genetic test is performed, said Katrina Goddard, senior investigator with the Kaiser Permanente Northwest Center for Health Research, in agreement with Berg. For example, actionability can be different depending on whether testing is done for the purposes of prenatal testing or newborn screening versus being performed during adulthood for disease screening (or preconception carrier testing), diagnostic, or monitoring reasons.

In the EGAPP working group with which Goddard has been involved, genes and conditions related to adult screening and predictive testing were proposed for full evidence review and evaluation based on the recommendations of subject matter experts or on the priorities of funding agencies. Topics then were selected for full review and evaluation based on the availability of evidence and other criteria.

Actionability was defined for adult incidental findings on the basis of the following three questions, Goddard said:

- Is there a practice guideline or systematic review for the genetic condition?
- Does the practice guideline or systematic review indicate that the result is actionable in *one or more* of the following ways?
  - Patient management
  - Surveillance or screening
  - Family management
  - Circumstances to avoid
- Is the result actionable in an undiagnosed adult with the genetic condition?

[2]Jain Foundation, http://www.jain-foundation.org (accessed April 22, 2014).

The group also decided that some areas were not actionable, such as incidental findings that are not related to the indication for testing at the end of a "diagnostic odyssey" where a patient or family has been searching for the explanation of a phenotype, findings that are not relevant for all patients in the EGAPP clinical scenario for reproductive decision making, and findings related to personal utility because they may not be actionable in a clinical context.

While results may not be clinically actionable, Berg said that just finding a molecular explanation for a patient's previously unexplained symptoms and ending a diagnostic odyssey can have significant personal utility for the patient and his or her family. The information provided in a report to the patient from a test for such a case may be helpful but the report would not necessarily contain information about variants of uncertain significance. For general clinical use, genomic incidental or secondary findings would not be considered to be part of the routine report. While variants that have sufficient clinical actionability should be part of a routine clinical report, consistent with the ACMG recommendations, other classes of conditions that are clinically valid but have insufficient clinical actionability would be subject to more careful consideration on the part of the patient and clinician about whether a patient would prefer to be given such information, Berg said.

Genomic testing at Washington University uses a definition of actionability with components that are very similar to those described by Goddard in that practice guidelines for the genetic condition exist and that professional society practice guidelines recommend action for the purposes of patient management, surveillance or screening, family management, and circumstances to avoid. However, Shashikant Kulkarni, director of cytogenomics and molecular pathology at the Washington University School of Medicine, added that actionability also implies that medical interventions based on new results are effective and that actions are acceptable to the individual in terms of burdens or risks.

Actionability in Oncology

At Memorial Sloan–Kettering Cancer Center, a consensus-based approach is taken for reviewing potential actionability for genomic findings. As Robson explained, a multidisciplinary panel of individuals with expertise in basic science, drug development, clinical trial design, assay development and interpretation, and computational biology and biostatistics does a case-by-case evaluation of the evidence. For a tumor specific

driver mutation, actionability relates to whether a targeted therapeutic is indicated and available while for a deleterious germline mutation, actionability relates to mutation penetrance and the efficacy of available preventive medical interventions.

Incidental germline findings from tumor profiling are reported only in discovery studies with approval from the institutional review board (Yang et al., 2013) and only with proper consent. A multidisciplinary panel within the institutional review board (IRB) reviews the findings and decides whether to initiate the process of contacting the physician and patient. The actionability criteria remain "a bit fluid," Robson said, and discussions have centered on what level of risk justifies contact. Very high penetrance predispositions, such as those associated with *BRCA1* and *BRCA2*, are relatively straightforward to make decisions about. But variants that confer more modest risks are more problematic. For example, a test result may not be directly relevant for the person who was tested but could be relevant for family members. This remains an issue even with knowledge gained from sequencing specimens from patients who are deceased. Reaching out to family members in such circumstances can be difficult, but this information can be extremely relevant to their health. Today these decisions are being worked out largely on a case-by-case basis, Robson said.

METHODS FOR ASSESSING GENETIC VARIANTS

The vast majority of genetic variants have no known clinical relevance. The challenge, Berg said, is therefore to parse through variants to determine which ones can be used to inform clinical decisions. This process requires setting a high bar for which variants from a genome-scale test to report; otherwise, reporting variants with unknown clinical validity (see Box 2-1) or unknown implications for the asymptomatic patient's health could potentially have negative impacts, such as patient concern about a test result or unnecessary medical costs for testing that may not be clinically useful. Different people may hold different views on the benefits and risks of obtaining genetic information, so individual preferences factor into decisions on whether to return results to patients. Variants reported to physicians and to patients need to be those that can be incorporated into clinical care in an evidence-based fashion, Berg said.

Binning the Genome

Berg and colleagues have developed an a priori structured framework for handling genomic findings that they described as "binning" the genome (Berg et al., 2011). The framework is organized according to the concepts of clinical validity and clinical utility (see Box 2-1), and the binning is intended to facilitate pre-test informed consent, analysis, and post-test return of results. Use of the framework makes it possible to avoid "one-off" decisions that may not be consistent from one patient to the next. "Ideally," Berg said, "we should know what we're going to do with different classes of variants up front, so that when we are analyzing the data and we come across something, we know how we will handle it."

The first step of the binning process is to categorize gene–phenotype pairs into bins according to the clinical actionability elements that Berg described earlier as well as to the risk for psychosocial harm. The second step defines the types of variants that should be reported. For example, known pathogenic variants are reportable, while likely pathogenic variants require further scrutiny before reporting. The third step is to sort an individual's variants computationally into predetermined bins. Only variants that meet defined bin criteria are reviewed and reported, and new evidence triggers new determinations of how a variant is binned, Berg said.

Using this framework, Berg and his colleagues developed three bins (see Figure 2-2). Bin 1 includes variants that meet clinical utility criteria based on the medical literature and are therefore defined as medically actionable; examples include variants that are known or presumed to be deleterious. Bin 2 includes variants that have clinical validity but not clinical utility. Because of the lack of evidence for clinical action, the return of results to patients for these variants will depend on the individual patient's interest in receiving the information balanced with any undue stress that may come with learning of the information. The amount of distress that the results could bring to patients is considered by dividing Bin 2 into low-, medium-, and high-risk information. Finally, Bin 3 includes all of the variants that have unknown clinical relevance related to phenotype, outcome, or clinical intervention.

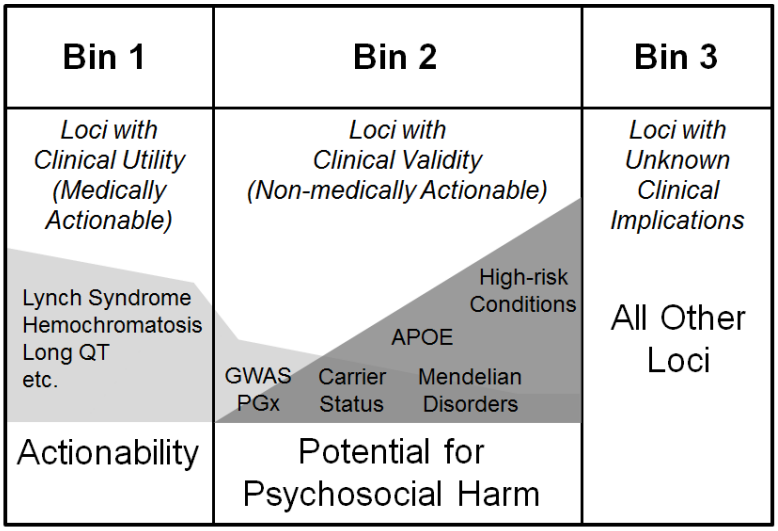

FIGURE 2-2 Genetic variants can be sorted into three bins depending on the level of clinical utility.
NOTE: *APOE* = apolipoprotein E gene; GWAS = genome-wide association study; Long QT = Long QT syndrome; PGx = pharmacogenomics.
SOURCE: Jonathan Berg, IOM workshop presentation, February 3, 2014.

Systematic Evidence Gathering and Actionability Determination

The recognition of weaknesses in gene–phenotype associations has led those in Rehm's laboratory to take a more systematic approach to evaluating and scoring the evidence. The approach divides gene–phenotype associations into the following categories: definitive, likely, weak, uncertain or unknown, and no association. Because the numbering systems currently in use vary and can cause confusion, some groups have moved away from labeling these or similar categories with numbers. Although it will take time and significant effort, it is important for those in the field to come to a consensus on a standard system for labeling variants, Rehm said. Genes in Rehm's first category—"definitive"—are included in predictive tests and can be returned as incidental findings, while genes in the first two categories—"definitive" and "likely"—are included in diagnostic panels where the patient already has a phenotype.

Rehm and her colleagues comprise one of three groups that are working together to define the content for newborn genomic screening. The groups have been using the same categorical gene–phenotype association-based approach described earlier, but they are structuring the

data for making decisions about what should be returned to patients with respect to the age of onset of the disease, the inheritance pattern, penetrance, the phenotype category, and the availability of a clinical test. More than 600 genes have been evaluated, with approximately 3,000 to go, Rehm said. "We hope that by structuring this data, it will allow groups to make cutoffs and decisions about what we think should be returned to individuals."

As part of the Clinical Sequencing Exploratory Research (CSER) consortium,[3] Goddard said, the NextGen project is integrating whole-genome sequencing into preconception carrier status testing and evaluating the downstream costs and use versus those of the current standard of care. Through expert analysis, surveys, and focus groups, the project is gathering information from participants about whether they want to receive results for preconception carrier status screening in various health categories (see Table 2-2). The hope is to gain a better understanding of

TABLE 2-2 Actionability Categories for Pre-Conception Carrier Status Screening

Category	Description
Shortened lifespan	Most children do not live past early childhood, even with medical intervention.
Serious	Most children will have medical problems that require regular medical visits, daily medications, carefully monitored diets, or surgeries; or will have serious problems with learning, vision, hearing, or mobility. Children may have shortened lifespans into early childhood.
Mild/moderate	Most children will have medical problems that require occasional extra medical visits, occasional medications, a slightly modified diet, or surgery; or will have mild problems with learning, vision, hearing, or mobility.
Unpredictable	It is difficult to predict the outcome for many children with these conditions. Some children will have more serious versions but others will have a more mild version or no problems at all.
Adult onset	Few have any symptoms as children, but medical, behavioral, vision, or hearing problems may begin as adults.

SOURCE: Katrina Goddard, IOM workshop presentation, February 3, 2014.

[3]More information is available at https://cser-consortium.org (accessed May 16, 2014).

what types of carrier status results patients will be interested in receiving in the future, Goddard said.

Three-Stage Evaluation Process

The evaluation process used to determine which results to return to patients for projects such as NextGen consists of three stages, Goddard said. The first stage is a preliminary assessment to determine whether sufficient information is available to do a full review. In this stage, the actionability concepts described earlier as well as variant penetrance and whether the condition is a significant and important health problem are considered. If the condition does not meet one of these criteria, a full review will not be undertaken. The objective of this stage is to provide a rapid mechanism for determining which conditions do not have sufficient information to warrant further evaluation.

In the second stage, an evidence-based process for each specific gene–phenotype pair is documented in a summary report. Reproducible search methods are used to identify studies and data, which are restricted to systematic reviews, evidence-based practice guidelines, or expert consensus-based practice guidelines. Each gene–phenotype pair is summarized in about two pages, with a goal of keeping the summaries brief, transparent, and reproducible. "This is not a comprehensive method, and we are aware of that, but that was [a] pragmatic choice," Goddard said. To assess the data, it is sorted into evidence tiers (see Box 2-2) to address expected disagreement among sources and to signal the overall quality of sources. Quality ratings are used as tie-breakers for conflicting evidence at the same tier. In Stage 3 the summary produced in Stage 2 is used by a decision-making group—whether EGAPP or another group—to make recommendations.

BOX 2-2
Tiers of Evidence

During the data assessment stage, Goddard said, information is categorized into tiers of evidence to classify the source of data and its quality. Those tiers are:

- **First Tier:** Evidence from a systematic review, meta-analysis, or clinical practice guideline based on a systematic review[a] of the objectives, methods, findings, and other criteria.

- **Second Tier:** Evidence from clinical practice guidelines or broad-based expert consensus with some level of evidence review, but using unclear methods or using sources that were not systematically identified.
- **Third Tier:** Evidence from another source with non-systematic review of evidence (e.g., GeneTest Reviews, OrphaNet, Clinical Utility Gene Cards, and the opinion of fewer than five experts), with additional primary literature cited.
- **Fourth Tier:** Evidence from another source with non-systematic review of evidence (e.g., GeneTest Reviews, OrphaNet, Clinical Utility Gene Cards, and the opinion of less than five experts) lacking citation of primary data sources.

[a]Systematic review according to the Cochrane Handbook. For more information, see http://handbook.cochrane.org (accessed May 6, 2014).

Methods for Variant Annotation in Cancer

In 2011 the Washington University School of Medicine began offering next-generation sequencing in addition to the other genomic tests it performs. Because of the school's particular expertise, it focused on cancer genomics. Curating genomic variants has proven to be a huge task, Kulkarni said. "If the germline is that difficult, consider how difficult cancer variation data curation could be."

A bioinformatics team is needed to analyze the sequencing data after it is generated, Kulkarni said. Even in the case with a 42-cancer gene panel, there is too much information to process manually, so a software system was designed to perform base calling, alignment, variant calling, and genome annotation in a semi-automated way. In the first phase, custom scripted software programs facilitate an automated step in which the data are compared against publicly available gene information and clinical and mutation terms. Criteria for the searches are set such that relevant papers must contain human data and one or more mutations and must describe a clinical outcome. Where there are commonalities in these three areas, an annotation worthiness score is generated for each variant, and the information is deposited into a searchable spreadsheet for the next phase.

Following this automated process, an external group of six annotators reviews the data over several months. A second evaluation is conducted by the clinical fellows and attending physicians at Washington

University School of Medicine, Kulkarni said. Variants are classified into five levels, which are based on the ACMG guidelines:

- Level 1—Predictive or prognostic in tumor type (includes inherited cancer susceptibility variants).
- Level 2—Predictive or prognostic in another tumor type or types.
- Level 3—Reported in cancer or other disease.
- Level 4—Variant of unknown significance.
- Level 5—Known polymorphism.

The data are then made available on a wiki-based user interface where other clinical fellows and attending physicians could review and modify information about the variants. Presentation of the results sorts the variants by level, with an interpretation of the role of the variants and references to the medical literature. The resulting report provides information about the variant and related data, as well as the ability to examine each step of the variant annotation filtering process. During monthly meetings, new evidence is collectively reviewed. "This is a very comprehensive effort," Kulkarni said, "and it's ongoing because there is a lot of new information coming out . . . on these cancer genes."

Since March 2012 about 1,500 clinical tests have been ordered, not including those from clinical trials, Kulkarni said. The tumor types tested cover a broad range, including brain, colorectal, lung, pancreatic, and sarcomas and the initial findings suggest that about 45 percent of sequenced cases have specific actionable mutations in targetable genes, including *EGFR*, *KIT*, *KRAS*, and *PIK3CA*, he said.

Challenges

Workshop participants described a number of challenges for the future. For example, more than 50 million genetic variants have been found in the human genome, Rehm said, with many of them unique to individuals, and misinterpretation of these variants can affect clinical care and study outcomes.

The vast majority of the variants seen in clinical testing and research studies are rare, which makes it difficult to generate sufficient evidence to make a claim. For example, Rehm said, diagnostic testing of 15,000 probands for a variety of hereditary disorders and for somatic cancer revealed about 1,600 variants reported as either pathogenic or likely patho-

genic; in this case, 68 percent of those variants were seen only once, and 96 percent of the variants were seen fewer than 10 times. Based on testing conducted in Rehm's laboratory, about one-third of the variants are categorized as having uncertain significance. "Our community will need to develop better approaches to evaluating these variants and their impact," she said.

The challenge is even greater for the return of incidental findings from exome or genomic sequencing. Rehm cited data from the MedSeq project that indicated that each patient in the study had 20 to 40 variants that had been published as disease causing or as pathogenic (Vassy et al., 2014). However, when these variants were reviewed with strict criteria for pathogenicity, 97 percent were excluded, most of them being uncertain, and many having clear evidence for being benign. Similarly, 30 to 50 variants were linked with loss of function in disease-associated genes in a MedSeq study, but strict review of the evidence determined that 94 percent of these variants did not meet the criteria for pathogenicity. "This is a lot of work with a low yield as we look through patients' genomes," Rehm said.

The group is now working to develop better guidance on the interpretation of sequence variants, and a draft of that guidance is expected to be ready for the community in the coming months, Rehm said. A further complication, she noted, is that the evidence constantly changes, so that new information needs to be returned to patients tested in the past. Berg agreed, noting that information will need to be updated over time. A system developed by Partners HealthCare, which features e-mails sent to physicians with new information that can be inserted into patients' electronic health records (EHRs), has been "very effective," Rehm said.

Future challenges include continuing to seek the right balance between brevity and comprehensiveness of the assessments and determining whether to relate variants on genes to conditions, Goddard said.

