Issues in Returning Individual Results from Genome Research Using Population-Based Banked Specimens, with a Focus on the National Health and Nutrition Examination Survey: A Workshop Summary

ISBN
978-0-309-30704-8

114 pages
6 x 9
PAPERBACK (2014)

Kevin Kinsella, Rapporteur; Steering Committee on the Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens; Committee on National Statistics; Division of Behavioral and Social Sciences and Education; National Research Council

Issues in Returning Individual Results from Genome Research Using Population-Based Banked Specimens, with a Focus on the National Health and Nutrition Examination Survey

WORKSHOP SUMMARY

Kevin Kinsella, *Rapporteur*

Steering Committee for the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens

Committee on National Statistics

Division of Behavioral and Social Sciences and Education

NATIONAL RESEARCH COUNCIL
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 project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by a transfer from the National Center for Health Statistics to Grant No. SES-1024012 between the National Academy of Sciences and the National Science Foundation, which provides funding for the Committee on National Statistics from a consortium of federal agencies. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number-13: 978-0-309-30704-8
International Standard Book Number-10: 0-309-30704-X

Additional copies of this report are available 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.

Printed in the United States of America

Suggested citation: National Research Council. (2014). *Issues in Returning Individual Results from Genome Research Using Population-Based Banked Specimens, with a Focus on the National Health and Nutrition Examination Survey: A Workshop Summary*. K. Kinsella, Rapporteur. Steering Committee for the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.

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

STEERING COMMITTEE FOR THE WORKSHOP ON GUIDELINES FOR RETURNING INDIVIDUAL RESULTS FROM GENOME RESEARCH USING POPULATION-BASED BANKED SPECIMENS

WYLIE BURKE (*Chair*), Department of Bioethics and Humanities, University of Washington
LESLIE G. BIESECKER, Genetic Disease Research Branch, National Human Genome Research Institute
JEFFREY BOTKIN, Division of Medical Ethics and Humanities, University of Utah
MILDRED K. CHO, Center for Biomedical Ethics, Stanford University School of Medicine
ELLEN WRIGHT CLAYTON, Center for Biomedical Ethics and Society, Vanderbilt University
EILEEN M. CRIMMINS, Davis School of Gerontology, University of Southern California

KEVIN KINSELLA, *Study Director*
JACQUELINE R. SOVDE, *Program Associate*

COMMITTEE ON NATIONAL STATISTICS
2013-2014

LAWRENCE D. BROWN (*Chair*), Department of Statistics, The Wharton School, University of Pennsylvania
JOHN M. ABOWD, School of Industrial and Labor Relations, Cornell University
MARY ELLEN BOCK, Department of Statistics, Purdue University
DAVID CARD, Department of Economics, University of California, Berkeley
ALICIA CARRIQUIRY, Department of Statistics, Iowa State University
MICHAEL E. CHERNEW, Department of Health Care Policy, Harvard Medical School
CONSTANTINE GATSONIS, Center for Statistical Sciences, Brown University
JAMES S. HOUSE, Survey Research Center, Institute for Social Research, University of Michigan
MICHAEL HOUT, Department of Sociology, New York University
SALLIE KELLER, Virginia Bioinformatics Institute at Virginia Tech, Arlington, VA
LISA LYNCH, The Heller School for Social Policy and Management, Brandeis University
COLM O'MUIRCHEARTAIGH, Harris School of Public Policy Studies, University of Chicago
RUTH PETERSON, Criminal Justice Research Center, Ohio State University
EDWARD H. SHORTLIFFE, Departments of Biomedical Informatics, Columbia University and Arizona State University
HAL STERN, Donald Bren School of Information and Computer Sciences, University of California, Irvine

CONSTANCE F. CITRO, *Director*

Acknowledgments

This report summarizes the proceedings of a workshop convened in February 2014 to consider guidelines for returning individual results from genomic research using population-based banked specimens. The workshop was sponsored by the National Center for Health Statistics (NCHS) and convened by the Committee on National Statistics (CNSTAT) in the Division of Behavioral and Social Sciences and Education (DBASSE) of the National Research Council (NRC).

The workshop was organized by a six-member steering committee composed of experts in the fields of bioethics, law and genetics, biomedical genetics, and demography. The committee was chaired by Wylie Burke, University of Washington, and included Leslie G. Biesecker, National Human Genome Research Institute; Jeffrey Botkin, University of Utah; Mildred K. Cho, Stanford University; Ellen Wright Clayton, Vanderbilt University; and Eileen M. Crimmins, University of Southern California. The committee provided indispensable guidance in developing the workshop agenda, securing expert presentations, and facilitating the conduct of the workshop. Although the steering committee members played a central role throughout, they did not actively participate in writing this summary.

The committee would like to thank NCHS staff members Virginia Cain, Jennifer Madans, Geraldine McQuillan, and Kathryn Porter for their planning-meeting input prior to the workshop. The presentations during the workshop provided the basis for lively and informative discussions. We greatly appreciate the contributions of Benjamin Berkman,

Laura Beskow, Barbara Biesecker, Jeffrey Botkin, Kelly Edwards, Carolyn Tucker Halpern, Tina Hambuch, Robert M. Hauser, Gail Jarvik, Steven Joffe, Sharon Kardia, Muin Khoury, Jennifer H. Madans, Martha McClintock, John Moye, Kathryn Porter, Henry S. Richardson, David Weir, Marc Williams, and Susan M. Wolf.

The steering committee acknowledges the work of the staff of the NRC in organizing the workshop and this report. Constance F. Citro, director of CNSTAT, provided overall direction and guidance for the project. Adam C. Berger of the Institute of Medicine offered valuable suggestions regarding steering committee membership and chaired a workshop session. Kevin Kinsella of the DBASSE Committee on Population assisted with organizing the steering committee and setting the agenda for the study, and served as rapporteur for the workshop. Jacqui Sovde of CNSTAT provided invaluable assistance with all aspects of the project, including myriad logistical details as well as report preparation. Paula Whitacre edited the report, and Kirsten Sampson Snyder orchestrated the review process.

This workshop summary was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the Report Review Committee of the NRC. The purpose of this independent review is to provide candid and critical comments that assist the institution in making its 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 deliberative process.

The panel thanks the following individuals for their review of this report: Eileen M. Crimmins, Andrus Gerontology Center, University of Southern California; Alan R. Fleischman, Clinical Pediatrics and Clinical Epidemiology and Population Health, Albert Einstein College of Medicine; Norman Fost, Pediatrics and Bioethics, University of Wisconsin School of Medicine and Public Health; and Jennifer R. Harris, Division of Epidemiology, The Norwegian Institute of Public Health, Oslo, Norway.

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the report nor did they see the final draft of the report before its release. The review of this report was overseen by Robert M. Groves, Provost and Department of Mathematics and Statistics, and Department of Sociology, Georgetown University. Appointed by the NRC, he was responsible for

making certain that the 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 the report rests entirely with the rapporteur and the NRC.

Wylie Burke, *Chair*
Steering Committee for the Workshop on
Guidelines for Returning Individual Results from
Genomic Research Using Population-Based Banked Specimens

Contents

1 INTRODUCTION 1

2 GENOMICS IN POPULATION-BASED DATA COLLECTION: THE EXAMPLE OF THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 5

3 PERSPECTIVES ON RETURNING GENOME-BASED RESEARCH RESULTS 9
Role-Based Obligations, 9
The Case for a Cautious Approach to Returning Results, 10
The Case for Broader Return of Results, 12

4 FRAMING THE DISCUSSION 17
The Evolution of Genomic Technology and Clinical Utility, 17
Ethical Frameworks, 20

5 HOW IS NHANES SIMILAR TO/DIFFERENT FROM OTHER POPULATION-BASED STUDIES? 25
The National Longitudinal Study of Adolescent Health, 25
The Health and Retirement Study, 26
The National Social Life, Health, and Aging Project, 28
The Wisconsin Longitudinal Study, 29
The National Children's Study, 30
Illumina, 31

6 ISSUES FOR NHANES 35
The Scientific Value of Incorporating Genomic Data Collection into NHANES, 35
Determining What Data Are Returnable, 36
Survey Participant Attitudes and Preferences, 41

7 THE LOGISTICS OF RETURNING GENOMIC RESULTS FROM NHANES 45
The NHANES View, 45
Retrospective Versus Prospective Samples, 47
Practical Aspects of Returning Results, 49

8 SPECIAL CONSIDERATIONS FOR REPORTING OF RESULTS IN NHANES 53
Statistical Agency Considerations in Releasing DNA Results, 53
The Notion of Genetic Exceptionalism, 55

9 SUMMARY OF PRESENTATIONS AND DISCUSSION 59
Genetics and the NHANES Mission, 59
Usefulness for Genetic Research, 60
Should Genetic Results Be Returned to Participants?, 61
Adaptive Governance and Communication with Participants, 62
Participant Consent or Re-Consent Regarding Genetic Data, 64
Participant Understanding of Trade-Offs, 64
Should Population-Based Biobank Research Live by Different Rules?, 64
Further Clarifications for NCHS, 66

REFERENCES 69

ACRONYMS 73

APPENDIXES
A Workshop Agenda 75
B List of Registrants 79
C Biographical Sketches of Steering Committee Members and Presenters 87

1

Introduction

Population surveys traditionally collect information from respondents about their circumstances, behaviors, attitudes, and other characteristics. In recent years, many surveys have been collecting not only questionnaire answers, but also biologic specimens such as blood samples, saliva, and buccal swabs, from which a respondent's DNA can be ascertained along with other biomarkers (e.g., the level of a certain protein in the blood). The National Health and Nutrition Examination Survey (NHANES), sponsored by the National Center for Health Statistics (NCHS), has been collecting and storing genetic specimens since 1991, and other surveys, such as the Health and Retirement Study (HRS) funded by the National Institute on Aging, have followed suit. In order to give their informed consent to participate in a survey, respondents need to know the disposition and use of their data. Will their data be used for one research project and then destroyed, or will they be archived for secondary use? Sponsors of repeated cross-sectional surveys, such as NHANES, and of longitudinal surveys that follow panels of individuals over time, such as HRS, generally want to retain data for a wide range of secondary uses, many of which are not explicitly foreseen at the time of data collection. They typically inform respondents that their data will be stored in a secure manner and may be provided to researchers with suitable protections against individual identification.

The addition of biologic specimens to a survey adds complications for storing, protecting, and providing access to such data and measurements made from them. There are also questions of whether, when, and

for which biologic measurements the results should be reported back to individual respondents. NHANES, which administers a complete physical examination including the taking of various biologic specimens, has developed protocols for informing respondents of which test results (e.g., cholesterol levels in blood) will be reported to the individual respondent. However, for genetic specimens, NHANES and other surveys have not until recently seen a need to do other than inform respondents that no DNA test results will be reported back to them. Two reasons supported this blanket nonreporting procedure: (1) the cost of DNA analysis; and, more importantly, (2) the paucity of robust research findings on the relationship of a gene or group of genes to specific diseases or syndromes, which meant that reporting of a respondent's possession of a gene or gene sequence would not be informative.

Recently, the cost of full genomic sequencing has plummeted, and research findings are beginning to accumulate that bear up under replication and that potentially have clinical implications for a respondent. For example, knowing that one possesses a certain gene or gene sequence might suggest that one should seek a certain kind of treatment or genetic counseling or inform one's blood relatives.

Biomedical research studies, in which participants are asked to donate tissues for genetic studies and are usually told that they will not be contacted with any results, are increasingly confronting the issue of when and which DNA results to return to participants. A two-year NIH study recently produced a set of recommendations for biobanks and archived datasets, and concluded that findings that are analytically valid, reveal an established and substantial risk of a serious health condition, and are clinically actionable should generally be offered to consenting contributors (Wolf et al., 2012).

Population surveys that collect biologic specimens are now confronting similar issues, with the added difficulty that survey organizations are not equipped to provide such services as genetic counseling that may be advisable when returning DNA results to individual participants. In addition, it may be years between when a respondent provided a specimen and when that specimen was accessed for research, or when the knowledge base progressed to the point where a meaningful, reportable result could be obtained from the data.

The National Center for Health Statistics and its Ethics Review Board have recognized the need to establish principles and best practices for reporting individual results from genomic research using archived specimens from NCHS surveys. NCHS developed an action plan for NHANES that would involve an attempt to re-contact all previous respondents and obtain their consent (or not) to report back findings and also a revision of consent information for future respondents. The plan also considered

how and by whom decisions should be reached regarding how to handle actionable findings. However, the NCHS Board of Scientific Counselors recommended that NCHS delay implementing its plan, which could be costly and have unintended consequences stemming from participants' reactions, until there had been further input from a wide range of perspectives through a workshop convened by the National Academies. NCHS instituted a moratorium on collecting genetic specimens in NHANES until the workshop was held and its discussions absorbed.