There are certain challenges that come with Kulkarni's approach to assessing variants for clinical use. It would be possible to scale the system to a large number of genes and variants, Kulkarni said, although it requires a large amount of upfront work. For example, a team of six annotators worked for 6 months on the initial 28-gene-variant curation, sorting out the variants based on given criteria. Additionally, both algorithmic and knowledge-based variant curation methods are necessary for clinical interpretation, and annotating and keeping up with variant management is expensive. As a result, there is an urgent need for implementing universal standards and a variant resource database, he said. Fortunately,

this work does not all have to be done by one organization, but rather can be done collaboratively.

Kulkarni observed that ethnicity is considered in the review of annotations, but more data need to be generated from different racial and ethnic groups. He also noted that data is available through the International Consortium of Cancer Genomics, which has data from different population groups, though in this area, too, more information from different groups is needed. Goddard identified concerns over extrapolating data from high-risk populations to the general population and considering the variation among individuals. For example, X-linked conditions are more relevant for males, and conditions with variable penetrance have different risks depending on the strength of family history.

UPDATING EVIDENCE

New data is often produced that can trigger the reinterpretation of a variant–disease link, but a key question is how those data should be communicated broadly so that clinicians and laboratories are working with current information. Perhaps, Berg said, this needs to be an ongoing process such that new evidence would initiate new reviews through a system that could be triggered by inquiries from physicians, researchers, or patients. The reclassification strategy developed at Emory University was designed so that clinicians could generate or point to evidence that a gene is probably not related to a disease, Hegde said. "The labs cannot do it on their own," she said. "The number of variants of unknown significance has grown so much [that] you can imagine how much time it takes for the lab to go through all those variants and reclassify them. It is a huge help for us if the clinicians actually approach us."

The ACMG guidelines require that a testing laboratory make an effort to contact physicians who previously tested patients in the event that new information changes the initial clinical interpretation of the sequence variant, Hegde said. To fulfill this guideline, the Emory Genetics Laboratory has set up a Web-based system to release updates on all the variants seen and analyzed by the laboratory (Bean et al., 2013). As variants are reclassified, the system automatically scans the internal database and identifies previously affected patients. It then sends an alert to laboratory directors and issues amended reports. In addition, the system reclassifies variants based on outside requests, with the information then returned to clinical targets.

Asking physicians to provide clinical data can be challenging because they are often too busy to fill out data forms, Rehm said. Nevertheless, these data can be extremely important—for example, when an affected patient in a family tests negative for a variant. "As a community, we need to underscore the importance of the dynamic relationship between the lab and the physician if we hope to improve our understanding of genomic variation," Rehm said. Berg agreed, noting that the paperwork needed to report on a variant can seem particularly extensive in the context of a pressured clinic. "There needs to be better mechanisms for physicians to be able to supply the phenotypic information to the labs in a structured format," he said, "because I think that adds to the specificity of the analysis." There are also challenges of how much clinical information can be shared because of Health Insurance Portability and Accountability Act (HIPAA) issues.

Data Quality

Related to the issue of updating variant information is a concern over the reproducibility of data in the literature. When published studies do not include complete procedures or the primary data are not accessible, it makes evaluating the quality of the data difficult. Rehm noted that the ClinGen project and the ClinVar database are creating a structured mechanism that requires the authors of a paper to make the raw data available so that their results can be verified and extended in a transparent way. But published associations that are inaccurate remain an unresolved problem, because the act of publishing data is often misconstrued as providing a quality piece of evidence in and of itself. Similarly, Hegde observed that important data may not be available in a database, may be out of date, or may be expensive to access. ClinVar will be important for that reason because it will be a free and open database. Other efforts, such as the Global Alliance for Genomics and Health, are also working on ways to responsibly share genomic and clinical information across groups (Callaway, 2014).

Standardized methods for rating quality in the field of genomics do not yet exist, Goddard said. Berg, too, pointed out that "there is really no specific definition of what constitutes a proven gene–phenotype association. There are certainly genes that we know because the evidence is compelling and overwhelming, but then you get to the many gene–phenotype associations based on a couple of case reports or a handful of families, and there are no specific guidelines to say this is where you draw the line."

There is also the issue of an evidence gap when there is no synthesized evidence in the literature to rely on for evaluating gene–phenotype pairs. When this occurs, we need to prioritize our reviews, Goddard said, so that researchers and clinicians do not spend too much time addressing gene–phenotype associations that have no systematic review or practice guideline that can be referred to.

Kulkarni added that an ideal situation dealing with these evidence gaps would be for researchers to have sufficient tools to model and assess disease progression, clonal evolution, and response to therapies. Maybe in 5 to 10 years, he said, we will have a Clinical Laboratory Improvement Amendments–certified mouse facility for treating primary, secondary, and metastatic tumors from the same patient and then reporting the results back to the clinic.

One collaborative approach to assessing data has been taken by the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Consortium,[4] an international consortium that is taking a multidisciplinary, multi-institutional approach to understanding the involvement of all variants of uncertain significance in *BRCA1* and *BRCA2* that may be related to breast and ovarian cancers, Robson said. The members of this organization have pooled their clinical expertise, their data, and their laboratory capabilities to resolve issues of evidence involving breast cancer predisposition genes.

TECHNICAL ISSUES

There are also technical issues with DNA sequencing that make interpretation of evidence difficult. Rehm said out that no whole-genome sequencing effort today is complete in covering all regions of the genome or detecting all types of variation including substitutions, insertion–deletions, copy number variations, structural variants, and gene fusions. In addition, the bioinformatics techniques applied to raw sequence data in different labs can produce differences in sequences. Finally, the interpretive process can vary from laboratory to laboratory, resulting in different

[4]Evidence-based Network for the Interpretation of Germline Mutant Alleles Consortium, http://enigmaconsortium.org (accessed April 22, 2014).

interpretations of results due to variation in data filtering, alignment, variant calling, quality thresholds, and annotation. "There are so many levels today that are non-standardized and distinct that you will often get different results for different reasons," Rehm said. "Those are all aspects of this process that we, as a community . . . need to address."

On the subject of assessing the comparability of genome sequencing results from different laboratories, Hegde observed that the College of American Pathologists has a next-generation sequencing committee that is working on a database for proficiency testing and cross-validation of variant detection. Select variants will be confirmed by Sanger sequencing, and then the data will be shared more broadly. "This is very important because, as we just heard, these platform differences are significant," Hegde said. Rehm added that the ClinVar database will help in this regard because it will provide transparency where interpretations differ. When data are submitted to ClinVar, a quality control report is generated that describes where the submitter's variant interpretations differ from those that are already in the system.

There is also a disadvantage for clinical laboratories in that they generally cannot do functional assays for the biological relevance of variants they observe, Hegde said. Instead, they need to connect with a research laboratory to work on a particular gene or disease. But researchers who have worked on a gene or disease in the past may no longer have the funding to do more research in that area. "The question of how you can do a biological relevance assay is a big one," Hegde said. Berg agreed, adding that there is an opportunity here for researchers who have robust assays and who can reproducibly separate benign from pathogenic variants in order to overcome these types of technical challenges. However, resources would be necessary to complete the work, he said.

Berg acknowledged the complexity related to genetic variants. Variants are interpreted as being pathogenic or benign with respect to particular disorders, but a given gene can be involved in multiple disorders. "Figuring out how you define pathogenicity means you have to explicitly link the pathogenicity assertion to the gene and the disease that is related to it," Berg said. Additionally, curation of variants of unknown significance can be more than a technical challenge because the level of understanding of the basic biology of the gene, protein, and pathway involved can influence how variants of unknown significance are classified.

Electronic Health Records

Genomic information needs to be available in some way, but various barriers exist to making it available through an EHR, such as the capacity of the record, Berg said. Rehm noted that the issue has been discussed in the past and that the thinking has been that the information should not be in an EHR. Only a percentage of the variants in genomic data have been rigorously confirmed, and these can be interpreted and put in a report that goes in the EHR. "The consensus right now is you can update [information] that you've already put there," she said, "but we are not ready to expose the 5 million variants in a genome to an environment where a clinician queries that, finds a variant, and goes and treats a patient when in fact that was an incorrect call." This view may change as the technology advances, she added, "but we are not there yet."

3

Patient Care and Health Decisions

Important Points Highlighted by the Individual Speakers

- Nurse practitioners, specialists, genetic counselors, social workers, and researchers compose a team that may be used to take a shared decision approach to genomic testing when gene panel results do not provide enough information to make a diagnosis.
- Individual patient preferences, accessibility, coverage, and reimbursement are all taken into consideration when deciding whether to order genetic and genomic testing.
- Taking a large gene-panel approach to sequencing may cost less than sequencing genes individually and provides an opportunity to collect more information faster; however, obtaining extra information that may not have clinical relevance can make clinical decision making more complicated.
- Identifying a process for producing consistent, reliable, and easy to understand genetic and genomic testing reports will enable patients to have greater trust in the information and how it is used for disease diagnosis and treatment.
- When little evidence exists for deciding when to obtain genetic or genomic data, a traditional approach of collecting family history and physical examination information can be used to inform the choice.

The clinic can be thought of as an interface where patients and clinicians convene for discussing the use of using genomic information to inform clinical decisions, said Gregory Feero, research director at the Maine–Dartmouth Family Medicine Residency program. For example, he said, it can be difficult for both clinicians and the most informed patients to sort through evidence related to genomic testing and to make decisions based on the available information. Feero asked the audience to consider that most patients will not be seen at large academic medical centers and that implementing these processes for evidence evaluation and making decisions about health could be even more challenging at smaller hospitals and clinics around the country. The accessibility of sequencing technologies also depends on its coverage by health insurance companies and on the affordability of what is not covered, as patients are increasingly more responsible for paying for their health care.

GENETIC TESTING IN A CARDIOLOGY CLINIC

In her work as a nurse practitioner with a specialization in genetics, Kathleen Hickey, an assistant professor of nursing and a family/adult nurse practitioner in the Division of Cardiology at Columbia University, is usually the first member of the health care team to interact with patients and families who have inherited cardiac disease. Cardiomyopathy—a group of disease characterized by enlarged heart muscle that can weaken over time and pump blood less efficiently—can be inherited, as is the case with hypertrophic cardiomyopathy, for which 50 to 60 percent of probands have a mutation in one of several genes involved in the sarcomere (Cirino and Ho, 2008).

A team-based approach is beneficial to diagnosing and treating cardiomyopathy patients. For example, Hickey said, during a cardiology visit a patient may encounter team members who are collecting a three-generation pedigree, asking targeted questions to detect the signs and symptoms of genetic conditions, providing counseling and education, working to support the patient and the patient's family, and monitoring treatment. Nurse practitioners can be part of that team. They can order tests, including electrocardiograms, echocardiograms, and genetic testing, within the scope of their practice. Nurse practitioners play a key role in helping individuals understand the complex language of genomics,

Hickey said. "Nurse practitioners are often the ones to hear a lot of additional details from patients, such as episodes where a patient passed out but did not think it was important enough to tell a physician."

In the Cardiac Electrophysiology Clinic at Columbia University Medical Center, clinical assessment findings inform decisions to order genetic testing for disease diagnosis. For example, a microarray panel for gene variants associated with hypertrophic obstructive cardiomyopathy would be ordered for a patient with echocardiogram findings of left ventricular hypertrophy along with reported episodes of syncope, or fainting. Other targeted panels (e.g., Brugada Syndrome or Long QT syndrome) are ordered for patients with characteristic changes on electrocardiograms (e.g., a prolonged QT interval) and associated family histories. In Hickey's current practice, targeted panels are preferred to whole-exome sequencing; however, next-generation sequencing is a future consideration, particularly in cases where targeted panels do not provide insight on a diagnosis.

In one case, an otherwise healthy woman in her mid-20s suffered an out-of-hospital cardiac arrest despite having no family history of cardiac problems. The patient's electrocardiogram, echocardiogram, and other test results were unremarkable, as was a genetic panel for sudden cardiac arrest arrhythmia. "She was young, she was planning her wedding, and she wanted answers as to why she had this cardiac arrest," Hickey said.

A "roundtable-type discussion" was held between the patient and her health care team, which consisted of a cardiac electrophysiologist, a genetic counselor, a social worker, and sometimes a basic scientist, and the decision was made jointly that whole-exome sequencing should be the next step. Whole-exome sequencing revealed a rare variant, and after database searches in the United States, Europe, and elsewhere, the team identified two other individuals with the same variant who were diagnosed with idiopathic ventricular fibrillation. "That helped us in her care management," Hickey said, and the patient underwent placement of an automatic internal cardiac defibrillator.

GENETIC TESTING IN A CANCER CLINIC

A large-scale project at the University of Michigan is sequencing tumor and germline dyads as part of the CSER consortium, said Jessica Everett, clinical instructor of internal medicine and a genetic counselor in the Cancer Genetics Clinic at the University of Michigan Comprehensive

Cancer Center. Cancer may seem to include a limited number of conditions, but in fact it is extremely complex, Everett said. Over the past 9 years at the University of Michigan Health System, almost 3,000 new patients have been seen with 21 different conditions in 15 different laboratories, and 3,800 individual genetic tests have been performed, creating a significant amount of data to sort through. Other CSER-funded projects include the Baylor College of Medicine's BASIC3 or Baylor Advancing Sequencing into Childhood Cancer Care which explores the use of blood and tumor exome sequencing for newly diagnosed pediatric patients with solid tumors (Parsons et al., 2013).

Next-generation sequencing, including the use of large gene panels, is "a game changer" with both positive and negative considerations for use in clinical practice, Everett said (Robson, 2014). Next-generation sequencing requires the evaluation of risks, benefits, and limitations for each patient. However, it can be less costly than previous approaches, because testing individual genes over time could cumulatively cost more than $25,000, while a large gene panel may cost about $5,000 total. Another advantage of next-generation sequencing is that it can get results in much less time than a step-wise testing approach. "A panel gives you the ability to do everything faster," Everett said.

Furthermore, this large-scale approach can generate additional clinically useful information compared with earlier approaches. For example, a family could carry additional mutations or exhibit mosaicism, which next-generation sequencing can identify. This may be especially helpful for patients who are on a diagnostic odyssey.

Other benefits of next-generation sequencing in cancer include the promise of expanded knowledge of phenotypes for a given mutation, better understanding of the clinical utility of lower penetrance or less studied genes, and generation of data for research and discovery without added cost.

Everett also described some of the limitations of using panels in cancer genetics. Identifying mutations where clinical utility is unclear can complicate risk assessment and clinical recommendations. Furthermore, she said, data generated for research on a small scale needs to be shared in order to be useful to others.

DECIDING WHEN TO USE LARGE-SCALE SEQUENCING

Emory University's Medical Genetics Clinic has about 1,500 visits per year, with about 30 new patients per week, said Michael Gambello,

section chief of the Division of Medical Genetics at the Emory School of Medicine. About 85 percent of the patients in the Medical Genetics Clinic at Emory are pediatric, and 15 percent adult, and most of the clinic's cases involve rare diseases. Indications include developmental delay, autism, and a family history of genetic disease. Typical questions asked by parents and patients include What's wrong with my child or with me? What caused it? What can be done about it? More broadly, from a research perspective, the study of rare diseases can be thought of as a chance to implement tools and procedures that will later be used in applications of genomic medicine to much larger populations, Gambello said.

It is clear that whole-exome sequencing can help identify the genes involved in Mendelian disorders. For example, a particular genetic disorder may involve so many genes that it is better to use a broad test (i.e., a microarray test panel) than one that focuses on just a few suspect genes. While large-scale sequencing can be used in this situation, there is little evidence to provide guidance on its first-time use in the clinic, Gambello said. He teaches his students that clinical reasoning and a targeted approach is good medicine. "We do a family history, we do a physical examination, and we make a differential diagnosis, which is the mainstay of medicine," he said. "Then we decide what test is likely to make a diagnosis."

In deciding whether to do large-scale sequencing, Gambello largely follows the ACMG guidelines (ACMG Board of Directors, 2012), which recommend such testing when:

- A condition is likely genetic, but no specific genetic test is available.
- A condition is a genetic disorder, but so many genes are involved that it is better to test many.
- A condition is likely genetic, but targeted tests have not yielded a diagnosis.
- A fetus likely has a genetic disorder, but targeted tests have not yielded a diagnosis.

As an example, Gambello described a pediatric patient with a movement disorder that was likely genetic. Targeted tests did not yield a diagnosis, so the team decided to use whole-exome sequencing. The sequencing results revealed a nonsense mutation in a novel gene called *NGLY1*. A group at Duke University had reported a patient with a similar variant a year earlier, and serendipity led to a connection with a Stanford

researcher, which resulted in a study of eight patients with *NGLY1* deficiency, which affects an endoplasmic reticulum–associated degradation pathway and is associated with neurological dysfunction (Enns et al., 2014). "That certainly has ended the diagnostic odyssey for this family," Gambello said. "Has it given us any insight into how to treat this disorder? No, it hasn't. But we have a lot of people thinking about this disorder now, and maybe there will be treatment soon."