The purpose of this workshop was to consider how population surveys, such as the National Health and Nutrition Examination Survey and others, should (1) implement the reporting of results from genomic research using stored specimens; and (2) address informed consent for future data collection as well as for the use of banked specimens covered by prior informed consent agreements. The workshop afforded an opportunity to think about the return of genomic results within the context of population-based studies, which increasingly incorporate genomic measures in overall data collection. The workshop addressed the conjunction of scientific opportunity, questions about risk and benefit to research participants, and questions about what constitutes trustworthy research practice. (See Box 1-1 for the steering committee's statement of task.)

The intent of the workshop was not to generate specific recommendations, but rather, to have a broad discussion that the NCHS could then draw from as it seeks to identify a clear path forward with respect to NHANES genomic data from both past and future participants. The immediate audience for this summary is the staff of the National Center for Health Statistics and its Ethics Review Board. The broader audience is all survey organizations that include or contemplate including the collection of biologic specimens in population surveys for storing for genetic research. The issues involved are important for advancing social, behavioral, and biomedical knowledge while appropriately respecting and protecting individual survey respondents.

A workshop titled "Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens" took place at the National Academy of Sciences in Washington, DC, February 10-11, 2014. There were seven main sessions and a final session conducted by members of the steering committee and invited speakers.[1] The workshop agenda can be found in Appendix A, and a list of workshop registrants can be found in Appendix B. Appendix C provides biographical sketches of steering committee members and presenters. Each of the following eight chapters (2 through 9) is dedicated to one of these workshop sessions.

[1]Slide presentations and related workshop materials can be found at http://sites.nationalacademies.org/DBASSE/CNSTAT/DBASSE_086008 [June 2014].

BOX 1-1
Steering Committee's Statement of Task

An ad hoc steering committee will organize a public workshop on guidelines and best practices for returning individual results from genome research using population-based banked specimens. The workshop is requested by the National Center for Health Statistics, which has collected genetic specimens in household-based population surveys dating back to 1991. The workshop agenda will address such issues as:

- How population surveys, such as the National Health and Nutrition Examination Survey (NHANES) and others, should implement the reporting of results from genomic research using stored specimens, identifying options for reporting and their advantages and challenges.
- In the context of ever-changing guidance in medical ethics for reporting results from genomic studies, how population surveys should address informed consent for future data collection, as well as implementing the return of results for banked specimens covered by informed consent that did not envision this possibility. Options will be identified and their advantages and challenges considered.

The steering committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussion. Following the workshop, a designated rapporteur will prepare an individually authored summary of the presentations and discussion. Commissioned papers may be published with the summary or posted on the Internet. A verbatim transcript of the workshop presentations and discussions will also be prepared and provided to the sponsor and others who may request it.

This report was prepared by a rapporteur as a factual summary of what occurred at the workshop. The steering committee's role was limited to planning and convening the workshop. The views contained in the report are those of individual workshop participants and do not necessarily represent the views of nonparticipants, other workshop participants, the steering committee, or the National Academies.

2

Genomics in Population-Based Data Collection: The Example of the National Health and Nutrition Examination Survey

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. NHANES is a major program of the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC) and has the responsibility for producing vital and health statistics for the nation. The NHANES program began in the early 1960s and has been conducted as a series of surveys focusing on different population groups or health topics. In 1999, the survey became a continuous program that has a changing focus on a variety of health and nutrition measurements to meet emerging needs. NHANES is a cross-sectional survey of the U.S. household population with an annual sample size of approximately 5,000 individuals. These persons are located in counties across the country, 15 of which are visited each year.

Information is collected through in-person home interviews and health examinations at mobile examination centers. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. Findings from this survey are used to determine the prevalence of major diseases and risk factors for diseases. Information is used to assess nutritional status and its association with health promotion and disease prevention. NHANES findings are also the basis for national standards for such measurements as height, weight, and

blood pressure. Data from the survey are used in epidemiological studies and health sciences research, which help develop public health policy and design health programs and services for the nation. The NHANES Website (http://www.cdc.gov/nchs/nhanes.htm [June 2014]) has a large amount of information about the survey and related research and results.

In this session of the workshop, Kathryn Porter, NCHS, provided an overview of the NHANES. The overall goal of NHANES is to assess the health and nutritional status of children and adults in the United States. The survey focuses on chronic disease, on measures of environmental toxicants, and on diet and nutrition. Another goal of NHANES, which is the focus of the workshop and this summary, is to create and maintain a nationally representative specimen bank.

To obtain participant permission for specimen collection, NHANES uses a four-consent design as part of its continuous survey. There is consent for a household interview and a separate consent for physical examination. The interview and exam response rates have hovered around 75-77 percent, quite high for a health survey (Zipf et al., 2013). NHANES also asks for consent to store blood and urine for nongenetic future research and asks for a separate consent from participants aged 20 and over to store blood for future genetic research. The latter two consents state that the survey organization does not know what tests will be done on the specimens in the future and that participants will not be contacted with results. About 85-90 percent of adults who agree to the exam also agree to allow NHANES to store specimens for genetic research (McQuillan, Pan, and Porter, 2006).

The NHANES staff processes a wide range of specimens, which are sent to 24 laboratories across the country and become the basis of more than 500 assays. Relatively few of these are reported back to participants, namely, only those that have clinical relevance to participants. Participants receive a final report with a preset number of findings in 12 to 16 weeks after the exam and are urged to discuss results with their doctors. If participants want help on how they should follow up on a condition, or about finding an appropriate clinic, referrals are provided. NHANES does not cover any of the costs of follow-up.

As Porter explained, NHANES seeks to report findings that are valid and obtained by a CLIA-certified laboratory.[1] Reportable findings should have significant implications for a participant's health concerns, and a course of action to ameliorate or treat the concerns should be readily available, both of which are in line with recommendations from the Presi-

[1]CLIA refers to regulations established by federal Clinical Laboratory Improvement Amendments; see http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/ [June 2014].

dential Commission for the Study of Bioethical Issues (see http://www.bioethics.gov [June 2014]). Survey participants always have the option to opt out; that is, to say that they do not want to receive any such results. A very small percentage of participants actively opt out.

NHANES DNA specimens have been banked since 1991 and are physically stored at the CDC in Atlanta. From various cycles of NHANES, about 26,000 individuals have given permission to store their specimens in the DNA bank. Data are held within the CDC for confidentiality purposes. No genomic results are allowed into the public domain.

The DNA bank was opened to researchers in 1999 after considerable effort to establish procedures for releasing specimens to researchers while maintaining confidentiality protections promised by law. It was decided that researchers could not investigate genes with clinical relevance because NCHS does not have the capability of providing genetic counseling. Hence, the agency only accepted research proposals that involved candidate genes; that is, single nucleotide polymorphisms (SNPs) of interest. NCHS could critically review these proposals and determine if those SNPs were reportable or not. Most approved research requests involved common gene variants with relatively low associated risk.

As time and science marched on, Porter said, two things changed. First, technology evolved and targeted gene analysis was no longer the standard. NCHS began to receive proposals for genome-wide association studies (GWAS) done with chips with millions of SNPs. Such studies may generate incidental findings, and the question arose as to how potentially reportable gene variants would be handled. The second change involved an evolving ethical context. There was increasing recognition among investigators, institutional review board (IRB) members, and bioethicists that blanket nondisclosure of individual research results and/or incidental findings may be inappropriate in public health research. The acceptability of the NHANES nondisclosure agreements that participants signed in the past came into question.

The NHANES program consulted with review boards and ethicists about how to proceed, and the upshot, Porter explained, was the concept of "binning" the genome, shown in Figure 2-1. Gene variants could be sorted into buckets or bins, with Bin Three having genes of unknown clinical implication and Bin Two containing variants within genes that are clinically valid but not directly actionable. The consensus was that NHANES would not have to act on or report back on items in Bins Two and Three.

Bin One contains variants within genes that have direct clinical utility and for which there are treatment guidelines. The NHANES consultative process recommended that Bin One variants should be reported to participants (Berg, Khoury, and Evans, 2011). This approach was presented

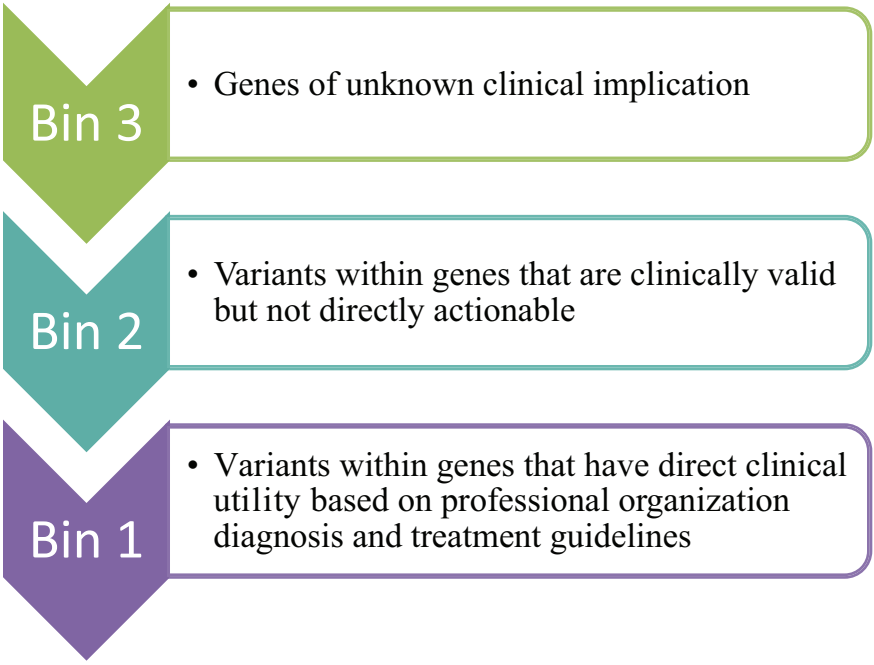

FIGURE 2-1 Binning the genome.
NOTE: An NHANES consultative process recommended that only Bin 1 variants should be considered for reporting.
SOURCE: Adapted from Berg, Khoury, and Evans (2011).

to the NCHS Board of Scientific Counselors, which then called for wider input on how to proceed, not only with regard to NHANES but also because this has become an important issue for many population-based studies.

3

Perspectives on Returning Genome-Based Research Results

Following the overview of the National Health and Nutrition Examination Survey (NHANES), the workshop considered different perspectives on returning genomic results to study participants, including a consideration of the philosophical foundations for returning results. Presenters reflected a vigorous recent debate about return of results, exemplified by a 2013 point-counterpoint exchange in *Science* with regard to incidental findings from clinical sequencing (see McGuire et al., 2013; Wolf, Annas, and Elias, 2013). Presenters included Henry S. Richardson, Georgetown University; Steven Joffe, University of Pennsylvania; and Susan M. Wolf, University of Minnesota, with the session chaired by Jeffrey Botkin, University of Utah.

ROLE-BASED OBLIGATIONS

The overriding question that underlies much of today's debate centers on whether there is an obligation on the part of researchers and/or organizations to report or follow up on unexpected or incidental results and, further, whether there is an obligation to search for incidental or secondary findings of significance. This question may arise in various health-related research contexts, such as, for example, the discovery of HIV infection while doing a study of malaria treatment protocol. Henry Richardson began by discussing a "general duty of rescue," a basic obligation that is incumbent on all persons at all times if one can save someone else from dire peril easily without expending enormous amounts of energy or put-

ting oneself at risk (Merritt, Taylor, and Mullany, 2010). This obligation covers simple warnings, referrals, and simple therapeutic efforts, but does not cover warnings that are logistically difficult, does not cover payments for care, and does not cover therapeutic efforts that are complex and difficult, which is often the case in the context of genetic findings.

Given the difficulties, why would it be obligatory to return results and what is the basis of the obligation? Richardson presented a partial entrustment model, developed initially to address ancillary care responsibility; that is, care that subjects need but which is not required for sound science or study safety. It is a partial model in that it does not cover everything that subjects need, but its scope does include information that comes to light via study procedures, and thus includes incidental findings. He suggested the model can be broadened to include care and help that subjects may need, including return of information (Belsky and Richardson, 2004; Richardson and Cho, 2012).

"Entrustment" comes about as a by-product of the informed consent process, Richardson said, noting that informed consent has a number of functions: a watchdog function, to prevent abuses; a more high-minded function of putting potential subjects in a position to decide autonomously whether to participate; and a basic permission function to proceed with research (e.g., special permissions to touch and sample bodies).[1] Such permissions are rights waivers. People have privacy rights that they are waiving in the informed consent procedure. When researchers accept these waivers, they take on special responsibilities vis-à-vis research participants, Richardson asserted.

In Richardson's view, the partial entrustment model explains why secondary researchers who use banked specimens, and hence have no direct contact with subjects, still may have obligations to report results (via some indirect chain) because the special permissions are inherited or passed along. Researchers have obtained permissions indirectly and therefore have accrued the special responsibilities. These obligations go beyond easy rescue, yet remain limited in strength and will not cover all cases of return of genetic findings (e.g., a case with some cost but little difference to a person's well-being). The model does not support a duty to hunt for findings, he added.