A PATIENT'S PERSPECTIVE

Many questions surround the variants that are revealed—or, in some cases, not revealed—by next-generation sequencing. A basic question is what is known and how reliable that knowledge is. Neuroscientist Amy Hower described how she gained a better understanding of how patients comprehend and process information during a diagnostic odyssey when she and her parents underwent whole-exome sequencing to see if she could find the underlying cause of her cardiomyopathy with ventricular tachycardia after exhausting all other options. "The decision is not just about my health," she said, "but if I want to have children, it could affect the life and the health of my children." Surprisingly, Hower said, sequencing turned up several candidate genes. However, because most of the variants were novel, they were not clearly actionable. "Because further functional testing would be needed in order to assign definitive causation, . . . I am at the beginning of my search."

There were also limitations to how much Hower thought she could trust the information. For example, Hower knew through newborn screening that she has the most common variant for cystic fibrosis as a carrier, but that variant was not uncovered by sequencing. Sequencing can have trouble detecting insertions and deletions and clearly cannot find everything, Hower observed, but she was also told that the top three hits from her sequencing information would be Sanger confirmed, yet according to her laboratory report, only the first two were. When her genetic counselor checked with the laboratory, the lab said that all three were confirmed. "If the report was that wrong," she asked, "then can I trust what was done?" The report also left Hower uncertain about how the top three hits were selected.

Another concern was that it was difficult or impossible to interpret from the report itself some aspects of how the test was done. As a scientist, she was at an advantage compared to most patients, few of whom

may be able to understand the report at this level, Hower acknowledged. The information contained in the report should be written as a material and methods section of a well-written peer-reviewed journal article, she suggested.

There were other findings concerning Hower that were unreported, such as a frameshift or splice site mutation in a gene now known to be related to the disease. "A splice site mutation in a gene that is expressed in the heart, and expressed in the right pathways to possibly cause the problems that I have, would probably be . . . a better candidate than two of the three that I got back," she said. But that information was not routinely provided to her physician (although it could be requested), so it was more difficult to personally weigh in on that information, she said. Also unreported were unknown variants in known genes, the parameters for defining relevance, and the actual coverage of the sequencing.

Additionally, in order for her physician to receive the raw data, Hower was asked to waive her rights to receive any raw data herself. Because she did not agree with this approach, the wording of the consent was altered after discussion.

DISCUSSING RESULTS WITH PATIENTS

Concerning how and to what extent the results of next-generation sequencing should be discussed with patients, Hickey said that, in order to put genetic results in context, she and her colleagues try to relate the results to a patient's condition and family history. Rather than relaying an entire panel of results gene by gene, they provide a general overview. In some cases, however, patients have done research, read the scientific literature, and want to know about detailed results, and for such patients the best approach may be to review the results of individual genes. "We try to make it very individualized," she said.

Everett noted that she has a tendency to group genes into bins when returning results to patients. She and her colleagues provide more information about genes known to be highly penetrant and less information about genes that may have less to do with cancer. She and her colleagues also tend to do less talking at the beginning and more talking later as patients have more questions.

Gambello pointed out that money is one of the reasons for talking less at the beginning. "Money is time, and we've not talked once about paying for all this genetic counseling," he said. "That's an issue that we

need to deal with, because we talk about spending all this time with these patients, and then, of course, none of our administrators want to pay for it. That's something to consider." Gambello also drew an analogy with prescribing pharmaceuticals, when physicians do not discuss with a patient every single possible adverse effect of a drug. "In some respects, we are finding ourselves in a similar situation," he said. "I don't know what the answer is, but there are only so many hours in a day, and I think you have to do the best you can."

Hower reported that she was generally pleased with how the findings deemed most important by the laboratory were reported, despite her qualms about some aspects of that reporting. She added that she would not expect her physician to go through the results gene by gene. But she did say that she would like the results to be accessible, especially because additional research may reveal a variant in a new light.

Health Literacy

Studies have shown that many patients have a relatively poor understanding of cancer genomics (Pellegrini et al., 2012). For example, Everett said, among breast cancer patients at French cancer centers who were interviewed about treatment decision making, only 20 of 37 had some understanding or knowledge of genomic testing. Among these, half thought that genomic testing referred to or included constitutional or germline analysis, she said.

Gambello agreed that patient understanding depends heavily on the level of education of the patient. Most patients do not ask the kinds of questions Hower described in her talk, he said, but some do. Gambello said that his patients tend to want all of the information generated in hope of coming to a diagnosis. Laboratory consent forms play an important role in these interactions because they help with the delivery of results to patients and parents. In Gambello's clinic, almost all of the patients and parents have wanted the information, although he has not yet had to deal much with the return of incidental findings.

Hickey's practice serves the diverse population of New York City, and the patients in that practice have various levels of health literacy and come from a wide variety of socioeconomic backgrounds. Access to care is an overarching issue, as is health literacy as it applies to patients' ability to comprehend complex genetic information. "Most patients, in a period of about 30 minutes or so, are completely saturated with information that we're providing," she said. Patients receive a general information

guide to take with them, available in both English and Spanish, which defines some general terms. Patients also have access to online resources.

Patient Preferences

It is difficult to elicit patient preferences about the disclosure of sequencing results without biasing their responses about which genomic information they would like to receive, Everett said. "Our personal attitudes about whether or not we think that information is valuable almost certainly color our interactions." One way to gauge the effects of these interactions would be to ask patients once information has been disclosed to them whether they would change their decisions in light of what they have learned. Additionally, Everett continued, the biggest distinction patients seem to make in deciding how much information to receive is whether something can be done on the basis of a genetic finding. Consent forms are helpful, but often they do not provide any context for the decisions that need to be made. In that respect, patients who have experience with a condition from someone else in their family have more background than patients who do not. The University of Michigan project received CSER funding in 2013 to address these issues. Most people adjust to the information they receive, Everett said. "They learn to cope with these diagnoses and work with them." Even when people are given a prognosis that they are at increased risk of Alzheimer's disease, they "do pretty well with that information," she said.

In their Michigan Oncology Sequencing Center project, Everett and her colleagues are studying patient preferences concerning the return of results (Roychowdhury et al., 2011). Cancer patients who have advanced or refractory disease and who are eligible for clinical trials will undergo whole-genome sequencing of their tumors and whole-exome sequencing of both tumor and germline DNA. The team takes a four-generation pedigree and then discusses the sequencing of the cancer genome and the germline, including the reasons for doing both. The team also responds to patient questions about family history or the testing process, discusses consent for the return of results, and reviews a flexible informed consent default plan for return of results. Of the 167 patients who enrolled through April 2013, almost all of them said that they wanted to receive germline findings, Everett said. Slightly fewer people want the information in a pediatric context, a finding that needs more study.

The findings from germline testing are separated into bins for disclosure, Everett said. Previously reported pathogenic mutations in high pen-

etrance cancer genes with known clinical utility are disclosed, while alleles associated with low to moderate cancer risk with an evolving or unknown clinical utility are disclosed only on a case-by-case basis. Mutations associated with autosomal recessive conditions are not disclosed, with the exception that all germline findings relevant to the current cancer are communicated.

With support from a Robert Wood Johnson Foundation Nurse Faculty Scholar Award, Hickey and colleagues have studied more than 50 patients to find out how they integrated information from cardiac genetic testing into their lives. Overall, they found a positive cardiac genetic diagnosis did not negatively impact a patient's well-being as self-reported through a quality-of-life measure (Hickey et al., 2014).

Patient preferences are very important, Hower said. "For example, because a result could affect the health of my children, I need an answer within a time frame that would be useful for preconception consideration." Patient preferences also factor into disclosure of information. "My opinion is, it's the patient's data, and it should be the patient's choice," she said. Furthermore, patients will need access to data if they change health care providers or specialists, if a laboratory goes out of business, or if updates to the data become available, Hower said. Insurance should not cover next-generation sequencing for someone who has no reason for getting it, Hower added. "If the patient preference doesn't make sense, then the clinician should be free to say so."

Because the data belong to the patient, the patient should be able to decide whether to receive reports of incidental findings, Hower said. "For me personally, I wanted full disclosure because I think it could be useful for preventive care." The ACMG recommendations support this position, though even more information with frequent updates and expansions would be desirable, she said. With relatively few variants confirmed through Sanger sequencing, a patient may have to pay for confirmation to be sure about a variant. Finally, a gene may be involved in more than one disease, and if a patient does not receive information about a gene, a secondary connection to a disease could be missed.

Hower said that she has leaned toward permitting her genetic information to be shared, without too much concern over privacy and security. This is mainly, she said, because "I want an answer, and the more people I release this information to, the more likely I will be able to get useful data. And the more of us who put the data out there, the more useful it becomes."

Everett observed that many cancer genetics clinics are working with laboratories that may or may not decide to include their information in publicly available databases. Any decision to not share such data is unfortunate because it is impossible to predict which information might prove critical in figuring out the answers to key questions.

It is also important to take patient preferences into account, Hickey said. In her practice, patients participate in the decision making for their treatment, including whether to undergo an invasive therapy such as the implantation of an automatic internal cardiac defibrillator, whether to initiate drug therapies with possible severe adverse effects, whether to receive information on incidental findings, whether to conduct screening of other family members, and whether to join a support group. Other strategies for engaging participants in studies are developing such as dynamic consent (Kaye et al., 2014). "Knowing our patients and presenting those options to them is critical," said Hickey.

REIMBURSEMENT CONSIDERATIONS

Coverage and reimbursement by insurance is "certainly a consideration when ordering testing in the clinical setting," Hickey said. (Reimbursement issues are covered in more detail in Chapter 5.) For patients who are uninsured, Columbia University determines payment on a case-by-case basis. Targeted cardiac panels can cost more than $3,000 each, and whole-exome sequencing for an individual and two parents is about $9,000, she said.

Gambello agreed that reimbursement definitely plays a role in ordering genomic tests. Sixty percent of the Medical Genetics Clinic patients receive Medicaid, which does not reimburse for whole-exome sequencing. Requests for the exome sequencing of inpatients for consultations are invariably reviewed by the pathology department before they are ordered. If the tests are deemed to not be required for the acute care of a child's admission, the requests will be denied. Because of this situation, discussions need to occur more often between the genetics and pathology departments about reasons to order large-scale sequencing, Gambello said. Patient out-of-pocket costs also factor into decisions about which test to order.

In some cases, research funds are available to counteract financial limitations. For instance, it may be possible to refer patients to the Centers for Mendelian Genomics at Baylor College of Medicine and Johns

Hopkins University School of Medicine to defray expenses. Waiting just a couple of years could allow prices to drop for whole-exome sequencing. Occasionally, philanthropic support is available. "I have a lot of patients that I would love to do an exome on, and we just don't have the funding," Gambello said.

Reimbursement did play a role in ordering a whole-exome test, Hower said. She suggested that next-generation sequencing should be covered by insurance for diagnostic purposes, just as smaller or more targeted kinds of sequencing would be covered. "If it's useful for your health and your life and even your offspring's life and health," she said, then it seems like it should be covered.

Clinicians will need to continue to evaluate targeted versus large-scale sequencing while also taking into account financial considerations, patient understandings and needs, and evidence-based recommendations, Gambello said. "Most physicians don't think like geneticists, so if we want these tests to eventually trickle down into general medicine clinics, there need to be evidence-based recommendations."

4

The Development of Practice Guidelines

Important Points Highlighted by the Individual Speakers

- Developing clinical practice guidelines for next-generation sequencing is complicated by the large amount of data and by underdeveloped evidence supporting clinical validity and utility and the time-consuming process of evidence review.
- An important element of guideline development is collecting feedback on implemented practice guidelines, including use and adherence information that could be used to inform revisions.
- The use of genomic information can be guided by established medical ethics principles for clinical practice and research, including autonomy, beneficence, non-maleficence, and justice.
- Obtaining informed consent from and providing genetic counseling for patients undergoing large-scale genome sequencing is essential to patient-centered care; opportunities remain to ensure consistent counseling by qualified clinicians across the health care delivery spectrum.

One objective in adopting clinical practice guidelines is to help standardize the application of genomic data in medical care. Workshop participants discussed processes and principles for developing guidelines for the clinical use of next-generation genome sequencing as well as various challenges, such as which principles should guide return of results for pediatric patients, test affordability, and who should order genetic testing and be responsible for discussing the results with patients. While rigorous processes exist for developing clinical guidelines, such as those in oncology, development can be time consuming and may not meet the demands of the field.

GUIDELINE DEVELOPMENT: LESSONS FROM ONCOLOGY

As is the case in many other fields of medicine, the oncology community is trying to come to grips with the rapidly emerging trove of genomic-driven data, said Gary Lyman, a full member in the Cancer Prevention Program, Public Health Sciences Division, at the Fred Hutchinson Cancer Research Center. Lyman addressed the active, rigorous process that the American Society of Clinical Oncology (ASCO) uses for developing clinical guidelines. He noted that the challenges of genomic-driven cancer medicine were summarized in a paper in a special issue of the *Journal of Clinical Oncology* with the following questions (Garraway, 2013):

- What mutation profiling approaches will enable genomics-driven cancer medicine?
- What interpretive frameworks are necessary to render complex genomic data accessible to oncologists?
- What clinical trial designs will be optimal for evaluating the utility of tumor genomic information?
- How will oncologists and patients handle the return of large-scale genomic information?

In the paper, two conclusions were drawn: "Oncology has served as a unique proving ground for genomic-driven medicine," while oncology has also highlighted a "well-recognized pitfall—the risk that large-scale genomic data generation can emerge without an evidence-based clinical approach to data analysis and interpretation" (Garraway, 2013).

"We have a great deal of work to do," Lyman said. As emerging technologies lead to an ever-increasing volume of genomic data, the evidence for clinical utility goes down, he said. Lyman referred to this situation as a "paradox."

The ASCO approach to developing clinical practice guidelines predates, but is mostly consistent with, the IOM standards for the creation of trustworthy clinical practice guidelines (IOM, 2011), Lyman said. The IOM standards call for a transparent guideline development process; management and disclosure of conflicts of interest; multidisciplinary expert panels; rigorous systematic reviews of existing evidence; grades for strength of evidence and strength of recommendations; standardized and clear recommendations; external review, including public comment; and a plan for revising and updating. The ASCO protocol starts with topic selection for clinical practice guideline development, followed by the appointment of a steering committee to define the relevant questions and facilitate a systematic review of published research with explicit criteria for inclusion and exclusion. A volunteer expert panel of stakeholders (vetted for conflicts of interest) examines the extracted body of evidence and generates recommendations, which undergo multiple levels of internal and external review (but no public comment), feedback, and modification. The recommendations are then disseminated through publication in the *Journal of Clinical Oncology*, ASCO's website, and other venues.

This process poses a dilemma, however, Lyman said. While the oncology society strives for an ideal, methodologically rigorous approach that is consistent with the IOM standards, the process is time consuming when dealing with cancer, which encompasses hundreds of distinct diseases involving different subsets or clinical scenarios. As a result, about 60 guidelines have been generated over 20 years, but many more guidelines are actually needed, Lyman said. One challenge is completing guideline development in a reasonable timeframe when the process often depends on volunteer experts. Typically, it requires a "champion" to expedite the process. "While there are other approaches that are more efficient or expedient," he said, "we are trying to find the right balance right now as we approach next-gen sequencing in the cancer arena."

Published ASCO clinical practice guidelines to date include several guidelines for testing select genetic mutations or molecular biomarkers to assist with the prevention, screening, or treatment of breast cancer, gastrointestinal cancer, colorectal cancer, and prostate cancer, among others, Lyman said. The selected mutations or biomarkers are evaluated for their clinical validity, or their ability to predict health outcomes, as well as for

their clinical utility. A set of recently developed guidelines focuses on biomarkers that might guide treatment decisions in early-stage breast cancer (Lyman et al., 2014).

The ability to capture how whole-genome sequencing tests are being used and what the outcomes are, perhaps in registries or other types of observational studies that could support guideline development, is extremely important, Lyman said. Several other experts also mentioned the need for more clinical annotation of the genetic data that are available. Lyman noted that ASCO is investing in a national initiative called CancerLinQ (Cancer Learning Intelligence Network for Quality), which is attempting to compile, analyze, and annotate clinical information on patients in real time, including their treatments, side effects, and, where available, tumor genomic or molecular profile information, with the goal of eventually including clinical decision support. With genomic and biomarker information integrated, the project offers the potential for mining this database to formulate hypotheses for improving cancer care that can be tested in randomized clinical trials, Lyman said.

Soliciting feedback on practice guidelines is of critical interest to ASCO. As part of the Quality Oncology Practice Initiative (QOPI), ASCO is integrating guideline recommendations as quality indicators for assessment and certification of cancer specialists. As clinical genomics guidelines are developed, Lyman said, QOPI can provide information about adherence to guideline recommendations. Moreover, ASCO plans to build the QOPI quality indicators into CancerLinQ, so that data on adherence to recommendations and validated clinical outcomes in patients seen in community oncology practices can be routinely accessed by guideline-development panels and other stakeholders. Hopefully, this will happen in the next 2 or 3 years, Lyman said.

MAKING GUIDELINES

The main reason why physicians order genetic testing for patients is to make a diagnosis, said Howard Saal, professor of pediatrics at the University of Cincinnati College of Medicine. Chromosome microarray analysis has increased the ability to determine a diagnosis by about 10 to 15 percent, Saal said, and next-generation sequencing may increase diagnoses by up to 25 percent, according to a recent study (Yang et al., 2013). Because genome sequencing is being used more broadly in clinical practice today and it is predicted that one day all newborns will be

sequenced to inform health care throughout their lives (Collins, 2010), it would be helpful to study how much front-line physicians understand about genome sequencing and its applications and also to develop guidelines for the use of this sequencing in various populations.

To study how genome sequencing is being incorporated into medical practice today and how physicians are responding to it, Green is currently working on a clinical trial, the Medical Sequencing (MedSeq) Research Project, which is part of the CSER consortium.[1] MedSeq is designed to test the hypothesis that primary care physicians will be overwhelmed by genomic information in their practices and find it difficult to negotiate this new kind of medical information, Green said. A one-page whole-genome summary report has been designed to distill results into different groupings—monogenic disease risk, carrier disease risk, pharmacogenomics associations, and blood group antigens—for clinicians to review. In addition, primary care physicians receive training in clinical genomics through a 6-hour orientation course. "In the first 20 or 30 disclosures that we are into right now, we are not finding that these admittedly volunteer, adventurous primary care docs are overwhelmed or frightened or compromised by the data," Green said.

Individual populations, such as pediatric patients, present unique challenges which require consideration and guidance. In a separate study, BabySeq, Green is examining sequencing in healthy newborns or in those who received care in neonatal intensive care units. Part of the study will examine the perspectives of parents who have this "book of life" genomic reference for their baby's future medical care from that day forward, Green said. Preliminary data captured from parents before the BabySeq clinical trial started and within 24 hours of giving birth revealed that the majority of those asked were at least "somewhat interested" in exploring genome sequencing for their newborns.[2]

Saal participated in generating updated guidelines on ethical and policy issues in genetic testing of children which were jointly released by the American Academy of Pediatrics (AAP) and ACMG in 2013 (Committee on Bioethics et al., 2013; Ross et al., 2013). The 2013 AAP/ACMG guidelines do not specifically address the newer genome sequencing technologies, but the rules for those technologies would be essentially the same, Saal said. The same ethical principles that doctors

[1]More information is available at https://cser-consortium.org (accessed July 11, 2014).

[2]The BabySeq Project, http://www.genomes2people.org/babyseqproject (accessed April 28, 2014).

learn in medical school—a respect for autonomy, beneficence, non-maleficence, justice, and so on—apply to genetic testing.

The first recommendation for genetic testing and screening of children is that decisions about the genetic testing of children should be driven by the best interests of the child. The recommendations advise offer-offering genetic and genomic testing in the context of genetic counseling that informs parents and patients about benefits, risks, and possible outcomes. Under the principle of respect for autonomy, it is important to obtain informed consent and assent for genetic testing, just as would be the case with any other diagnostic test; parents, guardians, and competent children should receive comprehensive pre-test genetic counseling, and Saal pointed out that patients need to receive further genetic counseling to understand the results. In addition, he said, the need to respect patient autonomy dictates that patients can approve or refuse any possible testing of their genomes. "Most patients probably would want that information," he said, "but on the other hand you need to document that they do or do not."

The obligation to treat all people equally, fairly, and impartially—that is, to assure justice in treatment—raises additional considerations about the significant issue of the high cost of genetic testing, given that health care has been unaffordable for many Americans and that health insurers often do not cover these tests, Saal said. Generally, genetic testing is not usually covered by third-party payers with the exception of cancer testing, he said. The protocols and policies used by third-party payers to evaluate which genetic conditions are covered may be dated and lack consistency between payers. For some families, an entire deductible could be used on just an exome sequence.

Making a diagnosis is a positive outcome (i.e., beneficence) for patients, not just because it may get them onto treatments, but also because it often ends diagnostic odysseys for families and the costs associated with them. As health care providers strive to do no harm—i.e., to practice non-maleficence—questions arise around whether a knowledge of genetic results may be harmful to patients, as in cases where a diagnosed disease is untreatable or may not develop until later in life (e.g., diagnosis in a minor of a disease that will not develop until adulthood), Lyman said.

Challenges

Several major challenges exist to writing guidelines for using whole-genome sequencing in clinical practice. "First," Saal said, "next-

generation testing is complex and generates a great deal of data. In addition, interpretation is difficult and challenging." Saal then asked who should be able to order the testing. Neurologists, developmental pediatricians, and family physicians, for example, may have the credentials to order this testing, but then the issue is who should be responsible for genetic counseling and ensuring that this component is an integral part of the testing.

Informed consent for such testing cannot be obtained without genetic counseling, Saal said, yet there may not be enough genetic counselors to meet future workforce needs. He urged medical schools and residency programs to expand their genetics and genomics curricula to better prepare doctors for the influx of genomic technologies into all realms of medicine.

5

How Insurers Decide Whether to Pay for Testing

Important Points Highlighted by the Individual Speakers

- Payers use well-recognized guidance from professional societies, evidence-based consensus reports, and health care organizations to establish the clinical validity and utility of molecular diagnostic tests.
- It is suggested that Medicare will likely not be the leader for setting genomic testing reimbursement policies.
- Payers will be increasingly challenged with processing an enormous volume of coverage and reimbursement requests as a rapidly growing number of new genomic tests become available for clinical use.

There are several steps between determining the actionability of a genetic variant (see Chapter 2) and deciding to take clinical action, said Bruce Blumberg, institutional director of graduate medical education, Northern California Kaiser Permanente, Permanente Medical Group. One of the steps between actionability and action is the consideration of whether or not genomic testing costs should be reimbursed by public and private payers. To shed light on this issue, representatives from the commercial and government payer sectors explained their processes for evaluating genomic or multi-gene panel sequencing tests as well as their criteria for deciding whether to provide coverage of such testing.

CLINICAL POLICY DEVELOPMENT AT AETNA

Aetna is a large multi-payer company that offers health insurance plans and other types of insurance throughout the United States. Its process for handling genomic testing requests is the same process used to develop clinical policy, said Robert McDonough, senior director of clinical policy and research and development at Aetna. The company applies very similar criteria for determining the coverage of such testing as it does for other types of medical technologies (e.g., positron emission tomography, or PET, scans). Aetna policies cover only medically necessary tests and treatments and exclude coverage for experimental and investigational technologies, McDonough said. All plans must have a definition for coverage that address certain elements—specifically whether use in clinical practice is experimental, investigational, or medically necessary.

"The goal is to develop objective, clinically supported, and defensible coverage determinations," McDonough said. To assess and to provide information about whether specific medical services are necessary or investigational, the Clinical Policy Unit has developed more than 700 clinical policy bulletins (CPBs), or medical policies, including bulletins about genomic and genetic tests, which are all posted on the company website.[1] CPBs describe which tests and procedures Aetna considers to be medically necessary versus those that are for cosmetic, experimental, or unproven uses. These determinations are based on information from consultation of different sources, including peer-reviewed medical journal articles and reviews, evidence-based consensus statements and other expert opinions, and guidelines from nationally recognized health care organizations. The CPB for genetic testing provides a list of criteria that all must be met before a genetic test can be considered medically necessary for disease diagnosis.[2] These criteria are

- The patient displays clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic); and
- The result of the test will directly impact the treatment; and
- After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a

[1]For more information, see Clinical Policy Bulletins, http://www.aetna.com/health-care-professionals/clinical-policy-bulletins.html (accessed May 15, 2014).

[2]Clinical Policy Bulletin for Genetic Testing, http://www.aetna.com/cpb.medical/data/100_199/0140.html (accessed May 15, 2014).

> definitive diagnosis remains uncertain, and one disease diagnosis, as defined by Aetna, is suspected.

Additional criteria are also defined for specific diseases before a test is considered medically necessary.

Explanations and references are included within these documents to help the reader understand why a particular test is or is not covered. The CPBs help to support a policy that is "applied consistently and fairly and has a sound basis" as well as to provide transparency about the coverage, McDonough said. Policies are not created for every technology; they are prioritized based on questions that arise during the claims, precertification, and preauthorization processes. Revisions to Aetna's policies are typically generated by new evidence, guidelines, consensus statements, and alterations in relevant regulations for a particular technology.

Coverage Criteria and Creating Policies

Aetna uses established criteria developed by the Blue Cross and Blue Shield Association's Technology Evaluation Center for assessing whether a medical technology warrants clinical coverage, McDonough said. The criteria[3] include the following:

1. The test or treatment must have final approval from appropriate governmental regulatory bodies, where required;
2. scientific evidence must permit conclusions about its effect on medical outcomes;
3. technology must improve net health outcomes;
4. the technology must provide as much health benefit as established alternatives; and
5. the improvement in health must be attainable outside investigational settings.

The CPB drafting process entails a comprehensive search of the peer-reviewed medical literature and an assessment of the current regulatory status of the technology of interest. The Clinical Policy Unit then considers evidence-based guidelines, such as those from the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) for cancer diagnostic testing. Aetna also performs

[3]Technology Evaluation Center, http://www.bcbs.com/blueresources/tec (accessed May 15, 2014).

technology assessments and solicits expert opinions (e.g., through a liaison group that regularly seeks input from specialty medical societies). All of this information is synthesized into an initial CPB draft which is then subjected to review by the head of Aetna's national medical policy and operations department and the legal department, and then it is finally reviewed for approval by the chief medical officer or a designee. Upon approval of a new policy, the Clinical Policy Unit helps facilitate implementation across coding and reimbursement areas.

Covered Genetic Testing

Examples of genomic technologies that are currently covered include noninvasive prenatal detection of chromosomal abnormalities, such as found in Down syndrome. Guidelines from the American College of Obstetrics and Gynecology[4] that supported the test were important in the decision to cover it, McDonough said; the covered tests sequence cell-free fetal DNA in blood samples taken from expecting mothers. When it comes to genomic sequencing for diagnosing individuals with suspected genetic disorders (e.g., cystic fibrosis), the approach that Aetna has taken is to reimburse genetic testing for core cystic fibrosis mutations. Because next-generation sequencing may potentially be used to identify additional cystic fibrosis mutations not included in the recommended panel, the testing laboratory may offer a separate test to the individual member, but the member, rather than the payer, would pay for it directly, McDonough said.

THE MEDICARE COVERAGE DETERMINATION PROCESS

Many people are looking to the Medicare program to lead the way in determining coverage of molecular diagnostics, said Louis Jacques, director of the Coverage and Analysis Group at the Centers for Medicare & Medicaid Services (CMS). However, while it is true that genomic testing of cancerous tumors is relevant for the aging population, if a predisposition for lung cancer could be identified and used to prevent someone from smoking, the target age for genetic testing would be in the teenage years, not at 65 years old. Thus from a practical standpoint, Jacques said,

[4]Noninvasive Prenatal Testing for Fetal Aneuploidy: Committee Opinion, http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Genetics/Noninvasive_Prenatal_Testing_for_Fetal_Aneuploidy (accessed April 29, 2014).

Medicare is "not going to be the major driver" on reimbursement for the genomic testing space.

Under Medicare regulations, a basic requirement for finding a diagnostic test to be medically reasonable and necessary is that the treating physician has to order it to help manage the patient, which automatically raises the question of how the physician is using the test for the patient, Jacques said. When considering coverage for such technology, CMS applies the same procedures it uses to evaluate any tests or treatments, Jacques said: the national coverage determination process (which takes 9 to 12 months), the local coverage determination process (which takes roughly 3 months), or a quicker, claim-by-claim adjudication process. Because of the variety of coverage determination mechanisms, the system has been criticized for not being transparent enough.

In 2009, the agency undertook a national coverage determination for pharmacogenomic testing to evaluate genetic tests predicting how a patient will respond to treatment with warfarin, a commonly prescribed anticoagulant.[5] Aside from a fair number of meetings by the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) to examine various genetic tests, "that's about the last you've heard from us on this topic," Jacques said. Because of the way that the current coding system functions, a non-unique test code makes it possible that the default decision may be to reimburse for test or services without needing an individual to make a conscious decision for the claim to be paid. However, Jacques noted that the agency has started a "novel and innovative" pilot program called MolDx, which manages molecular diagnostic services and identifies and establishes unique identifiers and coverage and payment for such testing.[6] The program is overseen by Palmetto GBA, an administrative contractor in South Carolina. Before potentially expanding it nationally, CMS would have to examine how the pilot program could evolve or grow and decide whether a nationwide program would be overseen by a single contractor or by a few regional contractors.

CMS can grant conditional coverage of testing or a procedure—a status called coverage with evidence development (CED)—only in selected patients enrolled in research studies that could provide further evi-

[5]For more information, see National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1), http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&bc=BAAAgAAAAAAA& (accessed May 15, 2014).

[6]For more details, visit MolDx, http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCatHome/MolDx (accessed May 15, 2014).

dence of its utility. In some cases, Jacques said, therapeutic knowledge is so well developed that it is possible to provide sufficient evidence to successfully argue for CMS coverage of a diagnostic test. For example, when the agency reviewed FDG-PET imaging (positron emission tomography using F-18 fluorodeoxyglucose) for cervical cancer, it found that the evidence indicated that physicians could use scan results to make meaningful changes in a patient's treatment plan; because anticancer therapies typically come with toxic side effects, it is meaningful for a patient if the physician determines that chemotherapy or invasive surgery is not appropriate. "Even though we did not have the perfect clinical trial from soup to nuts, we said, well, we've got enough [evidence]," Jacques said.

Medicare used a MEDCAC to review the evidence for the use of beta-amyloid PET imaging for diagnosis or treatment of dementia or neurodegenerative disease, Jacques said. While the review found that there was insufficient evidence for coverage, a decision was made to identify the status as CED for the purposes of excluding Alzheimer's disease in specific diagnoses and for the purpose of enriching clinical trials that addressed disease treatment and prevention strategies.[7]

Another example of evidence consideration was in the case of pharmacogenetic testing to predict patient response to warfarin. Variations in the genes that encode CYP2C9 or VKORC1 enzymes (among others) affect disposition, response, and toxicity for individual patients receiving chronic warfarin therapy (Dean, 2013). While there was no doubt that this testing would provide clinically valid results, the real question was what difference the results would make in the medical management of typical Medicare patients, Jacques said. The FDA package label[8] for warfarin specifies that prescribers should individualize the dosing regimen for each patient, adjusting it based on the international normalized ratio response, or a test to measure the clotting time of blood; additionally, Jacques said, knowledge of genotype can inform initial dose selection if a patient is taking drugs known to affect warfarin metabolism and either has an adverse genetic profile or is an older adult who has multiple illnesses. The latter describes most Medicare beneficiaries, he said, "so we were left with a clinical utility vacuum" for the genotyping. Given that

[7]Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N), http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=265 (accessed April 29, 2014).

[8]Coumadin® Package Label, Bristol-Myers Squibb Company, Princeton, New Jersey 08543 USA, revised October 2011.

physicians already know if a given patient is elderly and has co-morbidities and which medications the patient takes, Jacques said, "Why would you go ahead and wait a few days or potentially a week to get a genetic test result? Even if results say the patient's genetic profile is fine, the doctor is not going to ignore the other factors." Thus CMS decided to grant CED of warfarin pharmacogenomic testing to assess utility, he said. Several clinical trials of genotype-guided warfarin dosing and similar drugs have found varying results (Kimmel et al., 2013; Pirmohamed et al., 2013; Verhoef et al., 2013). There is still uncertainty about the use of genetic testing for warfarin dosing even after randomized controlled trials were conducted.

FACTORS THAT INFLUENCE COVERAGE DECISIONS

In its coverage determination process, Medicare is required by law to consider public comments, Jacques said, and how persuasive those comments are depends on a variety of factors. For example, the clinical policy unit will not find thousands of form letters driven by interested stakeholders to be as convincing as a few well-considered public comments that point out, for instance, that an entire body of relevant evidence was omitted from the determination analysis. But public sentiment might sway other players who can influence agency decisions; in particular, Congress has the final say in decision making.

Commercial insurance companies are highly regulated, McDonough said. In certain circumstances, individual states may mandate coverage for certain treatments despite a lack of evidence for the value of such treatments, such as the use of bone marrow transplantation in treating breast cancer patients. Demand from members and plan sponsors can also have an impact on policy, McDonough said, but overall the primary coverage decision is based on "high-quality evidence and outcomes."

Because decisions are based on a rigorous review of the evidence, it is unusual for coverage to be withdrawn based on new information, McDonough said. A disinvestment would need to go through a process similar to the one described earlier for coverage decisions. Jacques said that the removal of coverage is also rare for Medicare, as most requests are for expanded coverage by those who say there is now evidence to support the use of a test or service.

PREPARING FOR A FUTURE FLOOD OF GENOMIC TESTING

How will payers cope as a rapidly growing number of new genomic tests become available and patients and their providers ask insurers to pay for them? As one participant put it, administrative systems are going to be facing "a giant train wreck" where they are unable to process the volume of reimbursement and prior authorization requests. A particularly troublesome challenge for CMS, Jacques said, is that the volume of new tests is so huge that is it difficult to assess all of them for clinical utility. Nonetheless, he said, if diagnostic testing companies or researchers "come to us with an argument that is fundamentally grounded in clinical utility, that will be a persuasive argument" for coverage. Other workshop speakers described examples of difficulties with obtaining reimbursement for clinical genomic testing, such as in cases where a patient at high risk for a genetic disorder would benefit if sequencing could be done on a DNA specimen from a family member who died from the illness (see Chapter 2).