THE CASE FOR A CAUTIOUS APPROACH TO RETURNING RESULTS

Steven Joffe discussed some of the reasons that he said might suggest a cautious approach to returning results to study participants. He framed

[1]See National Research Council (2010) for additional aspects of informed consent.

his discussion in terms of two important questions: (1) ought researchers to offer to return results (or some subset) to participants and, if so, (2) can they actually carry out such a return policy?

Regarding the "ought" issue, he said common guidelines for both nongenetic and genetic results suggest that individual genetic results should be offered to study participants in a timely manner if the results meet all of the following criteria:

a. The finding(s) has important health implications for the participant, and the associated risks are established and substantial.
b. The finding(s) is actionable.
c. The test is analytically valid, and the disclosure plan complies with all applicable laws.
d. The participant has opted to receive his or her individual genetic results.

Joffe continued that the issue then arises as to whether it should be permissible for investigators and participants to agree that findings will not be returned, as has often been the case in past consent procedures (including NHANES). Informed consent, as Richardson noted previously, spells out terms of agreement between an investigator and participant, and is a quasi-contract. As a general matter, competent adults have wide latitude to set the terms of their agreements. Joffe asked if this should be true in the research arena as well. He noted that some terms are or could be considered unconscionable, while others are expressly prohibited by applicable regulations or laws. In the case of return of results, an agreement not to return could be unconscionable if subjects agree to accept a risk of serious harm, but it is more likely the case that the agreement to forego results relates to some potential side benefit. As to whether such an agreement is expressly prohibited, Joffe pointed out there does not appear to be anything in the Common Rule[2] (which governs biomedical and behavioral research with human subjects conducted by federal agencies), or in other laws or regulations at the federal level, that would proscribe it.

This leads to the "can" question, he said: Can researchers carry out the duty (if they accept a duty) to return results given the state of current technologies, which includes not only genomic technologies such as sequencing, but also database technologies, informatics, and curation technologies? It seems extraordinarily difficult to ask a group of researchers to identify pathogenic variants in an unselected population, stated Joffe. To illustrate the difficulties, he used data from a study of participants in ClinSeq, a large-scale medical sequencing clinical research pilot study that

[2]See http://www.hhs.gov/ohrp/humansubjects/commonrule/ [June 2014].

seeks to identify "likely pathogenic" and "definitely pathogenic" variants in 37 high-penetrance cancer-susceptibility genes (Johnston et al., 2012; National Human Genome Research Institute, 2012). There is a potentially large problem with false-positive results, which may stem from several sources: technical error in reading sequences; false-positive associations in the literature (e.g., due to multiple hypothesis testing); incorrect penetrance estimates, especially because most data are based on variants from individuals with known phenotypes or family histories; and inaccurate annotation in reference databases. In Joffe's view, asking research teams to navigate these and related issues would be feasible only if a project were to prospectively specify the genes of interest and the particular variants within those genes, such that all of the curation work could be done prospectively and was not something that research teams had to confront as they dealt with participants and samples.

Joffe said he sees four choices regarding return of genomic results: (1) have no requirement for return as a general matter; (2) require return, but accept a lesser standard of interpretive validity than in a clinical genetics lab, particularly with regard to false positives; (3) expect research teams to achieve clinical-lab standards (which he said seems most unlikely); and (4) send every sample (or every screen-positive sample) to a clinical lab. He concluded that an informed agreement between investigator and prospective participant that no results will be returned is ethically and legally permissible. Further, he said, unless a list of returnable variants (not genes) is specified in advance, the requirement to return secondary findings would be immensely costly, do more harm than good, or both.

THE CASE FOR BROADER RETURN OF RESULTS

Susan Wolf added another dimension to the discussion by focusing her remarks around the notion of public accountability. NHANES is a publicly funded, population-based study that relies on public trust, she noted, and NHANES should approach the return-of-results question in a way that will fulfill its responsibilities to the public and maintain public trust. Involvement of the public in setting policy will be important, in part to understand what study participants regard as valuable information and, in their own lives, actionable information.

Her work on return of results and incidental findings in the context of a biobank or a biorepository suggests that the key concept is that of a biobank research system. One cannot adequately address the return-of-results question if biobank responsibilities are analyzed in isolation. Rather, she stated, biobanks are part of an information flow that often begins with primary research and collections sites (stage 1) feeding data and specimens into a central biobank or similar resource (stage 2). In

addition to storing data and specimens, biobanks can do their own data and sample collections, curation, annotation, analyses and reanalyses, perform quality control, and confirm pathology. And importantly, biobanks can supply secondary research sites (stage 3) with data and specimens. Incidental findings and individual research results that may be considered for return to participants can arise at all three stages (Wolf et al., 2012; Wolf, 2013). A decade or so ago, Wolf said the conventional view was that biobanks should not be concerned with return of results. If something were discovered in a biobank or secondary research site, it would, at most, be returned to the primary research site. More recently, there has been substantial pushback on this view, acknowledging a growing public (participant) interest in results. NHANES should address the role of the biobank research system, she suggested, which in this case is a biobank research system with the responsibilities of a public entity doing a population-based study. NHANES has been returning nongenetic findings for decades, and there is no sharp distinction between genetic and nongenetic findings for the purpose of potential return. Indeed, NHANES has the potential to pioneer publicly accountable return of results and incidental findings in the context of public health. Wolf said that NHANES should undertake a deep consultation with the public in terms of what results and findings they are interested in being offered. She noted that withholding data from subjects may make them "passive purveyors of biomaterials and data" rather than research partners (Kohane et al., 2007).

Wolf mentioned governance innovation already going on via a number of consortia, including the GENEVA Committee on Incidental Findings,[3] the eMERGE Network Return of Results Oversight Committee,[4] the UK Biobank Ethics and Governance Council,[5] and the Coriell Personalized Medicine Collaborative's Informed Cohort Oversight Board.[6] Dynamic

[3]The Gene Environment Association Studies (GENEVA) consortium was initiated by the National Human Genome Research Institute (NHGRI) to identify genetic variants related to complex diseases; to identify variations in gene-trait associations related to environmental exposures; and to ensure rapid sharing of data through the Database of Genotypes and Phenotypes (dbGaP). See https://www.genome.gov/27541319 [June 2014].

[4]The eMERGE (electronic MEdical Records and GEnomics) Network is an NHGRI-supported consortium of five institutions exploring the utility of DNA repositories coupled to Electronic Medical Record (EMR) systems for advancing discovery in genome science. eMERGE also includes an emphasis on the ethical, legal, and social issues related to these endeavors. See http://www.biomedcentral.com/1755-8794/4/13 [June 2014].

[5]The UK Biobank is a national health resource established by the Wellcome Trust Medical Charity, the UK Medical Research Council, the UK Department of Health, the Scottish Government, and the Northwest Regional Development Agency. See https://www.ukbiobank.ac.uk/ [June 2014].

[6]See http://cpmc1.coriell.org/about-the-cpmc-study/advisory-boards [June 2014].

consent processes are being developed to use informatics to track preferences over time.

The cost of return is an important issue, though little research has been published to date rigorously specifying that cost. Another important issue is whether to offer results and incidental findings to a study participant's family members, including after the death of the participant, as genetic and genomic findings may have health and reproductive implications for family members.

Wolf said her main message is that NHANES needs more participatory governance and a governance structure that brings the public into the discussion on return of results and incidental findings. There are many research opportunities in this rich study, she suggested. To simply say "no return" due to technical difficulties is no longer feasible because, as she characterized it, NHANES is a public study with major public responsibilities. The next steps, in her view, involve figuring out how to calibrate the return of results, obtaining accurate costs for different options, and beginning a serious process of public engagement. She suggested that telephonic genetic counseling may be an avenue to explore for containing costs.

Wolf went on to discuss a temporal aspect of DNA and genomic information, one that involves the notion of durability. Basic genomic information does not appreciably change over an individual's lifespan. Wolf said one issue for NHANES would be identifying the types of analyses that can be done, and the resources needed, in order to produce participant information in the 12- to 16-week window after the survey, if NHANES continues to adhere to that timeframe. A second issue, Wolf said, is that science does not know nearly as much about the genome now as it will in two or five years in the future. Gene variants that do not appear actionable at this point in time will be interpreted as actionable going forward.

When thinking about ethical responsibilities in the NHANES study context, Wolf said it is important to recognize the roles of the different actors in the process: data collectors, data curators, and secondary researchers (the three stages she identified in a biobank research system). The National Center for Health Statistics (NCHS) is tasked and funded to collect data, return individual test results to the subjects, make summary statistics available to the public, and provide anonymized data to researchers. NCHS does very little research and is not funded to come up with findings or to determine whether something is actionable or not actionable. After the survey data collection, the genomic specimens go to the Centers for Disease Control and Prevention (CDC) laboratory. The laboratory's duty is curation; its duty does not extend to analysis, evaluation, or a responsibility for reporting results to participants. The third set of actors is researchers, those who analyze the data in the CDC biobank.

Wolf urged careful consideration of the ethical responsibilities in the context of each of these three roles. Those occupying these roles have distinct capabilities and limitations when it comes to determining when there is a responsibility to get back to a participant, and in actually doing so. Although this is the reality of how the NHANES program has operated in the past, Wolf suggested considering how the program should operate going forward. There is widespread national and international consensus that biorepositories have duties of stewardship and ethical responsibility. Specifying NHANES responsibilities with regard to return of results and incidental findings is a crucial next step.

4

Framing the Discussion

As further background for workshop discussion, the next session sought to review the range of information provided by genomic technology and its implications for the concept of clinical utility. The presenters were Gail Jarvik, University of Washington, and Benjamin Berkman, National Human Genome Research Institute. In the session, chaired by Ellen Clayton, Vanderbilt University, two recent ethical frameworks that address the issue of return of results were also considered.

THE EVOLUTION OF GENOMIC TECHNOLOGY AND CLINICAL UTILITY

Gail Jarvik talked about the current state of genetic technology and clinical utility. Genomics in medicine is still new, she began. Although being able to sequence a genome for $1,000 has not yet been reached, as some had predicted, the costs of genome sequencing have dropped substantially due to computing informatics. NextGeneration sequencing[1] is much more rapid and less expensive than prior technologies, she explained, and sequencing is essential to identifying rare genetic variants. Rare variants tend to be more penetrant and more predictive of human health.

Jarvik said several important concepts around this new sequencing

[1]NextGeneration sequencing refers to a variety of methods for DNA sequencing originally developed in the mid-to-late 1990s.

technology should be understood. The first is coverage. When one refers to a whole-genome analysis, this does not mean that the entire genome is being fully analyzed. One cannot reliably determine trinucleotide repeat diseases, such as Huntington's disease. In addition, there are genome regions that are of high homology to another region, and one does not know if the variant being observed is in the gene of concern or in another part of the genome that looks similar. She cited the pharmacogenetic gene CYP2D6 as a good example; although the desire to know people's sequences for CYP2D6 is strong, the information cannot be determined using current technology because there is a highly homologous region. Many other regions of the genome are not read well for various technical reasons.

She identified a second concept, called capture. One can do a whole-genome analysis, but usually an exome or a panel of genes is analyzed, which is much less costly, in order to try to capture areas of the genome of greatest interest. She noted another advantage of capture, which is that it avoids most bacterial and viral DNA that is not important to a given analysis.

Read depth is another key concept. A whole-genome procedure may have a read depth of 20, meaning that everything has been looked at or read 20 times, and a sequence has been generated from those results. The greater the depth—one might have a read depth of 1,000 sequences for a particular region—the more certain are the results. Accuracy for common gene variants is extremely high with sequencing. Accuracy for rare variants, she said, is slightly less so, and is improved by higher read depth. Higher read depth also allows better evaluation for mosaicism.[2]

Copy number variation is also important, she said.[3] SNP arrays are often used to determine copy number variation, as are other technologies that look for stretches of homozygosity[4] across genotypes. There are numerous methods for detecting copy number variation in sequence data, but they are not perfect. They are better for smaller areas, and not as good for large runs. Jarvik explained that, clinically and in research, SNP arrays tend to be favored when looking for larger copy number variations.

The more challenging step in sequencing, she noted, is interpretation.

[2]Mosaicism indicates the presence of two or more cell populations with different genotypes in one individual who has developed from a single fertilized egg.

[3]Copy number variation refers to alterations of the DNA of a genome that result in a cell having an abnormal or, for certain genes, a normal variation in the number of copies of one or more DNA sections.

[4]Homozygosity is the state of having two identical forms of a particular gene, one inherited from each parent.

If something in the ClinGen[5] database has a variant, or if a pathogenic variant has been clearly established, this helps greatly in interpreting results. However, there are many false positives in the literature and in the human genome mutation database, which is why the National Human Genome Research Institute (NHGRI) is investing a great deal of money in ClinGen for better annotation. Variant interpretation of items that one has never seen before can be quite challenging, Jarvik noted.