Jacques acknowledged the general challenge ahead at CMS. If several genomic tests come along that are all claimed to do the same thing but that are built on different platforms or look at different parts of the genome with some overlap, he asked, "how do we know whether those differences are significant or not? I don't know that the best paradigm currently exists to handle that." CMS would be open to hearing input from stakeholders on innovative or collaborative solutions, he added.

McDonough observed that Medicare and commercial payers have addressed similar challenges, such as handling different indications for cancer drugs by recognizing medications that are listed in certain published compendia. Similarly, he suggested, it is possible that a molecular diagnostics compendia could be created for which payers would recognize oncology markers identified in certain listings. The challenge with compendia, Jacques said, is that they are proprietary publications and not publicly accessible.

McDonough also suggested that concerns about the huge volume of different genomic tests on the horizon will be tempered because payers will only be aware of the most common tests—those with specific, identified codes—which will limit the number of tests that need to really be evaluated. Other, uncommon tests will be billed with generic codes, which generally get paid without review, he said.

A STANDARD FOR ACCEPTABLE EVIDENCE

No matter what the disease of focus, Jacques said, the type of evidence that is acceptable to public or private payers in their coverage decisions about genetic testing could be the subject of a vigorous, open debate held in a credible and bias-free public forum, where participants can discuss which types of evidence they find to be persuasive and which types they do not believe to be persuasive. As one potential starting point, Jacques suggested that interested stakeholder groups (such as professional societies or public interest groups) could go to Capitol Hill with a proposal for rule making to determine what is "reasonable and necessary" and to establish a particular process within Medicare.

The evaluation process, McDonough noted, is an important source of information for effectiveness guidance documents (EGDs), which discuss the type of research that is needed to provide reliable evidence for payers on the effectiveness and safety of medical technologies for specific diseases. For example, the nonprofit Center for Medical Technology Policy (CMTP) in Baltimore has completed an EGD on evidence standards for studies of the clinical validity and utility of molecular diagnostics for oncology (CMTP, 2013).[9] The center is now planning an EGD on evidence standards for next-generation sequencing in oncology.

McDonough observed that the CMTP effectiveness guidance documents for evidence standards recommend convening a multidisciplinary group of stakeholders to determine the preferred evidence-based decision-making process for certain classes of technologies. But, he added, "I don't think we can rely solely on expert opinion in making these decisions." If the expert opinion "is not really bounded by reliable evidence, then one really needs to question the validity of the expert opinion." What may be more important is the quality of the evidence; however, if stakeholders can agree on an evidentiary framework for assessing new genomic tests, that will make the process predictable, he noted.

The CED process needs to be more efficient and accessible, Jacques said, but that is a matter of resources, because the process is mostly done under a national coverage determination, which takes a total of 2 years of staff work. The analysts on his staff have been affected by the sequester and furloughs, which means that his unit can only manage 5 or 6 national coverage determinations a year, including areas beyond diagnostic testing. "If we want CED more broadly," Jacques said—and he agreed it

[9]For more information, see www.cmtpnet.org/resource-center/view/egd-on-mdx (accessed July 11, 2014).

makes sense to do that—"we need to find a better way to do CED." One possibility, he suggested, would be to have a voluntary process in which CED could "essentially be a default position for medical technologies that meet certain criteria." Test developers might be given, say, a 3-year grace period to establish sufficient evidence for full coverage approval. Such a system, he said, could motivate everybody to say, "Okay, we've got 3 years to get the answer on this. Let's do it."

6

Addressing Challenges

During the final session of the workshop, a panel of discussants each sought to identify the top challenges and areas that could be pursued for evaluating genomic information in the era of next-generation sequencing. The group addressed such issues as a framework for reimbursement of genetic testing; understanding the clinical context in which testing information is used, or "evidence fit for purpose," as David Veenstra, the workshop chair, said; forming data resource collaborations, such as ClinGen; and population-based studies for evidence generation.

Box 6-1 lists the major themes that emerged during the workshop. Box 6-2 contains suggestions and proposals from individual workshop speakers for assessing genomic sequencing information.

BOX 6-1
Topics That Were Addressed During the Workshop

David Veenstra, the workshop chair, listed several points that had been mentioned repeatedly during the course of discussion about evaluating evidence:

- Greater consensus, or at least consistency, in the ways that genomic data are gathered, analyzed, graded, reimbursed, and used to shape practice guidelines could greatly advance their application in the clinic.
- The context in which genomic information is to be used can be a major influence on that use.

- Collaborations among researchers and clinicians may be useful in generating and applying genomic data effectively.
- Patient preferences and financial costs are likely to be important factors in the application of genomic data to medicine.

BOX 6-2
Proposals Made By Individual Speakers

- Establishing the minimum amount of data that is needed to include a gene on a test panel would reduce the variation in the genes evaluated for the same condition. (Rehm)
- Strategies and terminology for classifying sequence variants vary by society and research group, and it will take work within the genomics community to agree on a common classification system that is easily understood by all users. (Rehm)
- A searchable, international database that contains large-scale sequencing data along with phenotypic information will be useful for identifying phenotype-related genetic commonalities that would otherwise be unknown. (Rehm)
- There is a need for prospective follow-up studies of individuals who have been found to have germline sequence variants in genes that are thought to be associated with disease risk. Partnerships with both academic and commercial testing laboratories will be an effective way to identify such individuals. (Robson)
- There must be an evidentiary basis for incorporating a variant into clinical care or reporting it to physicians or patients. (Berg)
- Collecting more population-based data in a central location from clinical or research studies could be a solution for extrapolating to larger populations instead of relying on what is currently used for this purpose—high-risk population data. (Goddard)
- Establishing central repositories for clinically relevant variants and phenotypes and encouraging laboratories to contribute to it would provide resources with a standardized format for studying the clinical validity of gene–phenotype associations. (Berg)
- Working collectively on assessing variants for clinical use would be a more efficient process as it would help alleviate the time required by individual groups. (Hegde, Kulkarni)

- Electronic health records with the capacity to handle genomic information are needed so that the data can be accessed throughout the course of care, but decisions need to be made about what specific genomic information should be included and where it will reside. (Berg)
- Taking an individualized approach to returning results to patients allows for the consideration of patient preferences and the ability to contextualize the information as it relates to the patient's condition and family history. (Everett)
- Discussing the content of laboratory testing consent forms can be valuable for delivering results to patients. (Gambello)
- A more efficient but still rigorous practice guideline development process is needed because current methods are time consuming and additional practice guidelines would be useful for the field of genomics. (Lyman)
- Medical schools and residency programs need to expand their genetics and genomics curricula so that physicians and other practitioners are better prepared to handle this type of information in clinical practice. (Saal)
- Evidence quality is more important than expert opinion for assessing new genomic tests and determining coverage. If stakeholders can agree on an evidentiary framework for making these assessments, it will bring predictability to the coverage determination process. (McDonough)

A FRAMEWORK FOR REIMBURSEMENT

Robert McDonough of Aetna said that the biggest challenge is coming up with a logical, pragmatic framework for reimbursement. "We need to be able to try to come to some consensus and have some consistency around what type of genomic testing is useful," he said.

With regard to reimbursement, Shashikant Kulkarni, director of cytogenomics and molecular pathology at the Washington University School of Medicine, observed that work is under way to identify genetic tests with established clinical utility so that reimbursement makes sense. But a lack of information about next-generation sequencing hinders reimbursement decisions. For example, amplicon-based tests cost much less than large-scale sequencing but are not equivalent to whole gene panels. "When it comes to reimbursement, the payers should take into consideration these differences in approaches."

A LACK OF EVIDENCE

The most significant difficulty is the lack of evidence, said Robert Green of Brigham and Women's Hospital and Harvard Medical School. "Lacking evidence is not something that is entirely new to doctors. Doctors have been practicing medicine without evidence for a long time and continue to do so in lots of domains. [But more evidence is] definitely something we need." In particular, Green called for more coordinated sharing of genotype–phenotype correlations over the next 5 to 10 years. The ClinGen collaboration is a good first step, he said, but even that "is probably underfunded for what is going to happen." Jonathan Berg of the University of North Carolina at Chapel Hill agreed that projects like ClinGen provide an opportunity to share data in a common format and language but that a clinically relevant resource is needed for mining variants from different sources.

"There is a significant body of data out there which we and others are mining: the Cancer Genome Atlas and the International Consortium of Cancer Genomics, which is beginning to produce an enormous amount of data," Kulkarni said. "Still, it's a huge amount of data which has to be mined." The data analysis and interpretation is time consuming, so even with a significant amount of information, he said, the field of oncology suffers from a similar lack of evidence for the majority of genetic variants.

Sequencing Standards

Establishing quality standards for sequencing studies—and also for how to report on such studies—would be valuable, said Katrina Goddard of the Kaiser Permanente Northwest Center for Health Research. For example, sometimes a study is rated as being of poor quality because the information needed to assess the quality of the study is not included in the literature. Green added that this idea could be implemented if journals led the way. Standards have been established for both conducting and reporting on randomized clinical trials, he observed, and something similar could be done for gene association studies.

Kulkarni also called attention to the lack of sequencing standards for such parameters as sensitivity and specificity. For example, some groups are using 200 nanograms of DNA for detecting 10 percent of the tumor cells, he said, while others claim that only 5 or 10 nanograms provides sufficient sensitivity. These issues are even more pressing in cancer,

where the frequency of alleles and composition of cells within a tumor can differ. "We need to address standards to understand what types of minimal requirements are essential," he said.

POPULATION-BASED STUDIES

Because of the concern that extrapolated data from high-risk populations may not be generalizable to the larger population, there is a need for collecting data from large population-based studies, Goddard said. Information from clinical studies and from research studies must be combined in order to arrive at valid conclusions at the population level, she said. "By combining across different efforts, you may be able to get a sufficient sample size," she said. Green noted that longitudinally collecting such information would be very expensive, to which Goddard responded that simply starting with unselected populations would be a step in the right direction.

Goddard pointed to initiatives that are using EHRs as a source of research data. Green also pointed to the need to look beyond single patients to entire families. Given there will be HIPAA challenges, it will be useful to use EHRs that contain phenotype data and link that information with genotypes and phenotypes from other family members, he said. Genetics does this at an individual level, but it has not made the transition to a macro level. Jessica Everett of the University of Michigan Comprehensive Cancer Center noted, however, that the sequencing of family members is typically not reimbursed, even when the information would be extremely useful in understanding a condition.

Large-scale genome sequencing efforts are now under way in the United States,[1] the United Kingdom, and Saudi Arabia,[2] Green said (Callaway, 2013). Berg observed, however, that the challenge is doing the phenotyping. "It's trivial to sequence a million genomes compared to phenotyping a million people," he said. Until enough people with rare variants are phenotyped, the penetrance of those variants will be largely unknown, he added. A million genomes may not even be close to the sample size that is needed for generating the evidence, Veenstra said.

---

[1]Regeneron and Geisinger Health System Announce Major Human Genetics Research Collaboration, http://investor.regeneron.com/releasedetail.cfm?ReleaseID=818844 (accessed May 15, 2014).

[2]Saudi Human Genome Program, http://rc.kfshrc.edu.sa/sgp (accessed May 15, 2014).

CONCLUDING REMARKS

"Next-generation sequencing is a disruptive technology," Veenstra said. In fact, it is likely also disruptive to the process of evidence-based medicine, especially with the issues related to many possible causative variants and secondary findings or incidental findings. The way these issues can be addressed, he said, is by continuing to increase our understanding of how policy and treatment decisions are made in an era of limited evidence and a large volume of information.

References

ACMG (American College of Medical Genetics and Genomics) Board of Directors. 2012. Points to consider in the clinical application of genomic sequencing. *Genetics in Medicine* 14(8):759–761.

Bean, L. J., S. W. Tinker, C. da Silva, and M. R. Hegde. 2013. Free the data: One laboratory's approach to knowledge-based genomic variant classification and preparation for emr integration of genomic data. *Human Mutatation* 34(9):1183–1188.

Berg, J. S., M. J. Khoury, and J. P. Evans. 2011. Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. *Genetics in Medicine* 13(6):499–504.

Berg, J. S., L. M. Amendola, C. Eng, E. Van Allen, S. W. Gray, N. Wagle, H. L. Rehm, E. T. DeChene, M. C. Dulik, F. M. Hisama, W. Burke, N. B. Spinner, L. Garraway, R. C. Green, S. Plon, J. P. Evans, G. P. Jarvik, and members of the CSER Actionability and Return of Results Working Group. 2013. Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the clinical sequencing exploratory research consortium. *Genetics in Medicine* 15(11): 860–867.

Bombard, Y., M. Robson, and K. Offit. 2013. Revealing the incidentalome when targeting the tumor genome. *Journal of the American Medical Association* 310(8):795–796.

Callaway, E. 2013. Open-access genome project lands in UK. In *Nature News Blog*, November 7. http://blogs.nature.com/news/2013/11/open-access-genome-project-lands-in-uk.html (accessed May 30, 2014).

Callaway, E. 2014. Global genomic data-sharing effort kicks off. Nature News: Q&A, March 6. http://www.nature.com/news/global-genomic-data-sharing-effort-kicks-off-1.14826 (accessed June 16, 2014).

Cirino, A. L., and C. Ho. 2008. Hypertrophic cardiomyopathy overview. R. A. Pagon, M. P. Adam, H. H. Ardinger, et al. (eds.), *GeneReviews*. Seattle: University of Washington. http://www.ncbi.nlm.nih.gov/books/NBK1768 (accessed May 16, 2014).

CMTP (Center for Medical Technology Policy). 2013. Evaluation of clinical validity and clinical utility of actionable molecular diagnostic tests in adult oncology. http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf (accessed May 15, 2014).

Collins, F. S. 2010. *The language of life: DNA and the revolution in personalized medicine*. New York: Harper.

Committee on Bioethics, Committee on Genetics, and the American College of Medical Genetics and Genomics Social, Ethical, and Legal Issues Committee. 2013. Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 131(3):620–622.

Coste, B., G. Houge, M. F. Murray, N. Stitziel, M. Bandell, M. A. Giovanni, A. Philippakis, A. Hoischen, G. Riemer, U. Steen, V. M. Steen, J. Mathur, J. Cox, M. Lebo, H. Rehm, S. T. Weiss, J. N. Wood, R. L. Maas, S. R. Sunyaev, and A. Patapoutian. 2013. Gain-of-function mutations in the mechanically activated ion channel PIEZO2 cause a subtype of distal arthrogryposis. *Proceedings of the National Academy of Sciences of the United States of America* 110(12):4667–4672.

Cruchaga, C., C. M. Karch, S. C. Jin, B. A. Benitez, Y. Cai, R. Guerreiro, O. Harari, J. Norton, J. Budde, S. Bertelsen, A. T. Jeng, B. Cooper, T. Skorupa, D. Carrell, D. Levitch, S. Hsu, J. Choi, M. Ryten, U. K. Brain Expression Consortium, J. Hardy, M. Ryten, D. Trabzuni, M. E. Weale, A. Ramasamy, C. Smith, C. Sassi, J. Bras, J. R. Gibbs, D. G. Hernandez M. K. Lupton, J. Powell, P. Forabosco, P. G. Ridge, C. D. Corcoran, J. T. Tschanz, M. C. Norton, R. G. Munger, C. Schmutz, M. Leary, F. Y. Demirci, M. N. Bamne, X. Wang, O. L. Lopez, M. Ganguli, C. Medway, J. Turton, J. Lord, A. Braae, I. Barber, K. Brown, Alzheimer's Research Consortium U.K., P. Passmore, D. Craig, J. Johnston, B. McGuinness, S. Todd, R. Heun, H. Kolsch, P. G. Kehoe, N. M. Hooper, E. R. Vardy, D. M. Mann, S. Pickering-Brown, K. Brown, N. Kalsheker, J. Lowe, K. Morgan, A. David Smith, G. Wilcock, D. Warden, C. Holmes, P. Pastor, O. Lorenzo-Betancor, Z. Brkanac, E. Scott, E. Topol, K. Morgan, E. Rogaeva, A. B. Singleton, J. Hardy, M. I. Kamboh, P. St George-Hyslop, N. Cairns, J. C. Morris, J. S. Kauwe, and A. M. Goate. 2014. Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease. *Nature* 505(7484):550–554.

Dean, L. 2013. Warfarin therapy and the genotypes CYP2C9 and VKORC1. *Medical Genetics* Summaries. http://www.ncbi.nlm.nih.gov/books/NBK84174 (accessed April 29, 2014).

EGAPP (Evaluation of Genomic Applications in Practice and Prevention). 2009. Recommendations from the EGAPP working group: Can tumor gene expression profiling improve outcomes in patients with breast cancer? *Genetics in Medicine* 11(1):66–73.

EGAPP. 2010. Recommendations from the EGAPP working group: Genomic profiling to assess cardiovascular risk to improve cardiovascular health. *Genetics in Medicine* 12(12):839–843.

EGAPP. 2014a. The EGAPP initiative: Lessons learned. *Genetics in Medicine* 16(3):217–224.