NextGeneration sequencing is primarily used in clinical panels rather than for whole exome or genome tests. As Jarvik explained, this is partly a cost issue; payers are more likely to cover panels. Panels have an advantage when one encounters unexpected results, because one does not need to order a first test, then possible subsequent tests, which was the common procedure prior to NextGeneration technology. Panels also reveal surprising results that may be thought of as incidental findings, she noted. A key question is how many incidental findings might likely be found in a genome. She pointed out that this has become important clinically, and referred to the American College of Medical Genetics and Genomics (ACMG) list of 56 genes that have been proposed for analysis and return to patients having genomic tests (Green et al., 2013).[6] This list may grow in the future; the Clinical Sequencing Research Project (CSER)[7] has proposed broader lists, including 118 genes that are medically actionable (Berg et al., 2013).

Jarvik highlighted other problems with reporting incidental findings. The current stock of knowledge is often insufficient for positive identification of findings, and there may be major differences in interpretation. CSER screened the human genome mutation database and concluded that 90 percent of what the ACMG said was pathogenic was not necessarily pathogenic (Dorschner et al., 2013). A larger problem she identified involves gene variants of uncertain significance; the vast majority of these

[5]ClinGen is a National Institute of Health-funded resource dedicated to harnessing both research data and the data from the hundreds of thousands of clinical genetics tests being performed each year, as well as supporting expert curation to determine which variants are most relevant to patient care. See http://www.nih.gov/news/health/sep2013/nhgri-25.htm [June 2014].

[6]There has been vigorous debate about the development of the ACMG list and other such lists, focusing in part on the processes by which recommendations are generated (see, e.g., Evans and Rothschild, 2012; McGuire et al., 2013; Wolf, Annas, and Elias, 2013). In 2014, the ACMG revised its recommendations with regard to patient opt-out of analyses of medically actionable genes. See https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf [June 2014].

[7]The Clinical Sequencing Exploratory Program, initiated by NHGRI in 2010, is intended to support the development of methods needed to integrate sequencing into the clinic, and also the ethical, legal, and psychosocial research required to responsibly apply personal genomic sequence data to medical care. See https://www.genome.gov/27546194 [June 2014].

have turned out to be benign as more knowledge is accrued, yet they may be over-interpreted by clinicians.

Jarvik explained that a combination of two consortia—CSER and eMERGE—is engaged in ongoing work aimed at finding a consensus about return-of-research results, motivated by discussions of whether the ACMG 56-gene list and policies around it should apply to research. This work is moving toward agreement that researchers should offer information on actionable variants discovered, whether purposively or incidentally, in the course of their analyses. If a research finding is pathogenic and actionable, Jarvik said in closing her presentation, it should be returned.[8]

ETHICAL FRAMEWORKS

The workshop delved further into the return-of-results discussion with Benjamin Berkman referencing the active debate in the bioethics literature about whether there is an obligation for researchers to return incidental findings. He said while there seems to be an evolving majority view that there is some obligation, the contours of that obligation remain unclear. According to Berkman, this lack of clarity is at least partially due to the fact that there is no consensus about the principle(s) on which such an obligation might rest.

Many reasons have been cited in the literature for why there might be an obligation to disclose genetic incidental findings (GIFs) to research participants, some of which have been mentioned previously during this workshop, Berkman pointed out. These reasons include beneficence, a broad principle that researchers should have the welfare of research participants as a goal, and a more narrow duty to rescue or warn participants if they are in significant imminent danger. Berkman described different formulations of respect for personal autonomy and for participants' right to know about their own information. There is the notion of reciprocity, the idea that investigators owe something to individuals participating in a research project. There are role-based reasons that may be similar to the doctor/patient relationship, and reasons relating to professional responsibility. Justice and fairness have been invoked in various ways, and there are other, more instrumental reasons involving legal liability, public trust in research, and the professional reputation of institutions.

In contrast, Berkman described several arguments against an obligation to return genetic incidental findings. There have been challenges to the notion that some of these broad principles—beneficence, respect for persons, reciprocity, and justice—are violated by lack of disclosure.

[8]For further information on genomic information and clinical practice, see Institute of Medicine (2012b).

He said it has been argued that the purpose of research is not to benefit the individual research participant but rather to produce generalizable knowledge, and that this is a fundamental difference between clinical and research enterprises. There are risks of conflating research and clinical care (the therapeutic or diagnostic misconception),[9] according to this argument, as well as the very important problem of resource limitations.

Berkman described the relevant sections from two major recent efforts that address the return-of-results issue, one issued by the Presidential Commission for the Study of Bioethical Issues (2013) and one published by the American College of Medical Genetics and Genomics (Green et al., 2013). The Presidential Commission distinguishes primary findings, that is, things one is looking for, from anticipatable incidental findings, those which occur when one is looking for A and finds B, but one is reasonably sure that one will find B. An example is misattributed parentage. Then there are unanticipatable incidental findings, where one is looking for A and perhaps discovers B but there was no way priori that one could have anticipated finding C.

The Presidential Commission developed several principles related to return of results and provided a list of relevant practical considerations that Berkman summarized. The Commission recommends that, during the informed consent process, studies/researchers need to tell participants that incidental findings might arise, describe the types of findings that might arise, and state whether or not such information will be disclosed. Studies should decide in advance how to honor participant preferences (including their right not to know). It is important to develop a plan to manage anticipatable and unanticipatable findings, subject to IRB approval, according to the Commission principles. If disclosure is very difficult or impossible (which may be the case with some biobank research), researchers must justify their plans for nondisclosure. The Commission stated that there is no duty to look for secondary findings.

With regard to the ACMG, Berkman said it is important to remember that its recommendations are explicitly limited to the clinical context. Nevertheless, researchers are starting to import the recommendations into their protocols, and there is considerable debate about whether or not this is appropriate. As noted earlier, the ACMG provides a minimum list of 56 findings to report from any clinical sequence. He said ACMG thinks there

[9]The therapeutic misconception, a term introduced by Appelbaum, Roth, and Lidz (1983), is said to occur when a research subject fails to appreciate the distinction between the aims of clinical research and of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures. The therapeutic misconception may present an ethical problem in clinical research insofar as the failure to distinguish the aims of research participation from those of receiving ordinary treatment may seriously undermine the informed consent of research subjects.

is a duty to look for incidental findings, and that these findings should be delivered to a clinician who then manages the information in the context of patient-specific circumstances. They do not favor the so-called right not to know or that patient preferences should be solicited. They are arguing that beneficence outweighs personal autonomy once the data have been collected.

Berkman then described recent work that seeks to develop the first extensive national study of institutional review board (IRB) professionals and their understanding, experience, and beliefs covering a range of domains. A survey of 796 IRB members and IRB professionals in the PRIM&R[10] consortium asked how they are grappling with questions about incidental findings. The intent was to understand the ethical and practical principles that they appeal to, and the extent to which they recognize limitations on a potential obligation.

As Berkman reported, almost 80 percent of respondents thought that there is always or sometimes an obligation to return incidental findings, with about 15 percent saying rarely or never. Respondents were asked to endorse different reasons why there might be an obligation, and three reasons received strong support: duty to warn, respect for autonomy, and beneficence. Reciprocity received low support, a surprising result to Berkman, given what is often encountered in the literature. The notion that research participants are equivalent to patients, and that the two groups should be treated similarly, also received low support, which tends to weaken the ACMG recommendation in the research realm. As the study showed, IRB members understand that research subjects are different than clinical subjects, and feel that something developed in the clinical context is not necessarily appropriate in the research context.

Perhaps most relevant to the workshop discussion, according to Berkman, respondents were asked what reasons or arguments might they accept to mitigate, limit, or reduce an obligation to disclose incidental findings. Only two received strong support: inadequate clinical or analytic validity, and inadequately demonstrated clinical utility. Other arguments that people cite fairly frequently as reasons why there should not be an obligation to disclose, in particular lack of funding resources and the time and effort required, got remarkably weak support. This suggests that IRBs might not accept arguments that projects involving the National Health and Nutrition Examination Survey (NHANES) data should be

[10]Public Responsibility in Medicine and Research is a membership organization for biomedical researchers and professionals responsible for ensuring research protections. Its principal activities include education, certification programs, public policy initiatives, and professional development programs. See https://www.primr.org/ [June 2014].

exempt from incidental findings obligations due to the difficulty in contacting participants.

During the discussion period at the end of this session, workshop participants further explored the question of whether there is an obligation to look for incidental findings. One participant noted that there are two ways not to look for findings. One is simply not to make the extra effort to look. Another is to actively not look, in other words, filter results in a way that will not produce results that one does not want to have to respond to. In a sense, the participant commented, NHANES has been taking the latter approach by not accepting protocols that would produce results that would potentially provide an obligation to disclose results. Jeffrey Botkin said he felt that it is perfectly acceptable to filter results so that incidental findings are reduced.

5

How Is NHANES Similar to/Different from Other Population-Based Studies?

Information from five ongoing studies in the United States was presented in the next workshop session to understand how other population-based studies approach the issues of genomic data collection and related research findings. One prominent difference between the National Health and Nutrition Examination Survey (NHANES) and the other studies is that the latter follow people over time and thus have a longitudinal relationship with their participants, whereas NHANES is a cross-sectional survey of the U.S. population. Session presenters included Carolyn Tucker Halpern, University of North Carolina at Chapel Hill; David Weir, University of Michigan; Martha McClintock, University of Chicago; Robert Hauser, National Research Council; John Moye, National Institute of Child Health and Human Development; and Tina Hambuch, Illumina, with the session chaired by Mildred Cho, Stanford University.

THE NATIONAL LONGITUDINAL STUDY OF ADOLESCENT HEALTH

Carolyn Halpern provided an overview of the National Longitudinal Study of Adolescent Health (Add Health).[1] It began in 1994 with the goal of assessing the health of adolescents in the United States and understanding the different processes that contribute to health in both social and environmental contexts. The study has a core sample of about 12,000

[1]See http://www.cpc.unc.edu/projects/addhealth [June 2014].

adolescents who were teenagers in grades 7-12 in 1994-1995, with additional oversamples of race-ethnic groups and of individuals with cognitive and physical disabilities. There is a saturation sample of 16 schools where all students in the schools were invited to complete an in-home survey. An embedded genetic sample has more than 3,000 pairs of monozygotic twins, dizygotic twins, full siblings, half siblings, and unrelated pairs who live in the same household.

At the first wave in 1994, more than 20,000 adolescents in grades 7-12 were interviewed in their homes, and more than 17,000 of their parents were also interviewed. There have been four study waves to date, and biological data collection has increased with time. In the most recent study wave in 2007-2008, Add Health added the use of dried blood spots to capture indicators of metabolic function, immune function, and inflammation. Cardiovascular indicators included blood pressure and pulse. The study requested buccal cell DNA from the entire wave IV sample and also did a complete prescription medication inventory.

Participation in providing biospecimens has been good: 96 percent of the sample consented to provide blood spots, and 78 percent consented to archiving those bloodspots for future testing. Halpern mentioned that genome-wide genotyping of the archived specimens is under way. Add Health has returned some measurement information to participants over time, but to date it has not returned any bloodspot or genetic result data, largely because these data are viewed as experimental rather than clinical-type data.

According to Halpern, the main genetic-related issues that face this study involve questions about research versus clinical techniques, the lack of clinically actionable markers that have been used to date, the lack of guidance from researchers about balancing harm and good for different kinds of results delivered in different ways, the lack of study resources to answer respondents' questions and provide tailored counseling if needed, and deciding what information is important to whom, given that the strength of associations may vary substantially across sub-populations.

THE HEALTH AND RETIREMENT STUDY

David Weir explained that the longitudinal Health and Retirement Study (HRS),[2] which started in 1992, shares some similarities with NHANES. Both studies aim for nationally representative samples and have multidisciplinary content. Both are characterized by rapid public data release, and both are fully committed to creating a national data resource for researchers.

[2]See http://hrsonline.isr.umich.edu/ [June 2014].

In 2006, the HRS started collecting biomarkers. These biomarkers included dried blood spots as Add Health uses, visible performance measures, and genetic data on approximately 20,000 people. The biomarker data were stored in a repository, with no funding and no definite plans for what would be done with these data. HRS considered candidate gene models, Weir said, but decided that the GWAS (genome-wide association study) model might be most appropriate. Broad coverage of the genome would permit exploratory work on a wide range of health and behavioral phenotypes, especially the longitudinally defined phenotypes that HRS sees as its comparative advantage.

It was preferable for HRS to manage GWAS centrally and then permit access under a common set of rules. In so doing, HRS managed the samples and could preserve the repository for future use in sequencing or some type of more detailed analysis. The Johns Hopkins Center for Inherited Disease Research does the genotyping, and the University of Washington has done quality control as well as imputation to 1,000 genomes, giving the HRS about 22 million SNPs. Different types of HRS data have different release policies, Weir explained. GWAS data are considered to be in the most-restricted category, and there are rather onerous requirements to access the data. The data are now in dbGaP,[3] and to date there are 76 authorized requests associated with the study.

The HRS has separate consents for the performance measures, the bloodspots, and the DNA. Consent rates in 2010 for dried blood and DNA exceeded 84 percent among white participants and ranged between 78 and 84 percent among Hispanic and African American respondents. For DNA, HRS adopted a broad general use release. The DNA specimen (saliva) is collected separately and the consent is separate, so, as Weir said, there is no confusion in the participant's mind about what it might be used for. HRS does not promise any return of genetic results.

Weir discussed several issues that HRS grapples with, including that the clinical value of the information contained in HRS DNA samples is increasing with time. As science learns more, how far does the obligation to report extend, and how does one draw the line? A second issue he discussed involves the recognition that the genome is heritable and that return of results has implications for later generations. If one is using philosophical notions of care and obligation, does one not have an obligation to later generations? That potentially puts a study such as HRS into conflict with the privacy of its participants, he suggested. And, if a no-

[3]The database of Genotypes and Phenotypes (dbGaP) was developed by the National Center for Biotechnology Information to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype. See http://www.ncbi.nlm.nih.gov/gap [June 2014].

return consent constitutes an agreement, then the criteria to violate that agreement by reporting should be higher than just some possible small benefit—the question is what is the standard. Where does one draw the line for a compelling need? Weir queried.

THE NATIONAL SOCIAL LIFE, HEALTH, AND AGING PROJECT

The National Social Life, Health, and Aging Project (NSHAP),[4] according to Martha McClintock, seeks to describe and re-conceptualize the health of older adults by including psychological and nervous system measures of sensorimotor frailty, sensory function, cognition, emotional states, health behaviors, activity, and sleep. The study began in 2005-2006 and now includes a nationally representative sample of about 6,000 community-dwelling older adults. Overall consent rates are on par with other studies, as is biomeasure consent given that participants already are in the study. Consent to use DNA from participant-collected Oragene kits is 83 percent and reaches 94 percent for future biomeasure analyses.

McClintock explained that in-home biosamples and biomeasures are collected by nonmedical field interviewers. NSHAP collects bloodspots in order to study C-reactive protein, Epstein Barr virus, hemoglobin A1c, and other markers. The study involves older adults' sexuality and asks about male impotence, as well as including direct measures of women's comfort and a bio-assay of women's estrogenization and balance with testosterone and progesterone. NSHAP also collects saliva to measure the circulating levels of these steroids. She noted NSHAP is interested in looking at genes for the receptors of these hormones and at variants for the glucocorticoid receptor, which has been shown in the past year to be associated with vulnerability or resilience to stressors that then lead to cardiovascular disease.

With regard to data reporting, McClintock said that there is limited return of nongenetic data, mainly well-established health indicators such as blood pressure and obesity and suggestions that participants consult a physician. NSHAP does not yet have policies for genetic data as DNA extraction is just now being done. She said conversations with people in the medical community, including IRB clinicians, suggest that it would be not only inappropriate but also irresponsible to report back genetic data from this kind of study. However, in conversations with social scientists, advice is more along the lines of "if you know the gene, you should report to participants." She said that the policy for return of results in NSHAP is currently caught between these two cultures.

[4]See http://www.norc.org/Research/Projects/Pages/national-social-life-health-and-aging-project.aspx [June 2014].

THE WISCONSIN LONGITUDINAL STUDY

Robert Hauser explained the Wisconsin Longitudinal Study (WLS)[5] follows a cohort of about 10,000 Wisconsin high school graduates in 1957, supplemented by data from random selections of siblings and graduates' spouses. Almost all are white, which makes them rather like two-thirds of Americans in their cohort, but they clearly are not like everybody, he pointed out. For genetic purposes, they represent a good study population because of their homogeneity.

Hauser noted a tradition in British social anthropology of community studies in which one starts with a survey and then engages with people in the community and helps them improve their lives. He stressed, however, the WLS does not fit this model; the WLS is engaged in observation and has very rarely strayed beyond that.

The study has not collected a great deal in the way of biomarkers. He said items that might be thought of as biometric or biological include several measures of body mass index; facial characteristics such as attractiveness, smiles, and facial mass (from high school yearbooks); DNA collection with Oragene saliva kits; experience with Medicare part D; and home interviews in the latest study round (with respondents aged 71-72) that include anthropometric and performance measures. The only biospecimen collected is saliva.

WLS uses three consent forms: one for use of Medicare records, one for saliva, and one for use of Social Security earnings. Hauser noted that response rates for Medicare data linkage and saliva collection are above 90 percent, both for the graduates and for the siblings, while consent for Social Security data is about 10 percentage points lower. The consent forms provide for unrestricted use for group analysis. The labs that WLS uses are not qualified to provide feedback for any medical purpose, Hauser said, and study participants are told that they will not receive any feedback. Analyses of genomic and Social Security data are only permitted within a secure data enclave.

A number of disclosure issues have arisen in terms of questions asked and not asked, Hauser stated. The WLS once thought about asking people about suicidal ideation but decided against doing so because of the issue of informing proper authorities. Respondents have been asked whether they were abused as children, including sexual abuse, but these respondents were consenting adults and there was no disclosure issue. Some respondents have been asked about their end-of-life plans, which Hauser said raises concerns not about disclosure but about whether respondent behavior is affected by the kinds of questions that are asked. In its latest

[5]See http://www.ssc.wisc.edu/wlsresearch/ [June 2014].

round, the WLS asked about elder abuse, an area where there is an obligation to report, especially because some of the interviewers were licensed in professions that required them to report such incidents. Another recently added study question involves whether people have had surgeries requiring a general anesthetic, asked in a way that would permit the WLS to identify through hospital records which anesthesia was used. Hauser said this is potentially useful because of the implications for later cognitive functioning and could conceivably lead to some kind of participant feedback, which has not happened yet.

THE NATIONAL CHILDREN'S STUDY

The National Children's Study (NCS),[6] now in its Vanguard or pilot testing phase, is a new national longitudinal study of environmental influences on children's health and development authorized by the Children's Health Act of 2000. John Moye explained that the Main Study will assess exposures and outcomes by following children to age 21. The NCS is a data acquisition resource, not a conventional study, with the majority of samples and information (including biological information) intended to be analyzed in the future.

Moye contrasted several aspects of NCS and NHANES. The NHANES has a long history, a cross-sectional design, and sample sizes in the range of 5,000 per wave. The NCS, he noted, is a recent undertaking with a longitudinal design and a planned sample size of 100,000. NCS will enroll prenatally or at birth, collect a wide variety of sample types, and request consent to store material for genetic testing from all participants. NHANES varies entry age with survey cycle, collects and stores linked blood and urine samples, and requests consent for DNA storage and genetic testing only from participants aged 20 or older. NCS focuses on pregnant women and children, while NHANES surveys a broader demographic.

Moye explained that the NCS consent booklet titled "What You Should Know About Joining the National Children's Study Vanguard Study" specifically addresses how respondents can find out about the results of the study, and it indicates that NCS will share what is learned from the study as a whole and will provide individual information when it becomes available. The booklet mentions that most samples will be tested in the future, that the "when or which tests" are not yet known, that an oversight committee will advise on which tests may be returned, and that participants may be asked if they wish to receive results when they are available. The consent signature page says that the participant under-

[6]See http://www.nationalchildrensstudy.gov/Pages/default.aspx [June 2014].

stands samples may be used for a variety of tests in the future (including genetic tests), that the participant will not routinely get results back from samples they contribute, and that permission is granted to use samples to obtain genetic information.

The NCS return strategy was developed in consultation with the study's advisory and oversight groups, the NCS Federal Advisory Committee, and the NCS Independent Study Monitoring and Oversight Committee (ISMOC). To inform the return strategy, Moye said, results were categorized according to health impact. Some results such as height and weight are simply descriptive information. Some have no clinical significance, such as routine genomic copy number variation and the salivary amylase gene. Some are clinically significant and amenable to medical interventions, such as elevated blood pressure or blood lead or gene mutations associated with colon, breast, or ovarian cancer. Others, such as Alzheimer's disease or spinocerebellar ataxia, are clinically significant but not medically actionable at present. Some are of unknown clinical significance; for example, environmental chemicals with no recognized safety thresholds or genetic mutations not yet associated with particular health or other outcomes. The consensus, according to Moye, was that clinically significant and medically actionable results warranted return. These are serious conditions that can be mitigated by timely intervention, or as he said, "something bad that we can do something about." The logistics of return require the participant to be recalled, permission to receive the information elicited, and arrangements made for the evaluation to be repeated, and, if confirmed, for appropriate referral to be made.

The NCS experience to date is limited to environmental contaminants and clinical chemistry obtained as part of the Vanguard pilot, he said. No genetic test results have yet been returned. An additional consultation will be planned for future analyses, and the development of the return strategy remains an ongoing process.

ILLUMINA

As part of the discussion of return of results, the workshop steering committee included experience in the private sector. Illumina is primarily known as a technology company, a maker of sequencers and chips that many people use for genomic work. Illumina also has a clinical laboratory that is Clinical Laboratory Improvement Amendments (CLIA) certified and CAP (College of American Pathologists) accredited.

Tina Hambuch, part of the group responsible for evaluating the information that emerges from the Illumina clinical lab, noted that today's genetics-testing landscape is increasingly complex. Individual reference sequences typically involve about 3.1 billion positions, and researchers see

on average 3.3 million variants, 1.5 million of which are in gene regions. Approximately 11 percent of the genes in the genome may be clinically tested. Clinical tests tend to focus on genes that are deterministic; that is, monogenic diseases where there is high confidence that observed gene mutations are related to disease in a predictive way. There are other genes that are related to disease and have strong predictive value for the probability of developing disease, but are not absolute. Other genes have clear relationships to disease and contribute to a risk of developing disease, but those risks are each very small. Given this complexity of information, which is now being gathered at the population level, it is unlikely that everyone who is part of the analytic process has the same level of understanding of that information, she commented.

Hambuch described an Illumina-sponsored project that brings together a range of stakeholders (physicians, primary health care workers, policy makers, administrators) and engages them in the process of genetic testing, including an informed consent process that involves the stakeholders' own doctors. Illumina does not counsel patients directly, but relies on a team of genetic counselors to support participants' physicians and help them understand what a given test does or does not do and how it can be used. Genetic samples are sequenced to Illumina standards, results are annotated and interpreted, and reports are returned to the participant's physician.

In this fairly healthy, high-functioning group of adults, Illumina has identified a set of 1,600 genes that correspond to about 1,200 monogenic, high-penetrance conditions. For every genome sequenced in this group of participants, there are on average 5,343 variants in the set of 1,600 genes. Researchers go through each of those variants and evaluate what they mean.

Results are returned to physicians who then presumably give that information back to their patients. Since this is more of a screen or predisposition, she said, it is questionable whether there even are secondary findings. However, Illumina follows the American College of Medical Genetics and Genomics (ACMG) guidelines for reporting on 56 genes. The clinical report only includes the pathogenic and likely pathogenic variants according to the ACMG standards. A section of the report highlights variants that are weakly suspicious for causing disease, not because they are thought to be pathogenic but because there might be reasons for the doctor and patient to make some follow-up decisions around additional testing or screening.

The report that is produced for the participants and their physicians also has an appendix that includes all annotated variant calls that pass quality scores, and the interpretations around those calls. Over time, Illumina tries to update any variants that were originally considered clini-

cally reportable and have changed status, or vice versa, and to update the physicians about those variants. As coverage of the genome improves, Illumina wants to offer people the opportunity to come back and have their genomes reinterpreted in light of technological improvements.

This process has turned what used to be series of clinical tests into a resource for additional research, Hambuch said. Some Illumina participants request their raw data as well as their complete genome-level variant calls. They may want to share their genomes with specific other individuals or donate genomes to help further research. Participants' right to their data raises many questions, she noted. What exactly constitutes their data? Does this mean raw data?[7] A clinical report? All the gene variant calls that were made in sequencing? She said there is not yet a common understanding of what people are entitled to in terms of levels of return of results. For example, if someone wishes to give results to a medical college one day and a church the next day, does this require separate consents for each use? Do the data recipients need to consent participants again? If a genome is donated for additional study, is a recipient institution required to obtain IRB input? There are no clear policies for these questions, she stated, but what is clear at least for Illumina is that its study participants would like their information back and would like to have more control over their information.

During the discussion at the end of this session, several participants raised the possibility that use of the term "return of results" may need to be more nuanced. There are three types of return that all probably require policy, a participant commented. One is investigator-initiated return or biobank-initiated return. The second is the offer of aggregate results, which may lead to further interaction with participants. A third involves participant-initiated requests for results. Various statutes and regulations come into play, particularly if a government authority is collecting information, a participant stated.

[7]See Lunshof, Church, and Prainsack (2014) for a discussion of issues concerning access to raw personal data.

6

Issues for NHANES

This workshop session focused on issues for consideration by the National Health and Nutrition Examination Survey (NHANES) as it goes forward in determining guidelines for returning results. Presenters in this session included Sharon Kardia, University of Michigan; Marc Williams, Geisinger Health System Genomic Medicine Institute; Muin Khoury, Centers for Disease Control and Prevention; and Laura Beskow, Duke University. Adam Berger, Institute of Medicine, chaired this session.