EGAPP. 2014b. Recommendations from the EGAPP working group: Does PCA3 testing for the diagnosis and management of prostate cancer improve patient health outcomes? *Genetics in Medicine* 16(4):338–346.

Enns, G. M., V. Shashi, M. Bainbridge, M. J. Gambello, F. R. Zahir, T. Bast, R. Crimian, K. Schoch, J. Platt, R. Cox, J. A. Bernstein, M. Scavina, R. S. Walter, A. Bibb, M. Jones, M. Hegde, B. H. Graham, A. C. Need, A. Oviedo, C. P. Schaaf, S. Boyle, A. J. Butte, R. Chen, M. J. Clark, R. Haraksingh, T. M. Cowan, P. He, S. Langlois, H. Y. Zoghbi, M. Snyder, R. A. Gibbs, H. H. Freeze, and D. B. Goldstein. 2014. Mutations in *NGLY1* cause an inherited disorder of the endoplasmic reticulum-associated degradation pathway. *Genetics in Medicine*, March 20. http://www.nature.com/gim/journal/vaop/ncurrent/full/gim201422a.html (accessed May 30, 2014).

Garraway, L. A. 2013. Genomics-driven oncology: Framework for an emerging paradigm. *Journal of Clinical Oncology* 31(15):1806–1814.

Green, R. C., J. S. Berg, W. W. Grody, S. S. Kalia, B. R. Korf, C. L. Martin, A. L. McGuire, R. L. Nussbaum, J. M. O'Daniel, K. E. Ormond, H. L. Rehm, M. S. Watson, M. S. Williams, and L. G. Biesecker. 2013. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine* 15(7):565–574.

Hayden, E. C. 2014. Technology: The $1,000 genome. *Nature* 507(7492):294–295.

Hickey, K. T., R. R. Sciacca, A. B. Biviano, W. Whang, J. M. Dizon, H. Garan, and W. K. Chung. 2014. The effect of cardiac genetic testing on psychological well-being and illness perceptions. *Heart & Lung* 43(2):127–132.

IOM (Institute of Medicine). 2011. *Clinical practice guidelines we can trust*. Washington, DC: The National Academies Press.

IOM. 2014. *Refining processes for the co-development of genome-based therapeutics and companion diagnostic tests: Workshop summary*. Washington, DC: The National Academies Press.

Kaye, J., E. A. Whitley, D. Lund, M. Morrison, H. Teare, and K. Melham. 2014. Dynamic consent: a patient interface for twenty-first century research networks. *European Journal of Human Genetics*. http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg201471a.html (accessed June 25, 2014) doi: 10.1038/ejhg.2014.71.

Kimmel, S. E., B. French, S. E. Kasner, J. A. Johnson, J. L. Anderson, B. F. Gage, Y. D. Rosenberg, C. S. Eby, R. A. Madigan, R. B. McBane, S. Z. Abdel-Rahman, S. M. Stevens, S. Yale, E. R. Mohler, M. C. Fang, V. Shah, R. B. Horenstein, N. A. Limdi, J. A. S. Muldowney, J. Gujral, P. Delafontaine, R. J. Desnick, T. L. Ortel, H. H. Billett, R. C. Pendleton, N. L. Geller, J. L. Halperin, S. Z. Goldhaber, M. D. Caldwell, R. M. Califf, and J. H. Ellenberg. 2013. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *New England Journal of Medicine* 369(24):2283–2293.

Kohane, I. S., D. R. Masys, and R. B. Altman. 2006. The incidentalome: A threat to genomic medicine. *Journal of the American Medical Association* 296(2):212–215.

Landrum, M. J., J. M. Lee, G. R. Riley, W. Jang, W. S. Rubinstein, D. M. Church, and D. R. Maglott. 2014. ClinVar: Public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Research* 42(Database issue):D980–D985.

Lyman, G. H., S. Temin, S. B. Edge, L. A. Newman, R. R. Turner, D. L. Weaver, A. B. Benson, 3rd, L. D. Bosserman, H. J. Burstein, H. Cody, 3rd, J. Hayman, C. L. Perkins, D. A. Podoloff, and A. E. Giuliano. 2014. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology* 32(13):1365–1383.

McCormack, R. T., J. Armstrong, and D. Leonard. 2014. Codevelopment of genome-based therapeutics and companion diagnostics: Insights from an Institute of Medicine roundtable. *Journal of the American Medical Association* 311(14):1395–1396.

NIH (National Institutes of Health). 2013. New NIH-funded resource focuses on use of genomic variants in medical care. http://www.nih.gov/news/health/sep2013/nhgri-25.htm (accessed April 16, 2014).

Parsons, D. W., M. M. Chintagumpala, S. L. Berg, D. H. López-Terrada, R. Angshumoy, R. A. Kerstein, S. Scollon, S. G. Hilsenbeck, U. Ramamurthy, C. M. Eng, Y. Yang, R. A. Gibbs, D. A. Wheeler, R. L. Street, L. B. McCullough, A. L. McGuire, F. A. Monzon, and S. E. Plon. 2013. Implementation and evaluation of clinical exome sequencing in childhood cancer care: The BASIC3 study. *Journal of Clinical Oncology* 31(suppl; abstr 10023).

Pellegrini, I., M. Rapti, J. M. Extra, A. Petri-Cal, T. Apostolidis, J. M. Ferrero, T. Bachelot, P. Viens, C. Julian-Reynier, and F. Bertucci. 2012. Tailored chemotherapy based on tumour gene expression analysis: Breast cancer patients' misinterpretations and positive attitudes. *European Journal of Cancer Care* 21(2):242–250.

Pirmohamed, M., G. Burnside, N. Eriksson, A. L. Jorgensen, C. H. Toh, T. Nicholson, P. Kesteven, C. Christersson, B. Wahlström, C. Stafberg, J. E. Zhang, J. B. Leathart, H. Kohnke, A. H. Maitland-van der Zee, P. R. Williamson, A. K. Daly, P. Avery, F. Kamali, and M. Wadelius. 2013. A randomized trial of genotype-guided dosing of warfarin. *New England Journal of Medicine* 369(24):2294–2303.

Rehm, H. L. 2013. Disease-targeted sequencing: A cornerstone in the clinic. *Nature Reviews Genetics* 14(4):295–300.

Robson, M. 2014. Multigene panel testing: Planning the next generation of research studies in clinical cancer genetics. *Journal of Clinical Oncology* published online on May 27, 2014; DOI:10.1200/JCO.2014.56.0474. http://jco.ascopubs.org/content/early/2014/05/20/JCO.2014.56.0474.long (accessed June 24, 2014).

Ross, L. F., H. M. Saal, K. L. David, R. R. Anderson, American Academy of Pediatrics, and American College of Medical Genetics and Genomics. 2013. Technical report: Ethical and policy issues in genetic testing and screening of children. *Genetics in Medicine* 15(3):234–245.

Roychowdhury, S., M. K. Iyer, D. R. Robinson, R. J. Lonigro, Y. M. Wu, X. Cao, S. Kalyana-Sundaram, L. Sam, O. A. Balbin, M. J. Quist, T. Barrette, J. Everett, J. Siddiqui, L. P. Kunju, N. Navone, J. C. Araujo, P. Troncoso, C. J. Logothetis, J. W. Innis, D. C. Smith, C. D. Lao, S. Y. Kim, J. S. Roberts, S. B. Gruber, K. J. Pienta, M. Talpaz, and A. M. Chinnaiyan. 2011. Personalized oncology through integrative high-throughput sequencing: A pilot study. *Science Transational Medicine* 3(111):111ra121.

Stadler, Z. K., K. A. Schrader, J. Vijai, M. E. Robson, and K. Offit. 2014. Cancer genomics and inherited risk. *Journal of Clinical Oncology* 32(7):687–698.

Stenson, P. D., E. V. Ball, M. Mort, A. D. Phillips, J. A. Shiel, N. S. Thomas, S. Abeysinghe, M. Krawczak, and D. N. Cooper. 2003. Human gene mutation database (HGMD): 2003 update. *Human Mutation* 21(6):577–581.

Stenson, P. D., M. Mort, E. V. Ball, K. Shaw, A. Phillips, and D. N. Cooper. 2014. The human gene mutation database: Building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. *Human Genetics* 133(1):1–9.

Vassy, J. L., D. M. Lautenbach, H. M. McLaughlin, S. W. Kong, K. D. Christensen, J. Krier, I. S. Kohane, L. Z. Feuerman, J. Blumenthal-Barby, J. S. Roberts, L. S. Lehmann, C. Y. Ho, P. A. Ubel, C. A. Macrae, C. E. Seidman, M. F. Murray, A. L. McGuire, H. L. Rehm, R. C. Green, and the MedSeq Project. 2014. The MedSeq project: A randomized trial of integrating whole genome sequencing into clinical medicine. *Trials* 15(1):85.

Verhoef, T. I., G. Ragia, A. de Boer, R. Barallon, G. Kolovou, V. Kolovou, S. Konstantinides, S. Le Cessie, E. Maltezos, F. J. M. van der Meer, W. K. Redekop, M. Remkes, F. R. Rosendaal, R. M. F. van Schie, A. Tavridou, D. Tziakas, M. Wadelius, V. G. Manolopoulos, and A. H. Maitland-van der Zee. 2013. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *New England Journal of Medicine* 369(24):2304–2312.

Wagle, N., M. F. Berger, M. J. Davis, B. Blumenstiel, M. Defelice, P. Pochanard, M. Ducar, P. Van Hummelen, L. E. Macconaill, W. C. Hahn, M. Meyerson, S. B. Gabriel, and L. A. Garraway. 2012. High-throughput detection of actionable genomic alterations in clinical tumor samples by targeted, massively parallel sequencing. *Cancer Discovery* 2(1):82–93.

Yang, Y., D. M. Muzny, J. G. Reid, M. N. Bainbridge, A. Willis, P. A. Ward, A. Braxton, J. Beuten, F. Xia, Z. Niu, M. Hardison, R. Person, M. R. Bekheirnia, M. S. Leduc, A. Kirby, P. Pham, J. Scull, M. Wang, Y. Ding, S. E. Plon, J. R. Lupski, A. L. Beaudet, R. A. Gibbs, and C. M. Eng. 2013. Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. *New England Journal of Medicine* 369(16):1502–1511.

Appendix A

Workshop Agenda

Assessing Genomic Sequencing Information for Health Care Decision Making: A Workshop

February 3, 2014

The Keck Center of the National Academies, Room 100
500 Fifth Street, NW
Washington, DC 20001

MEETING OBJECTIVES

- Provide a forum for diverse stakeholders to present approaches for assessing genome sequencing information for clinical use.
- Compare and contrast evidence evaluation processes for different clinical indications and across stakeholders.
- Identify key challenges in the evidence evaluation process.
- Elicit pragmatic approaches to facilitate the effective translation of genomics into the clinic by improving evidence-based policy development.

AGENDA

8:30–8:35 a.m. **Welcoming Remarks**

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

Geoffrey Ginsburg, *Roundtable Co-Chair*
Director, Genomic Medicine, Duke Institute for Genome Sciences & Policy
Executive Director, Center for Personalized Medicine, Duke Medicine
Professor of Medicine and Pathology, Duke University Medical Center

8:35–8:45 a.m. **Charge to Workshop Speakers and Participants**

David Veenstra
Professor, Pharmaceutical Outcomes Research and Policy Program
University of Washington

SESSION I: HOW EVIDENCE IS GATHERED AND ASSESSED/GRADED/EVALUATED

Moderator: Debra Leonard, University of Vermont

8:45–10:15 a.m. **Systematic Evidence Gathering and Actionability Determination**

- What process do you use to identify studies and data?
- How are you selecting tests/variants for full evidence review and assessment?
- How do you critically assess the data and synthesize for conclusion?
- How do you present the results of the evidence review and evaluation to policy makers?

- How do you determine if clinical action is recommended or taken for specific genomic variants?
- How do you define actionability?
- What are the challenges you have encountered?
- What have you done to overcome these challenges?

Jonathan Berg
Assistant Professor
Department of Genetics
University of North Carolina School of Medicine

Katrina Goddard
Senior Investigator
Kaiser Permanente Center for Health Research

Shashikant Kulkarni
Director of Cytogenomics and Molecular Pathology
Genomics and Pathology Services
Washington University School of Medicine

Heidi Rehm
Associate Professor of Pathology, Brigham and Women's Hospital and Harvard Medical School
Director, Laboratory for Molecular Medicine
Partners Healthcare Center for Personalized Genetic Medicine

Madhuri Hegde
Executive Director, Emory Genetics Laboratory
Professor, Department of Human Genetics
Emory University School of Medicine

Mark Robson
Clinic Director, Clinical Genetics Service
Department of Human Genetics
Memorial Sloan–Kettering Cancer Center

10:15–10:30 a.m. **BREAK**

10:30–11:30 a.m. **Discussion with Speakers and Attendees**

11:30 a.m.–12:30 p.m. **WORKING LUNCH**

SESSION II: PROCESS FOR DECISION MAKING ONCE EVIDENCE IS ASSESSED/GRADED/EVALUATED

Moderator: Bruce Blumberg, Kaiser Permanente

12:30–1:00 p.m. **Reimbursement Decisions**

- Under what process (existing or novel) would genome or multi-gene panel sequencing be evaluated? Describe the process.
- What are your criteria for coverage?
- Does the extent to which information is reported in the electronic health record affect your decision?
- Under what circumstances are high-throughput sequencing tests covered by payers?

Robert McDonough
Head of Clinical Policy and Research
Aetna

Louis Jacques
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services

1:00–1:35 p.m. **Discussion with Speakers and Attendees**

Moderator: Muin Khoury, Centers for Disease Control and Prevention

1:35–2:20 p.m. **Guideline Development**

- How are you applying your guideline development process to next-generation sequencing?
- What do you think are the top three challenges to developing guidelines in the era of next-generation sequencing?
- Do you consider the Institute of Medicine recommendations for developing clinical practice guidelines in your process?

Robert C. Green
Director, Genomes to People (G2P) Research Program
Associate Director for Research, Partners Center for Personalized Genetic Medicine
Division of Genetics, Department of Medicine
Brigham and Women's Hospital and Harvard Medical School

Howard M. Saal
Director, Clinical Genetics
Division of Human Genetics
Cincinnati Children's Hospital Medical Center

Gary Lyman
Co-Director, Hutchinson Institute for Cancer Outcomes Research
Fred Hutchinson Cancer Research Center
University of Washington

2:20–2:55 p.m. **Discussion with Speakers and Attendees**

2:55–3:10 p.m. **BREAK**

Moderator: W. Gregory Feero, Maine Dartmouth Family Medicine

3:10–4:10 p.m. **Patient Care and Health Decisions**

- Upon what evidence is the decision made to use large-scale sequencing over a more targeted approach?
- Does reimbursement play a role in ordering a whole genome test?
- How do you see the role of patient preferences in what testing is done and what information is disclosed?
- How well do patients understand discussions about genomic testing? And, what is the patient response to reports of incidental findings?

Kathleen Hickey
Assistant Professor of Nursing
Columbia University School of Nursing

Jessica Everett
Clinical Instructor, Internal Medicine
Certified Genetic Counselor
Cancer Genetics Clinic
University of Michigan

Amy Hower
Neuroscientist and Patient

Michael Gambello
Associate Professor of Human Genetics and Pediatrics
Section Chief, Division of Medical Genetics
Emory University School of Medicine

4:10–4:45 p.m. **Discussion with Speakers and Attendees**

SESSION III: NEXT STEPS AND ADDRESSING CHALLENGES

Moderator: David Veenstra, University of Washington

4:45–5:30 p.m. **Developing Transparent and Pragmatic Frameworks for Evidence Evaluation and Policy Development in the Absence of an Ideal Evidence Base**

- What are the top three challenges to developing clinical and reimbursement policies in the era of genomic testing?
- What approaches do you think can help address these challenges?
- To what extent does clinical context matter?
- How do risk–benefit tradeoffs influence evidentiary requirements?