THE SCIENTIFIC VALUE OF INCORPORATING GENOMIC DATA COLLECTION INTO NHANES

Sharon Kardia talked about changes in both epidemiology and genomics during the past 15 years. Most modern epidemiology does not have within its design a replication as a litmus test for whether or not significant results have been found. Genetics needed to move to this higher level, and with that came the need for very large sample sizes and for individual-level data to be shared across researchers, she explained. Understanding of gene mutations has been aided by pooling data from large cohort analyses and by the emergence of large research consortia that have pooled hundreds of thousands of participants across nations.

As Kardia described, momentum accelerated in the mid-2000s with the resources that the National Human Genome Research Institute (NHGRI) put together from the HapMap project and the creation of dbGaP (data-

base of Genotypes and Phenotypes). As technology continues to change, it is shifting the way in which science conceptualizes its measurements. The point of doing whole-genome sequencing on epidemiological studies has not been reached, but she predicted it will come. Researchers will encounter many issues related to the handling of incidental findings. "Where we are today is back in the GWAS space waiting for new data to come online and to find the rare mutations or any mutation that could be considered functional in the epidemiological space," Kardia said.

What is particularly promising about NHANES, in Kardia's view, is the availability of data in the tough areas in genomic study: environmental exposures, infectious diseases, mental health, nutrition, and risky behaviors. Research has mostly stayed away from these areas because of a lack of data. There are new territories at the intersection of infectious, chronic, and environmental health outcomes that have yet to be explored because researchers cannot study them jointly. Enhanced collection and use of genetic data in NHANES, combined with the extant large sample size and high quality measures, could enable key scientific contributions, she said.

Kardia touched on several options for genomic data in NHANES. The first option is to not measure genomes at all. She said that this would waste a national treasure, could significantly delay gene-environment interaction studies, and could also delay understanding of rare functional mutations. The second option is to measure genomes and not report the data. Today, there are not enough replicated findings for most variants to report on the probability of a disease given a particular genotype, and NHANES could help develop this knowledge base. Another option is to measure genomes and only report "Bin One" actionable variants. (See Figure 2-1 for a description of binning.) She characterized this as a "potentially frustrating option" where participants might be able to know their results, but researchers could not study or report data because of confidentiality policies. She asked why, at this point in time, one would measure something that would then have no opportunity to be incorporated into genomics research.

DETERMINING WHAT DATA ARE RETURNABLE

Marc Williams reported on work by the Geisinger Health System, a large integrated health care delivery system. Geisinger has a biorepository called MyCode that is a tool for patient engagement and ongoing participation research activities. Current work includes studying how to return whole sequencing results in a clinical setting, developing standardized institutional approaches to the return of results, and research on many of

the questions related to return of results that have been articulated in this workshop, he said.

When considering the types of genetic results that might be returned to study participants, Williams suggested the usefulness of contrasting the clinical perspective with the research perspective. From the clinical perspective, actionable results should be returned; these occur in genes with known clinical effect. There are different types of such genes, he noted. Some might be called deterministic, such as a known deleterious BRCA1 mutation that confers a very high risk for an individual of developing breast or ovarian cancer. There are predisposing mutations, such as a mutation in the HFE gene that makes one more likely to develop hemochromatosis, but where the likelihood is very much lower than with a deterministic variant. He further noted some variants could convey carrier status, such as variants in the CFTR gene for cystic fibrosis. And there are pharmacogenomic variants such as those in CYP2C19 that can affect metabolism of antiplatelet drugs like clopidogrel.

Williams pointed out that nonactionable variants occur in genes that are associated with clinical conditions, but for which there is no treatment or change in care available, such as ApoE4 and Huntington's disease. In general, the genetics community thinks that information about nonactionable variants that are found incidentally rather than as part of a diagnostic testing protocol should not generally be returned, Williams asserted, because doing so would create concern in patients, would provide no benefit, and could increase health care costs. For variants of uncertain significance that occur in genes that are associated with a clinical condition but the effect of the variant is still unknown, he suggested the approach should be "we do not know what this means at the present time, but we will stay abreast of new information and be in touch with you if our knowledge changes."

From the research perspective, Williams said, issues involving return of results will depend heavily on the type of research study. If it is an anonymized study, he asked, do highly actionable variants warrant breaking anonymization for return? Should participants be consented for the return of results? Can and should highly actionable results be returned even if there is no explicit consent for the return? If the purpose of the study is to examine the question of return of results, he continued, what if a participant with a highly actionable result is randomized to the nonreturn group?

Williams posed a further question: If clinical relevance is the motivation for returning of research results, how does this process differ from returning test results in clinical care? Drawing on soon-to-be-published work in the *American Journal of Medical Genetics*, he offered a side-by-side comparison (see Table 6-1). In clinical care, the goal is to optimize the

TABLE 6-1 Clinical Care Versus Research

Clinical Care	Research
• Optimize health care of individuals • Provide care in best interest of patient • Patient has the right to access all clinical information • Treatment takes place in context of provider-patient relationship	• Production of generalizable knowledge • Protect participant from harm • Preserve integrity of study • Avoid the "therapeutic misconception" • No consensus or legal requirement that participants have access to information • Provider-patient relationship is not created through participation in research study

SOURCE: Adapted from Williams (2014) presented at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC.

health of individuals, while in research the goal is the production of generalizable knowledge. In clinical care, the goal is to provide care in the best interest of the patient. Researchers want to protect participants from harm, preserve the integrity of the study, and avoid the therapeutic misconception. In clinical care, the patient has the right to access all clinical information. In research, there is no consensus or legal requirement that participants have access to research information. In clinical care, treatment takes place in the context of a provider-patient relationship. In research, the provider-patient relationship is not created through participation in a research study.

In his presentation, Muin Khoury argued that the primary issue involving the return of results in NHANES is the nature of the survey. It is a government statistical survey, not clinical care and not typical research. He suggested that the public health utility of NHANES goes well beyond gene discovery and genotype-phenotype correlations. NHANES is a unique, highly representative, population-based cross-sectional survey. In many ways it can serve as the ultimate control group for most genomic research done in the United States. The participants generally are not sick people. If one wants to find sequences or gene variants for rare conditions, one does not want to start with NHANES, he said.

Khoury addressed the potential evidentiary basis for return of results and described ongoing work at the CDC that seeks to develop an evidence-based approach for clinical and public health practice. The Evaluation of Genomic Applications in Practice and Prevention Initiative (EGAPP) Working Group is an independent, nonfederal, multidisciplinary panel, and one of its contributions has been to focus on the clinical scenarios for

which genetic testing is done and to differentiate between clinical validity and clinical utility.

Khoury noted there has been a lot of work on establishing clinical validity in terms of genotype-phenotype correlations and determining whether or not they rise to the level of actionability as far as health care. The concept of the binning of genome sequence results, described earlier by Kathryn Porter (Chapter 2), is now undergoing evolution. A prominent characteristic of Bin One right now is that it is rather empty, Khoury observed. Even if one takes the 56-gene list from the American College of Medical Genetics and Genomics (ACMG) and assumes most of the genes on the list are in Bin One, this probably reflects about one-half percent of the general population. In the context of NHANES, Khoury pointed out, that number is a small proportion of survey participants.

Khoury said that the EGAPP Working Group has developed and piloted an approach to evaluating the clinical relevance of genetic variation that is systematic, transparent, applicable, and credible (Goddard et al., 2013). The approach is to ask whether there is a practice guideline or systematic review for a genetic condition, whether the practice guideline or systematic review indicates that the result is actionable in one or more of several ways (e.g., patient management, surveillance/screening, family management), and whether the result is actionable in an undiagnosed adult with the genetic condition. This approach uses the criteria of actionability, penetrance, and significance to potentially sort conditions into and outside of Bin One (stage 1), followed by a stage 2 that involves further evidence review and expert consultation regarding potential Bin One items and then a re-sorting of these items into Bin One versus not-Bin One. Eventually, he said, the process ends up with tiers of evidence for the return of results (see Box 6-1). The 10 years of EGAPP work has now come to bear on a new project spearheaded by NHGRI and the National Cancer Institute that seeks to develop a more rigorous approach to the binning of genomic variants.

From the audience, Jeffrey Botkin raised a policy question about how to define clinical utility. Actionability is a key word, he said, but there is a huge difference between what is theoretically actionable and what might be recommended that people do with information versus what people actually do and how that impacts morbidity and mortality. For much of what EGAPP considered, there are not many data on the longer-term outcomes of actually providing that information. This raises the question, he said, "should we be satisfied with theoretical actionability, or should we set a higher standard and say we would like to have evidence that conveying this information back to people positively impacts their health?"

BOX 6-1
Tiers of Evidence Proposed by the Evaluation of Genomic Applications in Practice and Prevention Initiative (EGAPP) Working Group in the Evaluation of Clinical Actionability of Genetic Variants

FIRST TIER	Evidence from a systematic review, or a meta-analysis, or a clinical practice guideline clearly based on a systematic review
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 nonsystematic review of evidence (e.g., GeneTest Reviews, OrphaNet, and Clinical Utility Gene Cards, opinion of a single or few (<5) experts) with additional primary literature cited
FOURTH TIER	Evidence from another source with nonsystematic review of evidence (e.g., GeneTest Reviews, OrphaNet, and Clinical Utility Gene Cards, opinion of a single or few (<5) experts) with no citations to primary data sources

A systematic review attempts to collate all empirical evidence that fits prespecified eligibility criteria in order to answer a specific research question. The key characteristics of a systematic review as explicated by the Cochrane Collaboration (2011) are

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of findings in the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

SOURCE: Data from Green et al. (2008) and Goddard et al. (2013) presented in Muin Khoury's presentation at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, 2014, National Research Council, Washington, DC.

SURVEY PARTICIPANT ATTITUDES AND PREFERENCES

The role of participant preferences is an important factor to consider when trying to establish an appropriate NHANES policy for the return of genetic information, said Laura Beskow. In her presentation, she reviewed some of the literature regarding participant perspectives about return of results, highlighting a large online survey of U.S. adults about a proposed national genetic cohort study. One of the findings of the study was that 9 in 10 people agreed they would want to know all of their individual research results (Kaufman et al., 2008). People wanted research results about health risks even when there is nothing they could do about them. Other surveys have found similar results, she reported.[1]

In terms of the reasons people give for wanting this information, Beskow presented a number of common themes that emerge when looking across different studies (see, e.g., Murphy et al., 2008; Daack-Hirsch et al., 2013):

- anticipation that this information will be valuable, now and in the future;
- perceptions that respondents could then obtain treatment or have a course of action for preventing the risk to their health;
- understanding of genetic information as having benefit for family members or other relatives;
- reciprocity, the idea that if one helps with research, then one ought to expect and receive something in return;
- interest in assisting in other research or seeking out opportunities to participate in future research;
- life planning, that is, changes that might be made based on this information; and
- a general right to the information. Some people feel this is information about them and they have a right to it.

However, other studies shed light on factors that may influence what people say when asked if they want access to genetic information, Beskow explained. One factor is the very effect of asking, and the concept of involuntary curiosity. Curiosity often is triggered in people by asking them something that brings to their attention a gap in the information that they have. Similarly, for someone to learn that someone else might possess information about him or her can trigger curiosity. Reports of participant preferences are often conditioned by how questions are asked, and

[1]It should be noted that there is a literature on the limits of and problems with the use of surveys and polling in the formulation of ethically sound policies; see, e.g., Hausman (2004).

whether people are asked about what they would prefer to have happen as opposed to what they would find acceptable, Beskow noted.

She pointed out that when using hypothetical scenarios to elicit respondent preferences, how people respond may not accurately reflect what they actually do when the time arrives. This has been demonstrated in terms of the gap between what people have said about their interest in genetic susceptibility testing versus uptake when the test is available in clinical practice.

The context in which questions are presented is also important, Beskow stated. There is a difference between having researchers or practitioners develop a full-fledged scenario to present to people versus relying on simple verbiage around a question. Ideally, in a consent form, people are given the context of what they are being asked to do. That information influences the way that people then position themselves and perceive themselves in relation to the research. Beskow pointed out that people will acquire different expectations depending, for example, on the type of study it is, the relationship that is being offered to them with the research, and so forth.

During the discussion period at the end of the session, Gail Jarvik mentioned work done at the University of Washington with regard to participant preferences that involved semi-structured interviews with biorepository subjects. When people were asked if they wanted aggregate results, the answer was no, but when asked if they wanted their individual-level results, they generally said yes. However, Jarvik reported, when asked if they wanted their individual results if there was a significant cost to producing the results, most respondents said no, if it costs money that would otherwise be spent on research.

Further discussion centered on the concept of actionability. Robert Hauser raised the case of people who have important genetically determined characteristics, for example, people who are carriers for Huntington's disease or have a very high probability of Alzheimer's disease, but might not be informed of these characteristics because they are not medically actionable. Williams noted that most clinicians would not want to deal with this information because it is not medically actionable. But what if, Hauser asked, the information is actionable in other ways? If one is a carrier for Huntington's disease and had this knowledge soon enough, one may decide not to get married or not to have children. Those are big decisions that may not be medically actionable, but they are certainly actionable. Williams commented further that there is traditional medical actionability, but there is also reproductive decision making, life planning, and other things that some characterize as personal utility. There may be

things that are very important to people that in fact exceed the importance that they place on medical actionability. According to Williams, it is incumbent on clinicians to discuss this with their patients, to understand their preferences and fears, and to contextualize results in that sense. This extends to research settings as well, he suggested.

7

The Logistics of Returning Genomic Results from NHANES

How the National Health and Nutrition Examination Survey (NHANES) might go about returning genomic results to individuals was the subject of the next workshop session, with presentations by Kathryn Porter, National Center for Health Statistics; Kelly Edwards, University of Washington; and Barbara Biesecker, National Human Genome Research Institute. Wylie Burke, University of Washington, chaired this session.

THE NHANES VIEW

Kathryn Porter began the session by presenting the NHANES view on the session topic. The NHANES program has considerable experience in reporting medically relevant results such as high cholesterol and high blood lead. When the program makes referrals to care providers, the providers typically know how to respond to study participants. However, there are some findings that health care providers may not know what to do with, Porter said. She offered the example of a study participant with a high urine arsenic level who receives a reporting letter saying that the level is high and that they should follow up with their provider. The provider then contacts NHANES and says "I am unfamiliar with this, what should I do?" This situation is difficult for the participant, for the doctor, and for NHANES, and necessitates a good deal of back and forth to properly address.

According to Porter, it seems that there would be similar issues with

regard to reporting gene variants. NHANES might proceed with developing a reporting letter to participants that they could share with their health care providers, but the providers are likely to be on tight visitation schedules. The sudden appearance of a Centers for Disease Control and Prevention (CDC) letter detailing an actionable variant and the need to do something is likely to create problems, Porter suggested. NHANES may need input from primary care providers on this concern. Further, given the importance of participant preferences that was discussed during the workshop, she said it is important to note that the NHANES program has never done any studies or surveys of its participants' preferences.

Porter explained that the survey program has considered several plans for returning results, one being a retrospective plan dealing with people who were previously consented. NHANES would need to develop procedures for returning results given that the prior consents stated that no results would be reported. Then, she added, there are the prospective considerations; there currently is a hiatus on obtaining permission to store specimens, and new consent language would be required to move forward.

With regard to the retrospective plan, she said NHANES received documented consent between 3 and 23 years ago for a sample of 26,000 adults. In the earlier years, the consent was only to store blood for future testing. There was no mention of genetic studies, and no return of results was stated on the consent form. NHANES has not resolved the ethical and logistical issues of reporting clinically actionable or medically actionable results years after DNA samples were collected, including how this would feel to a participant. She said the question remains about whether the results would be valid, although she noted the consensus seems to be that they would be if genetic tests were done in CLIA (Clinical Laboratory Improvement Amendments)-certified laboratories.

There is no active tracking of past survey participants, Porter explained. Records include their last mailing address, street address, and phone number. Some NHANES data have been linked to mortality files to ascertain who is still living. The survey program could get a listing of those participants still alive with their last best-known address, she noted, and one possibility is to contact them again by mail. This would not be a re-consent but rather a notification, she clarified. There might be a multistage process, the first step being to let participants know about procedural changes. Next, if there were results or developments that participants should know about, they would receive a letter. There could be subsequent phone contact to discuss specific results and provide counseling.

Before undertaking such an approach, Porter said the NHANES program would first have to determine a universe of clinically actionable

gene variants and reassess them annually. The assessment would require recruiting and convening a medical advisory panel of genetic clinicians, research scientists, bioethicists, and possibly genetic epidemiologists. If the DNA bank is reopened to new research proposals, Porter said, the survey program would need to obtain full-time genetic counseling expertise to support operations, enhance its computing infrastructure, and address a variety of language-related issues for participants who do not speak English or Spanish. Everything, she stressed, would be contingent on having a sound reporting protocol. NHANES would not want the potential research proposals to drive the reporting plan, and therefore would require that the reporting plan be developed prior to considering research proposals.

Porter described two plans that have been considered going forward in time. The first involves restarting the collection and storage of DNA specimens, with appropriate modifications of the consent process and perhaps a menu of participant choices. The second would not involve banking specimens, but would consider whole-genome sequencing as part of the live NHANES data collection. This is wishful thinking at this point in time, she observed, but may make the most sense for recruiting participants who would be told they are going to have a physical exam, a bone scan, an oral health exam, have blood drawn, and also some genetic tests, and that they will receive all the findings. Porter said this plan would be very expensive, bureaucratically difficult, and likely require major funding partners to help with lab logistics and staffing requirements.

RETROSPECTIVE VERSUS PROSPECTIVE SAMPLES

Kelly Edwards pursued the differences in the return of results between retrospective and prospective collections. She framed her remarks in terms of what is guiding behavior today by invoking the idea that people are governed by laws, technologies, markets, and norms, and asking which of these is moving faster and slower. At least in the area of genomics, she said, it seems clear that technologies and markets, and in some case norms, have moved past current legal structures and regulatory processes. Edwards noted that researchers and practitioners are running to catch up and running to build a common infrastructure and standards of excellence, treating the regulations as a floor for behavior.

In Edwards' view, it is important to focus on participant expectations when talking about retrospective and prospective data collections, and on managing the expectations that people have about participation. When thinking about how participant expectations arise, she noted many people who work with ethical considerations and with institutional review boards (IRBs) think that expectations come from consent forms. A

good deal of effort goes into creating and finessing those forms, Edwards observed, and the creators think they are conveying what participants need to know and will understand. However, as known from a wide range of social science, people's expectations about what is going to happen in the course of a project come from many different sources: their own experience with past projects, assumptions about what might happen, what they hope will happen, and sometimes from misunderstandings or miscommunication.

Edwards pointed out that the workshop has highlighted the issue of how research activities are different from clinical care or public health activities and has considered the trade-offs regarding the obligation to return results. She suggested that the debate over obligations for and obligations against a duty to return results may have reached a saturation point, and what is most important are the expectations and values guiding a particular data collection that will help to make a decision going forward. She highlighted three mechanisms for getting input from community members on research initiatives.

First, community advisory boards are the classic mode by which large research initiatives obtain community input on policies. She referred to guidance on the CDC Website that addresses the various challenges with community advisory boards: How can projects develop a representative collection of participants who can provide guidance? How can projects help their community advisory board be informed enough about the issues without co-opting them into the research enterprise? How can boards maintain enough perspective to provide fresh participant perspectives? How can projects work with community advisory boards so that boards might be able to speak more broadly than just for themselves?

A second, different kind of engagement that Edwards discussed is the process of intensive community deliberation, events that involve representative groups and engage them deeply over a period of time. This process has been used successfully in California to help generate biobank policy, with community participants giving feedback directly to biobank owners and researchers and influencing policy on the fly.

Edwards noted that a third approach is beginning to emerge. Instead of asking a representative board for input, individuals are asked to directly develop and manage their own preferences. The Genetic Alliance's Platform for Engaging Everyone Responsibly (PEER) is an example, using private access technology. She said such personalized tools allow individuals to set their own preferences about data sharing, data access, re-contact, and communication about returning results.

As an example of building a governance process, Edwards described an Institute of Medicine ([IOM], 2012a) study that was tasked with developing suggestions for how to deal with an historic collection of 90 million

specimens dating back to the Civil War that was housed at the Armed Forces Institute of Pathology. She explained that it is an existing collection, the samples had been collected for clinical pathology purposes, and the still-living participants do not know that their samples are in the collection. The issues before the IOM committee were whether this collection can be used for future purposes, including research, and if so under what circumstances. Re-consent was impractical given the size of the specimen collection, and the question was what else could be done.

She explained the proposed solution involved a governance process that focused on ways of doing as much de-identified research as possible, and on the establishment of a third-party review system for all data access requests, including a scientific advisory board and data access committee. The IOM committee did not look in depth at the return-of-results issue, but did propose the idea of an entity similar to the Data and Safety Monitoring Board, an independent group of experts that advises the National Institute of Dental and Craniofacial Research and its study investigators. The IOM committee envisioned an entity that would have a mixture of stakeholders, including primary care doctors, study participants, and researchers. This group would look at requests involving return of results on a case-by-case basis and make determinations about whether a given result rose to the level of actionability and how to go about disclosing the result. The entity would be independent of any investments of the data repository or investments of the research itself.

Because re-contact and re-consent were so impractical, she said the IOM committee emphasized Internet communication and other tools to get the word out about this resource and to make as much publically available as possible in terms of aggregate findings and ongoing research activities. It was also deemed important to make it as straightforward as possible for people to opt out of this activity if an individual or family member wanted to remove a sample. The committee recognized that all of these governance plans needed to be under constant review and responsive and dynamic in light of changing norms, laws, and technologies.

PRACTICAL ASPECTS OF RETURNING RESULTS

Barbara Biesecker addressed several practical aspects of returning genomic results from NHANES. The main issues she discussed involved how to consent people, how to help people make informed choices if they want to learn information, the ways in which results are returned, and how NHANES might help participants act on the results.

As Edwards had noted with regard to consent, people enter into studies with their own mental models, prior experiences, and beliefs, and therefore the consent itself probably has little to do with their decisions.

Biesecker commented that people can appreciate uncertainties and the tentative nature of information, and they do embrace the idea of multiple causes. An obvious question is whether or not NHANES participants want genomic information, and she said the answer is "we do not know because we have not asked." Research done with different cohorts at the National Institutes of Health (NIH) suggests people do indeed want genetic information, Biesecker pointed out. For example, ClinSeq participants can discriminate different types of information. They are most interested in actionable variants and carrier results, but are almost as interested in information that they cannot do much about (Facio et al., 2013). Parents of children enrolled in NIH studies are also eager to learn about secondary variants (Sapp et al., 2014).

Biesecker asserted that this is an era of advocacy rights for patients and citizens, an era of partnerships and transparency in the delivery of health care. She said people increasingly desire better access to their medical records, and, in general, place increasing value on staying healthy and taking personal responsibility for health. Data suggest that if information about individual health becomes knowable, people want to know it. If they are not sure they want to know it, they at least want to be offered the choice.

Questions have been raised about people's overall ability to learn about or understand genetic information. Hence, she said, one might ask if NHANES participants will internalize the genetic information that may be provided. Early research from other studies suggests more likely than not, she said, as the personalized nature of the results makes it likely that people will have further conversations about interpretation. It does not take a great deal of time for people to sort out what they need to learn, Biesecker suggested. They do not need to learn about DNA composition and where chromosomes are situated, but will seek out practical outcomes, the estimated chances of getting an illness, what could potentially be done to prevent or mitigate the risk, and what specialist they need to talk to in order to come up with a plan. Participants may learn about certain findings as effectively from a Web-based platform as from an in-person consultation, she commented. An ongoing large randomized control trial to return carrier results from ClinSeq is now under way to understand differential outcomes when participants are randomized to a Web-based platform versus a genetic counselor who provides education.

Biesecker noted that it is still unclear if NHANES participants will likely use the information they receive. Respondents are likely to tell their providers, who can help ensure follow-up on their recommendations. However, as she pointed out, it is difficult to induce people to change their health behaviors even with evidence-based interventions. As of 2014, she said, many people likely need the interpretative help of a genetic coun-

selor or someone trained by a genetic counselor or medical geneticist in order to understand genomic information. Counseling usually is done in person, and if a project like NHANES were to incorporate genetic counseling, the cost implications would be considerable. That said, Biesecker mentioned that better follow-up can be integrated into the general health care system, and more innovative use of social media and other Internet resources can assist people to take control over their information and not leave matters to a specialist or sub-specialist.

8

Special Considerations for Reporting of Results in NHANES

This portion of the workshop considered the implications of genomic data in the context of current National Health and Nutrition Examination Survey (NHANES) policies for return of results, and whether genomic results should be viewed differently from other research results. Presenters included Jennifer Madans, National Center for Health Statistics, and Jeffrey Botkin, University of Utah. Les Biesecker, National Human Genome Research Institute, chaired the session.

STATISTICAL AGENCY CONSIDERATIONS IN RELEASING DNA RESULTS

Jennifer Madans mentioned some advantages of being part of the federal statistical system, which include an institutional commitment to long-term data collection and a commitment to maintaining the storage of specimens. While budgets will change, a project such as NHANES does not have the pressing worries that other population-based studies may have in terms of expired grants or investigator turnover. At the same time, she noted, NHANES operates under federal statistical agency regulations pertaining to confidentiality and protection, regulations that are transmitted through the informed consent process. If one thinks of a continuum of places where genetic work is done, with the clinical setting on one end, she described NHANES as being at the far "other end," further to the extreme than the other population-based research discussed during the workshop.

Madans discussed several possible unintended consequences of or drawbacks to DNA collection that she said need to be considered (see Figure 8-1). One is the potential impact on participation in NHANES due to a perception that the government is going too far in collecting this kind of information, raising the issue of what is appropriate for the government to know. There is concern about whether the mere collection of genomic information is beyond the scope of a statistical agency, and if DNA is too sensitive a topic. If NHANES were to move to reporting genetic results, she asked, does that overstep the line of what is appropriate, and would this impact the core mission of monitoring the nation's health?