Jonathan Berg
Assistant Professor
Department of Genetics
University of North Carolina School of Medicine

Jessica Everett
Clinical Instructor, Internal Medicine
Certified Genetic Counselor
Cancer Genetics Clinic
University of Michigan

Katrina Goddard
Senior Investigator
Kaiser Permanente Center for Health Research

Robert C. Green
Director, Genomes to People (G2P) Research Program
Associate Director for Research
Partners Center for Personalized Genetic Medicine
Division of Genetics, Department of Medicine

Brigham and Women's Hospital and Harvard Medical School

Shashikant Kulkarni
Director of Cytogenomics and Molecular Pathology
Genomics and Pathology Services
Washington University School of Medicine

Robert McDonough
Head of Clinical Policy and Research
Aetna

5:30–5:45 p.m. **Summary and Concluding Remarks**

5:45 p.m. **ADJOURN**

Appendix B

Speaker Biographical Sketches

Jonathan S. Berg, M.D., Ph.D., is an assistant professor in the Department of Genetics at the University of North Carolina at Chapel Hill (UNC). He also has a clinical appointment in the Department of Medicine, Division of Hematology–Oncology and the Lineberger Comprehensive Cancer Center. He graduated from Emory University with a B.S. in biology and completed the M.D./Ph.D. program at UNC in the curriculum in neuroscience. He subsequently underwent residency training in clinical genetics at Baylor College of Medicine. Dr. Berg is now a physician and researcher interested in the development and application of genetic tests in patients and their families. The recent revolution in genetic sequencing technology has led to an unprecedented opportunity to investigate the underlying etiology in families with genetic conditions, and yet it raises potential pitfalls that must be addressed in order to translate these new technologies into the practice of clinical genomics. Dr. Berg is particularly interested in the range of "incidental," or "secondary," findings that are discovered during the course of genome-scale sequencing, including the pre-test counseling and informed consent process; computational analysis required to determine the likely clinical relevance of variants; best practices for return of these findings to patients; and the impact of genomic findings on patients and their families. He is co-principal investigator of two National Institutes of Health (NIH) grants, one of them to investigate the use of genome-scale sequencing as a diagnostic test in patients with suspected genetic disorders and as a potential screening tool in healthy newborns and the other to develop a publicly available database of clinically relevant genes and variants through the "ClinGen" project. He is also an investigator in the UNC Center for Genomics and Society, which was recently renewed as a National Human

Genome Research Institute (NHGRI) Center for Excellence in Ethical, Legal, and Social Implications Research to evaluate the prospect of using genomics to improve the health of adults in the general public. Dr. Berg has led the development of a novel semi-quantitative metric that evaluates several key aspects of "actionability" in order to score gene–phenotype pairs in a transparent, unbiased fashion. This approach was adopted by the Evaluation of Genome Applications in Practice and Prevention (EGAPP) Working Group as a means of approaching the problem of systematically evaluating the clinical utility of genomic information, and it is being studied as a way to guide the return of genomic findings in projects at UNC.

Bruce D. Blumberg, M.D., is the director of graduate medical education (the resident physician training programs) for Northern California Kaiser Permanente. He currently maintains a clinical practice in medical genetics at Kaiser Permanente Oakland. 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, who holds a medical degree from the Yale University School of Medicine, completed his residency in pediatrics at Stanford University Hospital and the University of California, Los Angeles (UCLA) Center for the Health Sciences as well as a fellowship in medical genetics at Harbor–UCLA Medical Center. He received his B.A. from Dartmouth College.

Jessica Everett, M.S., is a clinical instructor of internal medicine and a genetic counselor in the Cancer Genetics Clinic at the University of Michigan Comprehensive Cancer Center. She also provides genetic counseling as part of multi-disciplinary teams in endocrine oncology, cutaneous oncology, and pancreatic cancer clinics. She currently works on the Michigan Oncology Sequencing Project, a Clinical Sequencing Exploratory Research project funded by NHGRI and the National Cancer Institute (NCI) which is exploring clinical implementation of whole-genome and whole-exome sequencing for targeted oncology treatment. Ms. Everett's research interests include clinical applications of genetic and genomic technologies and the evolving role of genetic counselors in providing comprehensive care. She participates in the education of health

professional trainees, including genetic counseling graduate students, medical students, and hematology/oncology fellows. Ms. Everett is also active in the National Society of Genetic Counselors, and she has served as co-chair of the Familial Cancer Special Interest Group. Ms. Everett completed her M.S. in medical genetics at the University of Cincinnati in 1999 and her certification with the American Board of Genetic Counseling in 2002.

W. Gregory Feero, M.D., Ph.D., obtained his M.D./Ph.D. from the University of Pittsburgh School of Medicine's medical scientist training program with his Ph.D. in human genetics. He then completed his residency in family medicine at the Maine–Dartmouth Family Medicine Residency Program in Augusta, Maine. After 5 years in practice in Maine, Dr. Feero accepted a position at NHGRI of NIH as senior advisor to the director for genomic medicine under Drs. Francis Collins and Alan Guttmacher. He played a key role in coordinating NHGRI's activities related to family health history and was the planning chair for the NIH Consensus Development Program's 2009 State of the Science Conference "Family History and Improving Health." He also participated in efforts to help ensure the appropriate representation of family health history and genomic data in electronic health records. Additionally, as chief of the Genomic Healthcare Branch in the Office of the Director, he oversaw efforts to advance genomics education for health professional disciplines, including nurses, physician assistants, physicians, and pharmacists. In 2012, Dr. Feero stepped down from his position at NHGRI and continued on in his role as faculty and research director at the Maine–Dartmouth family medicine residency program. Currently he serves on the Institute of Medicine (IOM) Roundtable on Translating Genomic-Based Research for Health and is a contributing editor for the *Journal of the American Medical Association*. Dr. Feero sees patients 4 days a week in Fairfield, Maine; is board certified in family medicine; and holds professional licenses in Maine and West Virginia. He has authored numerous peer-reviewed and invited publications.

Michael J. Gambello, M.D., Ph.D., is the section chief of the Division of Medical Genetics at the Emory School of Medicine. His team diagnoses and cares for children and adults with birth defects, intellectual disability, lysosomal storage diseases, inborn errors of metabolism, and many other rare disorders. He is board certified by the American Board of Medical Genetics (ABMG) in clinical and medical biochemical genetics.

He is a member of the ABMG board of directors. He teaches genetic medicine and serves as the program director for the Accreditation Council for Graduate Medical Education–accredited medical genetics residency program. He completed his pediatric residency at St. Louis Children's Hospital/Washington University and his clinical genetics training in the Metropolitan Washington, DC, Medical Genetics Residency Program. His laboratory studies the neurogenetic disorder tuberous sclerosis complex and its association with autism. He also has interest in identifying new Mendelian neurodevelopmental disorders using whole-exome sequencing.

Geoffrey Ginsburg, M.D., Ph.D., is the founding director for genomic medicine at Duke University and assumed his current position in the Duke Institute for Genome Sciences & Policy in 2004. He is also the founding executive director of the Center for Personalized Medicine, which was established in the Duke University Health System in 2010. He is currently professor of medicine and pathology at the Duke University Medical Center. While at Duke, Dr. Ginsburg has pioneered translational genomics, initiating programs in genome-enabled biomarker discovery, longitudinal registries with linked molecular and clinical data, biomarker-informed clinical trials, and the development of novel practice models and implementation research for the integration of genomic tools in health care systems. With a strong commitment to interdisciplinary science, he has led projects to develop predictive models for common complex diseases using high-dimensional genomic data as well as collaborations with engineering groups to develop novel point-of-care sensors. His work spans oncology, infectious diseases, cardiovascular disease, and metabolic disorders, and his research addresses the challenges for translating genomic information into medical practice using new and innovative paradigms and also examines the integration of personalized medicine into health care. He is an internationally recognized expert in genomics and personalized medicine with more than 200 published papers, and he has received funding from NIH, the Department of Defense, the Defense Advanced Research Projects Agency, the Bill & Melinda Gates Foundation, and industry. In 1990, he joined the faculty of Harvard Medical School, where he was director of preventive cardiology at Beth Israel Hospital and led a laboratory in applied genetics of cardiovascular disease at Children's Hospital. In 1997, he joined Millennium Pharmaceuticals, Inc., as senior program director for cardiovascular diseases and was eventually appointed vice president of molecular and

personalized medicine, with responsibility for developing pharmacogenomic strategies for therapeutics as well as biomarkers for disease and their implementation in the drug development process. He has received a number of awards for his research accomplishments, including the Innovator in Medicine Award from Millennium in 2004 and the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005. He is a founding member and former board member of the Personalized Medicine Coalition, a senior consulting editor for the *Journal of the American College of Cardiology*, an editor for *The HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition, he is the editor of *Genomic and Personalized Medicine* (Elsevier), whose first edition was published in 2009. He has been a member of the Secretary of Veterans Affairs Advisory Council on Genomic Medicine and the National Advisory Council for Human Genome Research at NIH. He is currently an international expert panel member for Genome Canada; a member of the board of external experts for the National Heart, Lung, and Blood Institute; co-chair of the IOM Roundtable on Translating Genomic-Based Research for Health; and a member of the external scientific panel for the Pharmacogenomics Research Network. He has recently been appointed to the advisory council for the newly established National Center for Advancing Translational Sciences at NIH. He has recently been nominated to serve on the World Economic Forum's Global Agenda Council on Personalized and Precision Medicine. He received his M.D. and Ph.D. in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, Massachusetts. Subsequently he pursued postdoctoral training in clinical cardiovascular medicine at Beth Israel Hospital and in molecular biology at Children's Hospital as a Bugher Foundation Fellow of the American Heart Association.

Katrina Goddard, Ph.D., is a senior investigator at the Kaiser Permanente Northwest Center for Health Research in Portland, Oregon. She focuses on public health genomics and the translation of genetic testing into practice. She co-directs a study that is part of the Clinical Sequencing Exploratory Research consortium to explore how to use a new technology—whole-genome sequencing—in everyday clinical practice. The study will test would-be parents before they conceive for genetic mutations that could cause rare but serious diseases in their children and will explore how to implement such testing in a health plan. Dr. Goddard also co-directs the Knowledge Synthesis Center for the EGAPP program, which supports

evidence-based recommendations on genomic applications. She is a co-investigator for the Clinical Genome Resource program funded by NHGRI. That program is designing and implementing a framework to evaluate which genes play a role in disease and are relevant to patient care. Dr. Goddard is director of the NW Biobank, a repository of blood and tissue samples linked to the comprehensive electronic medical records of Kaiser Permanente's members. The NW Biobank enables researchers to connect people's genetic information with their health care, including vital signs, diagnoses, and treatments. In 2007, Dr. Goddard completed a 1-year fellowship in the National Office of Public Health Genomics, which was jointly sponsored by the Centers for Disease Control and the American Society of Human Genetics. Prior to her appointment as a senior investigator at the Kaiser Permanente Center for Health Research, Dr. Goddard was on the faculty at Case Western Reserve University in the Division of Genetic and Molecular Epidemiology. She received her Ph.D. in biostatistics from the University of Washington in 1999 and a B.S. in molecular biology from the University of Wisconsin–Madison.

Robert C. Green, M.D., M.P.H., is a medical geneticist and physician–scientist who directs the Genomes to People (G2P) Research Program (genomes2people.org) in translational genomics and health outcomes in the Division of Genetics at Brigham and Women's Hospital and Harvard Medical School. Dr. Green is the principal investigator of the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, funded by NIH, in which a cross-disciplinary team has conducted four separate multi-center randomized clinical trials, collectively enrolling 1,100 individuals to disclose a genetic risk factor for Alzheimer's disease in order to explore emerging themes in translational genomics. Dr. Green also co-directs the NIH-funded PGen Study, the first prospective study of direct-to-consumer genetic testing services. He is the principal investigator of the MedSeq Project, the first NIH-funded research study to explore the use of whole-genome sequencing in the clinical practice of medicine, and he co-directs the BabySeq Project, the first NIH-funded trial of sequencing in newborns. The MedSeq and BabySeq projects are conducing pilot trials in utilizing whole-genome sequencing, both in patients who are affected with hereditary disease and in those who are healthy, and studying downstream impact on health, behavior, and economics. Dr. Green is currently the associate director for research at the Partners Center for Personalized Genetic Medicine, a board member of the Council for Responsible Genetics and a member of the informed cohort oversight

boards for both the Children's Hospital Boston Gene Partnership Program and the Coriell Personalized Medicine Collaborative. He was lead author of the recently published recommendations from the American College of Medical Genetics and Genomics for the management of incidental findings in clinical sequencing.

Madhuri Hegde, Ph.D., FACMG, is a professor of human genetics and the executive director of the Emory Genetics Laboratory at Emory University. Her areas of specialty and interest are muscular dystrophy and novel and high-throughput methodologies to detect and interpret 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 next-generation sequencing strategies for rare disorders using sequence capture technologies, robotics, clinical exome and genome sequencing, oligonucleotide array platforms, and robotics. Her research is focused on gene discovery and the functional analysis of sequence variants in disease-associated genes, specifically muscular dystrophies and translating what is learned in the basic research laboratory to clinical practice. 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 Baylor College of Medicine and is board certified in clinical molecular genetics.

Kathleen T. Hickey, Ed.D., FNP-BC, ANP-BC, R.N., CCRN, APNG, FAHA, FAAN, is an assistant professor of nursing and a family/adult nurse practitioner in the Division of Cardiology at Columbia University. She is also a Robert Wood Johnson Foundation Nurse Faculty Alumni, focusing her research on the interrelated areas of arrhythmias, cardiogenetics, and the prevention of sudden cardiac death. Dr. Hickey has received funding from NIH, the Robert Wood Johnson Foundation, and Columbia University to support her research endeavors. For more than 20 years she has collaborated with interdisciplinary teams in her role as a nurse practitioner on several landmark multi-center NIH clinical trials that contributed significant advances in knowledge to the fields of arrhythmia, heart failure, and overall cardiovascular research. She consistently advocates for nursing's critical role in the rapidly evolving field of genomics while raising public awareness of potentially life-threatening cardiac conditions. Dr. Hickey is part of a small cadre of cardiogenetic

nurse practitioners in the United States who focus on improving the lives of families with inherited cardiac conditions. She is actively involved in the American Heart Association Council on Cardiovascular Nursing and Functional Genomics and the International Society of Nursing Genetics (ISONG). She is the past president of ISONG, and her efforts are recognized on both a national and international level. Dr. Hickey received her doctorate from Columbia University, and her postdoctoral education includes participation in the National Institute of Nursing Research Summer Genetics Institute and NHGRI. She is recognized as a nurse leader who shapes and improves the lives of cardiovascular patients and their families.

Amy Hower, Ph.D., is a neuroscientist focused largely in the fields of neural development and regeneration. Her thesis work was concentrated in the areas of axon growth and guidance, receptor biology, enzyme biology, cell signaling, and oncogenesis. She has technical expertise in many aspects of molecular biology, protein biochemistry, imaging, cell culture, and behavior. Dr. Hower received her Ph.D. in neuroscience from the University of Miami School of Medicine and her bachelors degrees from the UNC at Chapel Hill. She has also carried out research projects at Harvard University, the University of Hawaii, Duke University, and field stations, including Mount Desert Island Biological Laboratory in Maine and Tiputini Research Station in Ecuador. Dr. Hower has authored multiple peer-reviewed papers and received various competitive awards and recognitions.

Louis B. Jacques, M.D., joined the Centers for Medicare & Medicaid Services (CMS) in 2003 and has been director of the Coverage and Analysis Group (CAG) since October 2009. The group reviews evidence and develops Medicare national coverage policy. From 2004 through 2009 he was director of the Division of Items and Devices within CAG. Prior to his arrival at CMS, Dr. Jacques was the associate dean for curriculum at Georgetown University School of Medicine, where he retains a faculty appointment. He served on a number of university committees including the executive faculty, committee on admissions, and the institutional review board. He previously worked in the palliative care program at Georgetown's Lombardi Cancer Center where he covered the gynecologic oncology service and he made home visits as a volunteer physician for a rural hospice on the Maryland Eastern Shore.

Muin J. Khoury, M.D., Ph.D., is the first and current director of the Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC). The office was formed in 1997 to evaluate how advances in human genomics can be used responsibly and effectively to improve health and prevent disease across the lifespan. CDC's 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 CDC as an epidemic intelligence service officer in 1980 in the Birth Defects and Genetic Diseases Branch and served as a medical epidemiologist in that branch beginning in 1987. In 1990 he became deputy chief of the same branch. In addition to his CDC role, since 2007 Dr. Khoury has served as a senior consultant in public health genomics at the NCI. Since 2011 he has also served as the acting associate director for the Epidemiology and Genomics Research Program in the Division of Cancer Control and Population Sciences at NCI. Dr. Khoury received his B.S. in biology and chemistry from the American University of Beirut, Lebanon, and received his medical degree and pediatrics training from the same institution. He received a Ph.D. in human genetics and 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, is a member of many professional societies, and serves on the editorial boards of several journals. He is an adjunct professor of epidemiology at the Emory University School of Public Health and an associate in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health.

Shashikant Kulkarni, Ph.D., is the director of cytogenomics and molecular pathology at Washington University School of Medicine in St. Louis. He is an associate professor in the departments of pathology and immunology, pediatrics, and genetics. He trained at Harvard Medical School, Imperial College in London, and at the All India Institute of Medical Sciences. He is a board-certified medical geneticist by the American Board of Medical Genetics. In his role at Washington University, Dr. Kulkarni oversees one of the most modern Clinical Laboratory Improvement Amendments–certified and College of American Pathologist–accredited state-of-the-art, full-service academic cytogenomics and molecular pathology laboratories in the country, which is currently staffed by more than 150 board-certified pathologists, clinical ge-

nomocists, clinical bioinformaticists, and certified genetic technologists. Test areas include prenatal diagnostics, perinatal and childhood studies in the evaluation of congenital and developmental disorders, infertility and pregnancy loss studies, and cancer. Dr. Kulkarni is actively involved in defining standards for next-generation sequencing in clinical diagnostics through his collaboration with CDC through the Clinical Next-Generation-Sequencing Quality Standards National Working Group, and he is a co-chairman of the Clinical Laboratory Standards Institute for microarray-based clinical diagnostics. He also serves on the scientific advisory board of the National Institute of General Medical Science. Dr. Kulkarni is considered an expert and key opinion leader in the field of clinical genomics and next-generation sequencing technology, and he has given numerous invited presentations both nationally and internationally. He is on the editorial board of several peer-reviewed journals. Dr. Kulkarni is the program director of the clinical genomics training program at the Washington University School of Medicine and trains residents and fellows in clinical genomics. He conducts basic research in the genomics of multiple myeloma and acute myeloid leukemia and has published extensively in such peer-reviewed journals as *Cell*, *Nature*, *Nature Biotechnology*, *Journal of American Medical Association*, and *New England Journal of Medicine*.

Debra G. B. Leonard, M.D., Ph.D., is professor and chair of the Department of Pathology, University of Vermont College of Medicine, and physician leader of pathology and laboratory medicine at Fletcher Allen Health Care in Burlington, Vermont. She is an expert in the molecular pathology of genetic and infectious diseases and cancer and in policy development for genomic medicine. Her M.D. and Ph.D. degrees were completed at the New York University School of Medicine, where she also did her postgraduate clinical training in anatomic pathology, including a surgical pathology fellowship. She is certified by the American Board of Pathology in anatomic pathology and by the American Boards of Pathology and Medical Genetics in molecular genetic pathology. Currently Dr. Leonard is a member of the IOM Roundtable on Translating Genomic-Based Research for Health, and she previously served as a member of the IOM Committee on the Review of Genomics-Based Tests for Predicting Outcomes in Clinical Trials. She is a fellow of the College of American Pathologists (CAP) and chair of CAP's personalized health care committee. Dr. Leonard is a past member of the Secretary's Advisory Committee on Genetics Health and Society to Secretary Michael O.

Leavitt and a past president and 2009 Leadership Award recipient of the Association for Molecular Pathology. She has spoken widely on various molecular pathology test services, the future of molecular pathology, the impact of gene patents on molecular pathology, and the practice of genomic medicine.

Gary Lyman, M.D., M.P.H., is a practicing medical oncologist and is nationally and internationally recognized for his leadership in comparative effectiveness, health services, and outcomes research. He is a full member in the Cancer Prevention Program, Public Health Sciences Division at the Fred Hutchinson Cancer Research Center, where he co-directs the Hutchinson Institute for Cancer Outcomes Research, a multidisciplinary team devoted to clinical and economic evaluations of new and existing cancer prevention, screening, and treatment technologies. In addition, Dr. Lyman is a professor in the School of Public Health and School of Pharmacy at the University of Washington. The overarching goal of Dr. Lyman's research is the reliable and valid demonstration of the efficacy, effectiveness, and safety of clinical interventions in real-world cancer patients, ranging from prevention and screening to treatment to survivorship and cancer surveillance. He has published some 400 research articles in the professional medical literature. Dr. Lyman's research has played a key role in establishing clinical practice guidelines for cancer management through the American Society of Clinical Oncology (ASCO), and he is co-leading the development of comprehensive ASCO breast cancer and survivorship guidelines. He has served on numerous ASCO committees, including the ASCO Value in Cancer Care Task Force, which is leading efforts to integrate economics into evidence-based medicine, policy, and research. Dr. Lyman currently serves on the ASCO board of directors and is also active with the American Society of Hematology and several other professional clinical and cancer research organizations.

Robert S. McDonough, M.D., J.D., is senior director of clinical policy research and development for Aetna, where he is responsible for developing Aetna's clinical policies. He is co-chairman of Aetna's Pharmacy and Therapeutics Committee and Aetna's Policy and Plan Design Committee. He is a member of the advisory board for the Institute for Clinical and Economic Review. He has special interests in preventive health services, technology assessment, and outcomes research. He is former senior analyst and project director with the health program of the Congressional

Office of Technology Assessment. He is a graduate of the Duke University School of Medicine and School of Law (J.D.), and he has a master's degree in policy analysis from Duke's Sanford Institute of Public Policy. He completed an internship in internal medicine at the Stanford University School of Medicine and is a fellow of the American College of Legal Medicine.

Heidi L. Rehm, Ph.D., FACMG, is the director of the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine and an assistant professor of pathology at Harvard Medical School. Her lab focuses on the translation of new genetic discoveries and technologies into clinical tests that can be used to improve patient outcomes, supporting the model of personalized medicine. Dr. Rehm also conducts research in hearing loss, Usher syndrome, genomic medicine, and health care information technology.

Mark Robson, M.D., is an attending physician of the Clinical Genetics and Breast Cancer Medicine Services in the Department of Medicine at Memorial Sloan–Kettering Cancer Center. He received his B.Sc. from Washington and Lee University and his M.D. from the University of Virginia. He performed residency and fellowship training at Walter Reed Army Medical center before coming to Memorial Sloan–Kettering in 1996. He is currently the clinic director of the Clinical Genetics Service and the immediate past chair of the Cancer Genetics Subcommittee of the Cancer Prevention Committee of the American Society of Clinical Oncology. Dr. Robson's research is primarily directed toward improving the integration of genetic information into the clinical management of women with breast cancer. He and his colleagues have conducted a number of studies examining outcomes in women with hereditary breast cancer in order to better define the risks and benefits of treatments such as breast-conserving therapy and adjuvant chemotherapy in this group. He and his co-workers have also conducted a number of studies examining the effectiveness of screening interventions such as breast magnetic resonance imaging or ovarian cancer screening in women at hereditary risk. He is currently conducting studies to evaluate the impact of intensive screening or surgical prevention upon women's quality of life and to develop new screening tools, such as serum peptide profiling. He is also investigating the optimal integration of new genetic technologies, such as genomic profiling, into the care of women at risk for breast cancer.

Howard M. Saal, M.D., is a professor of pediatrics at the University of Cincinnati College of Medicine. He is the director of the Section of Clinical Genetics in the Division of Human Genetics at Cincinnati Children's Hospital Medical Center and medical director of the Cytogenetics Laboratory. Dr. Saal is board certified in clinical genetics, clinical cytogenetics, and pediatrics. Prior to moving to Cincinnati, Dr. Saal was the director of the Cytogenetics Laboratory at the University of Connecticut Health Center and subsequently vice-chairman of the Department of Medical Genetics at Children's National Medical Center in Washington, DC, where he was also the director of the Craniofacial Center. Dr. Saal is interested in the genetic etiologies and natural histories of craniofacial disorders, especially cleft lip and cleft palate. He is also has an interest in the ethical aspects of genetics, genomics, and genetic testing. Dr. Saal has authored or co-authored more than 100 publications primarily centered on the etiology, natural history, and management of various genetic conditions, with special attention to neurofibromatosis, cleft lip, cleft palate, and Pierre Robin sequence. His career has also included involvement in community activities, having been named to the health professionals advisory committee and later to the board of directors of the National Capital Area March of Dimes, and he serves on the medical advisory council for the Ohio Bureau for Children with Medical Handicaps and Developmental Disorders. His national committee activities include having been chair of the American Academy of Pediatrics (AAP) Section on Genetics and Birth Defects, chair of the AAP Committee on Genetics, and president of the American Cleft Palate–Craniofacial Association. Dr. Saal has been at Cincinnati Children's Hospital Medical Center for 20 years, and his accomplishments have included establishing urban genetics outreach clinics in Hamilton County, developing the Cincinnati Children's Hereditary Cancer Program, and acting as director of the Craniofacial Center at Cincinnati Children's, where he continues to cultivate his interests in the care of children and families with genetic conditions and craniofacial disorders.

Sharon Terry, M.A., is president and chief executive officer of the Genetic Alliance, a network of more than 10,000 organizations, 1,200 of which are disease advocacy organizations. Genetic Alliance improves health through the authentic engagement of communities and individuals. It develops innovative solutions through novel partnerships, connecting consumers to smart services. Ms. Terry is the founding chief executive officer of PXE International, a research advocacy organization for the

genetic condition pseudoxanthoma elasticum (PXE). As co-discoverer of the gene associated with PXE, *ABCC6*, she holds the patent for that gene and has assigned her rights to the foundation. She developed a diagnostic test for PXE and is conducting clinical trials. Ms. Terry is also a co-founder of the Genetic Alliance Registry and Biobank. She is the author of more than 90 peer-reviewed articles. In her position at the forefront of consumer participation in genetics research, services, and policy, she serves in a leadership role on many of the major international and national organizations, including the IOM Health Sciences Policy Board, the National Coalition for Health Professional Education in Genetics board, and the International Rare Disease Research Consortium Interim Executive Committee, and is a member of the IOM Roundtable on Translating Genomic-Based Research for Health. She is on the editorial boards of several journals. She was instrumental in the passage of the Genetic Information Nondiscrimination Act. She received an honorary doctorate from Iona College in 2005 for her work in community engagement, the first Patient Service Award from the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy in 2007, the Research!America Distinguished Organization Advocacy Award in 2009, and the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011. She is an Ashoka Fellow.

David L. Veenstra, Pharm.D., Ph.D., is a professor in the Pharmaceutical Outcomes Research and Policy Program in the Department of Pharmacy and a member of the Institute for Public Health Genetics at the University of Washington, Seattle. He graduated from the University of California, San Francisco, with doctoral degrees in clinical pharmacy and computational chemistry. He carried out his postdoctoral training in outcomes research with the University of Washington, including a 1-year externship with Roche Global Pharmacoeconomics. Dr. Veenstra's primary research interests are the clinical, economic, and policy implications of using genomic information in health care. His major research projects include evaluation of warfarin pharmacogenomics and decision modeling in breast and lung cancer to inform research prioritization and stakeholder decision making. Dr. Veenstra's research is funded through grants from the CDC, NCI, NHGRI, and the National Institute for General Medical Sciences. Dr. Veenstra is a member of EGAPP, a CDC-sponsored, evidence-based recommendation group for genetic tests. Dr. Veenstra's other major research interest is the development of disease-simulation models for chronic diseases. He has worked extensively with

the Academy of Managed Care Pharmacy to develop guidelines and train decision makers in the practical application of cost-effectiveness models. Dr. Veenstra is an author or co-author of 100 peer-reviewed publications and 5 book chapters.

Appendix C

Statement of Task

An ad hoc planning committee will organize and conduct a public workshop to examine the process for evaluating evidence for genomic applications. The workshop goal is to evaluate how evidence for genomic applications is gathered and assessed for clinical decision making, reimbursement decisions, and guideline development in the absence of an ideal information base. The workshop will also address how evidence is evaluated for determining what secondary genome sequencing information should be returned to patients. Current models will be evaluated to advance discussions among diverse stakeholder groups which may include academic researchers, industry and professional society representatives, clinicians, patients, payers, and laboratory test developers. The planning committee will develop the workshop agenda, select speakers and discussants, and moderate the discussions. An individually authored summary of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures.

Appendix D

Registered Attendees

Diane Allingham-Hawkins
Hayes, Inc.

Euan Ashley
Stanford University

James Battle
University of California, Santa Cruz

Judith Benkendorf
American College of Medical Genetics and Genomics

Jonathan Berg
University of North Carolina at Chapel Hill

Barbara Biesecker
National Human Genome Research Institute, National Institutes of Health

Paul Billings
Life Technologies

Bruce Blumberg
Kaiser Permanente Northern California

Jan Blusztajn
Boston University

Khaled Bouri
U.S. Food and Drug Administration

Pam Bradley
U.S. Food and Drug Administration

Ruth Brenner
Air Force Medical Support Agency

P. J. Brooks
Office of Rare Diseases Research, National Institutes of Health

Susie Calhoun
Blue Cross and Blue Shield Association
Federal Employee Program

Khatereh Calleja
Advanced Medical Technology Association

Kathryn Camp
Office of Dietary Supplements
National Institutes of Health

Sarah Carter
J. Craig Venter Institute

Ann Cashion
National Institute of Nursing Research
National Institutes of Health

Robert Cook-Deegan
Duke University

Michael Crossey
TriCore Reference Laboratories

Bob Darnell
New York Genome Center
Howard Hughes Medical Institute Rockefeller University

Patricia Deverka
Center for Medical Technology Policy

Jordan Dimitrakoff
Brady Urological Institute

Maria DeTolve Donoghue
G&M Consulting

Michael Dougherty
American Society of Human Genetics

Tonya Dowd
Quorum Consulting

Lynn Dressler
Mission Health

Jennifer Dreyfus
Dreyfus Consulting, LLC

Emily Edelman
Jackson Laboratory

Stanley Edlavitch
University of Missouri–Kansas City, School of Medicine

Raith Erickson
Complete Genomics

Jessica Everett
University of Michigan

Altovise Ewing
Johns Hopkins University

Greg Feero
Journal of the American Medical Association

Tamara Feldblyum
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Lynn Fellman
Fellman Studios

Shannon Firth
U.S. News & World Report

Mark Fleury
American Cancer Society, Cancer Action Network

Phyllis Frosst
Personalized Medicine Coalition

Michael Gambello
Emory University School of Medicine

Jonn Gardenier
Retired

Turkan Gardenier
Pragmatica Corporation

Geoff Ginsburg
Duke University

Katrina Goddard
Kaiser Center for Health Research

Gabriela Gomez
Innova Translational Medicine Institute

Peter Goodhand
Global Alliance for Genomics and Health

Kristi Graves
Georgetown University

Robert Green
Brigham & Women's Hospital and Harvard Medical School

Paula Grossman
Blue Cross and Blue Shield Association

Pertti Hakkinen
National Library of Medicine
National Institutes of Health

Jennifer Hall
Lillehei Heart Institute
University of Minnesota

Alyson Hanish
National Institutes of Health

Madhuri Hegde
Emory University

Kathleen Hickey
Columbia University

Amy Hower
Stanford University

Louis Jacques
Centers for Medicare & Medicaid Services

Samuel Johnson
Kaiser Permanente Colorado

Kristina Krasnov
U.S. Department of State

Shashikant Kulkarni
Washington University

Gabriela Lavezzari
Pharmaceutical Research and Manufacturers of America

Thomas Lehner
National Institute of Mental Health
National Institutes of Health

Debra G. B. Leonard
Fletcher Allen Health Care
University of Vermont College of Medicine

Laura Levit
Institute of Medicine

Emily Levy
Synergy Partners

Mark Lim
FasterCures

Mel Limson
Association for Molecular Pathology

Maggie Linak
U.S. Agency for International Development

David Litwack
U.S. Food and Drug Administration

Suzanne Luther
Social Security Administration

Gary Lyman
Fred Hutchinson Cancer Research Center

Julie Lynch
Veterans Health Administration

Jennifer Madsen
College of American Pathologists

Teri Manolio
National Human Genome Research Institute

Saralyn Mark
National Aeronautics and Space Administration

Anna Mazzucco
National Research Center for Women and Families

Bob McCormack
Veridex, LLC

Robert McDonough
Aetna

Andrew Meltzer
George Washington University

Ronald Miller
Air Force Medical Support Agency

Suman Mukherjee
Genetic Alliance

Padmaja Mummaneni
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Becky Nagy
Ohio State

Shelley Fuld Nasso
National Coalition for Cancer Survivorship

Ernie Niblack
WaferGen Biosystems, Inc.

Casey Overby
University of Maryland

Erin Payne
Northrop Grumman Health IT

Michelle Penny
Eli Lilly and Company

Vicky Pratt
Association for Molecular Pathology

Ron Przygodzki
Department of Veterans Affairs

Nalini Raghavachari
National Institutes of Health

Kate Reed
Jackson Laboratory

Heidi Rehm
Partners Center for Personalized Genetic Medicine

Kris Rickhoff
Washington University School of Medicine

Mark Robson
Memorial Sloan–Kettering Cancer Center

Allen Roses
Duke University

Julie Rousseau
Claritas Genomics

Howard Saal
Cincinnati Children's Hospital Medical Center

Sarah Savage
Boston Children's Hospital

Mari Savickis
American Medical Association

Kate Saylor
National Human Genome Research Institute

Derek Scholes
National Human Genome Research Institute

Joan Scott
Health Resources and Services Administration

Prashant Shah
Intel Corporation

Fay Shamanski
College of American Pathologists

Sam Shekar
Northrop Grumman Health IT

Deborah Smith
Blue Cross and Blue Shield Association
Federal Employee Program

Allen Spiegel
Albert Einstein College of Medicine

Kimberly Strong
Center for Bioethics and Medical Humanities
Medical College of Wisconsin

Katie Johansen Taber
American Medical Association

Darius Tahir
"The Gray Sheet"

Zivana Tezak
U.S. Food and Drug Administration

Lyubov Tmanova
Weill Cornell Medical College

Kemi Tomobi
Student National Medical Association

Hoang-Lan Tran
Quorum Consulting

Sylvia Trujillo
American Medical Association

Lois Tully
National Institute of Nursing Research
National Institutes of Health

David Veenstra
University of Washington

Catharine Wang
Boston University School of Public Health

Michael Watson
American College of Medical Genetics and Genomics

Meredith Weaver
American College of Medical Genetics and Genomics

Jennifer Weisman
Strategic Analysis, Inc.

Jon White
Agency for Healthcare Research and Quality

Janet Williams
University of Iowa

Mary Steele Williams
Association for Molecular Pathology

Catherine Witkop
U.S. Air Force

Rina Wolf
XIFIN, Inc.