There are consequences involved with the timing of testing and reporting of results, Madans said. In the case where NHANES results are returned very soon after the initial participant encounter, how different is that from contacting people 5 or 10 years later to say "remember us, we

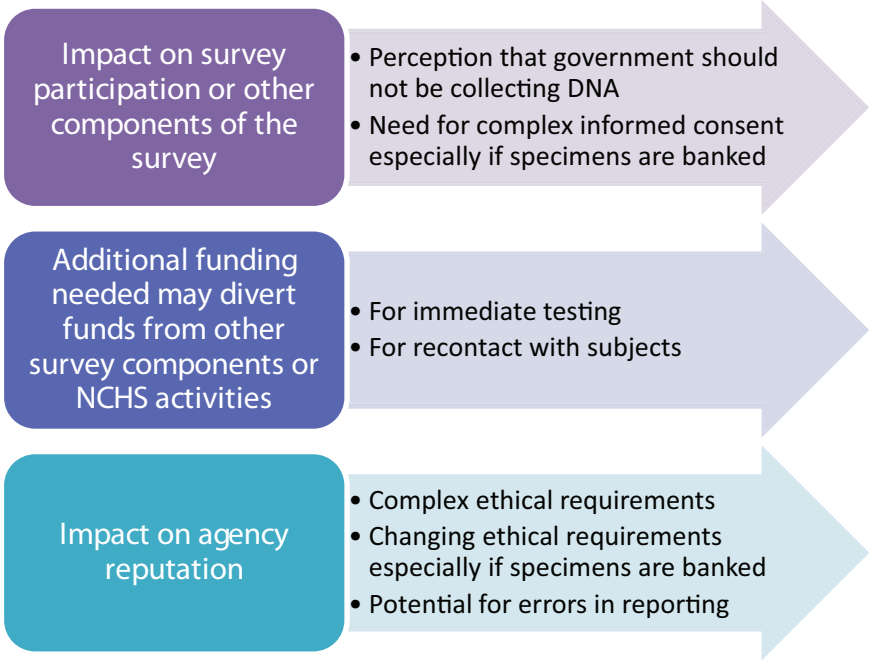

FIGURE 8-1 Potential unintended consequences or drawbacks to an expanded NHANES genomic data collection.
SOURCE: Adapted from Madans (2014) presented at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC.

may know something about you that you really might want to know?" There may be different ethical considerations in terms of agency obligations in these two scenarios, she suggested. And if genetic testing is done over time, there has to be a constant reevaluation and ongoing determination of what is reported, as is the case with other tests that NHANES does. There is likely to be increased volatility in decisions regarding genetic results and rapid changes in procedures and relatively less consensus about what should be reported, in Madans' view.

Financial implications loom large, Madans added. NHANES does not currently have substantial in-house expertise concerning return of genetic results, and the processes of interpretation and counseling would be much more costly and complex than for nongenetic tests. These areas are outside of the existing program framework.

Madans noted potential negative impacts on agency reputation. While these impacts are difficult to anticipate, she said, agencies do have to consider whether there is an elevated risk of such impacts when dealing with highly complex and changing issues such as the ethical considerations and requirements discussed during this workshop. The thinking within the NHANES program 10 years ago was that, perhaps in 10 years, science will have coalesced and there will be more agreement on how to move forward, but this does not yet seem to be the case.

THE NOTION OF GENETIC EXCEPTIONALISM

People sometimes ask if genetic information is sufficiently different from other types of biomedical information and hence merits special rules or management, Jeffery Botkin said. He approached this question by noting that there are two angles to consider: Genetics might be treated differently than other forms of testing or information when this is not justified, which is the typical notion of exceptionalism. But the reverse might be true: Genetic information may be treated the same when, in fact, differences are justified.

Botkin said he is on record as supporting what he calls "soft genetic exceptionalism," the idea that the aspects of a test itself or the information itself are important, not so much whether they are genetic or nongenetic (Green and Botkin, 2003). To Botkin, features of information may make it more sensitive or more problematic in certain circumstances. Genetic information may yield information relevant to the welfare of others, for example, vertical transmission wherein learning something about one's own genetics tells one something about parental genetics. As Botkin noted, genetic information can be highly predictive of future disease; tests for BRCA1 and HNPCC have a higher predictive power than nongenetic tests for blood pressure and cholesterol. Such information

can be stigmatizing and is often more complex to analyze and interpret than that from other types of testing.[1] Botkin observed that it is true that genetic tests often lack these sensitive aspects, and those are genetic tests that one need not spend a great deal of time worrying about. But when the aforementioned constellation is present, it calls for a higher level of scrutiny regardless of the platform being used.

The use of the term "genetic exceptionalism" implies a set of rules that people agree on and are making exceptions for with regard to genetics, Botkin said. It does not appear that today's debate is sufficiently ripe to say that those rules exist, he posited. Speaking about exceptionalism is premature simply because nothing is an exception yet from a standard set of acceptable rules. In NHANES at this point in time, results for physical examinations and tests that are routinely conducted in clinical care as part of the original survey assessment are provided back to participants. But, he noted, there is no return-of-research results generated later, whether those results are genetic or not. So in that sense, Botkin said, there is no genetic exceptionalism at the present time.

Botkin presented a simple schematic (see Figure 8-2) of broad differences between different forms of testing, which he grouped into three categories: (1) physiologic tests, tests of current biological function, blood counts, blood gases, electrolytes, renal function tests, etc.; (2) imaging and other types of physical or anatomic testing; and (3) genetic or genomic testing. In physiologic testing, he explained, there is clinical validity and clinical utility for the sorts of things tested, and results often suggest a reasonably urgent response. Results are plainly evident and easy to interpret (one does not need a sophisticated analytic protocol to determine if many of these results are problematic) and for the most part are not context specific.

With imaging, clinical validity is variable depending on the finding. Utility is often present, Botkin said, as when one observes an anatomic abnormality and considers appropriate interventions. Similarly with urgency: A brain tumor on a scan is something that needs a response. Results are often plainly evident, but are often not context-specific; a brain tumor is a brain tumor whether one is 10 years old or 50 years old.

Genomic testing has variable clinical validity and variable clinical utility, depending on what is targeted. There usually is no urgency of action because for the most part genetic results do not need to be responded to

[1]Concern about stigma resulting from genetic testing may have increased in response to increases in genetic research (see, e.g., Sankar et al., 2006, and World Health Organization (http://www.who.int/genomics/gender/en/index3.html [June 2014]). This workshop did not directly consider the risks of stigmatization following the return of genetic (and other) information.

	Clinical Validity	Clinical Utility	Urgency	Plainly Evident	Context Specific
Physiologic	Yes	Yes	Yes	Yes	No
Imaging	Variable	Yes	Yes	Yes	No
Genomic	Variable	Variable	No	No	Yes

FIGURE 8-2 Characteristics of three forms of testing.
SOURCE: Botkin (2014) presented at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC.

today or this week. They are not plainly evident, as it takes a fair amount of sophisticated analysis to figure out what is occurring, Botkin added. And they often are context-specific, an example being someone who has already lived through much of their risk; hence the risk is contingent upon the person's age.

According to Botkin, these differences among test characteristics tend to favor return of results for physiologic and imaging tests above genetics, which may be an argument in favor of genetic exceptionalism. The big differences are the urgency, the plainly evident nature of results, and the fact that results often are not context-specific. Botkin said these differences make it easier to say "these are results that will not be returned," as opposed to saying "maybe these are returnable depending on the specific situation of the person."

Further discussion at the end of the workshop session about incidental findings and return of results highlighted the fact that discrete analyzers have now replaced most automated laboratory equipment that used to routinely perform a wide range of tests on a panel, regardless of the test or tests ordered. A participant pointed out that laboratories now try to focus analyses to include only what has been ordered, and clinicians

and laboratorians are comfortable with "gating" machines to produce only ordered results. The widespread use of discrete analyzers makes it unlikely that a laboratory would conduct tests other than those that are specifically requested. Further, the participant elaborated, CLIA requires laboratories to perform tests only at the written or electronic request of an authorized person, thereby further decreasing the likelihood that a laboratory would conduct a test without receiving a specific order from an authorized person to do so. In light of these developments and in view of ethical analyses suggesting that investigators do not have an obligation to search for incidental findings, it can be argued that any new standards saying that additional genomic analyses should routinely be done to identify actionable results would constitute genetic exceptionalism. Another participant noted that the NHANES practice of screening DNA bank proposals based on the potential for finding reportable results might be in the same category as gating genetic/genomic analyses to avoid known pathologic variants that are not relevant to specified research.

9

Summary of Presentations and Discussion

In the final session of the workshop, a panel of speakers and steering committee members reviewed the issues and discussions that they thought arose during the workshop and identified questions that, in their views, remain unresolved. The floor was then opened for questions and general discussion.

GENETICS AND THE NHANES MISSION

Most participants agreed that the National Health and Nutrition Examination Survey (NHANES) has great potential to help medical science, and the question is whether or not NHANES should become a 21st-century public health and medicine research study. As Les Biesecker noted, there are very good reasons to keep doing exactly the same thing over a long period of time, but hard questions should be asked about what the study is trying to accomplish, and whether a conservative approach or a more novel and creative approach is the right way to go.

Biesecker commented that only two things affect health: genes and environment. Further, he said, it may be the case that NHANES does not have, as an objective, a goal of understanding how one or the other of those things affects health. It would be scientifically justifiable to not have one or the other of them as an objective, and that justification should drive how the study is designed and carried out. Whether or not NHANES should explore what might be called this ideological terrain seems to

be, as he interpreted from some of the workshop discussion, an open question.

Gail Jarvik noted that the NHANES program espouses a dual mission: a primary mission involving participant health assessments and a secondary mission of biobanking for research. In her opinion, understanding and collecting genetic data is essential to the primary mission and to the scientific study of health. Gene-environment interactions are important in human health but very difficult to study, she said, and NHANES offers a unique opportunity to understand how these interactions impact health.

Wiley Burke and Marc Williams wondered about stopping to rethink what genomic parameters should or could be included in NHANES and what is reasonable within the context of NHANES. Williams suggested it would be useful to reevaluate why DNA collection was initiated in the survey, given the regulatory constraints that affect secondary use of the data. He said it may be helpful to restart the thought processes, better understand the landscape, and then take purposive steps forward. Burke noted that once NHANES leadership is clear on that and has carefully analyzed the ways in which genomic parameters could be added to the NHANES database, there would then be the question of what is returnable. Several workshop participants have suggested that there are not many returnable results to date. If this is so, Burke suggested, the process is to first figure out what research is worth doing, then figure out what DNA-based information will be generated, and then address which genetic information (presumably only highly actionable information) would be returned.

USEFULNESS FOR GENETIC RESEARCH

Ellen Clayton stated that, in her view, the first matter to be resolved is the extent to which NHANES data and samples can be used for research under the current constraints, or under any constraints that are foreseeable. She said there is a radical disconnect at this point in time between what is going on with regard to scientific data sharing generally and what is going on with regard to NHANES. The NHANES program needs to figure out what can be done with genetic data and how they can be made more readily available to investigators in a way that permits research.

Jennifer Madans stated it would be helpful for NHANES to have people who are interested in gene-environment relationships look at what is currently in the survey in terms of environmental information and the sample size, and try to simulate the array of useful information that could be derived. Many workshop participants expressed their opinions that the gene-environment data are a potentially unique source of research information. However, said Madans, NHANES has been counseled that

the sample sizes may be too small and that the statistical power to explore interactions may be lacking. It would be very useful to have a range of input on this empirical question, she suggested.

David Weir said he saw as a pressing need that the NHANES program has an ongoing system by which markers, preferably those that are attached to commercial chips, are identified and binned appropriately. Although different thresholds for when and where to report (based, for example, on how old the sample is) might be set, at least there would be an ordering that would provide a shared understanding.

SHOULD GENETIC RESULTS BE RETURNED TO PARTICIPANTS?

As illustrated by different presenters and participants during this workshop, there is considerable ongoing debate among scientists, medical professionals, and researchers about the need to return results. Clayton argued that, to her, the answer depends on what is acceptable, rather than on individual preferences. Jarvik said that NHANES is not compelled to return results, and noted that at this point in time, there are no genetic results that are returnable. Not only are there consents saying that results will not be returned, she continued, but also some if not most of the genetic data are from non-CLIA (Clinical Laboratory Improvement Amendments) samples run in non-CLIA labs using non-CLIA procedures, and none has a high enough expected validity to compel return.

Clayton noted that the study context is particularly salient for this discussion. NHANES is a one-time, highly involved engagement with participants, but after a written report, there is no further contact. A question to consider is whether this one-time intervention leads to some long-term obligation to follow up.

This discussion led to exploration of duration of the responsibility to follow up. Susan Wolf mentioned some recent convergence around the idea that, in primary research, the duration of project funding may limit the duration of the responsibility. But with a biorepository, she said, there is no clear indicator of where responsibility ends.

With regard to the cost of returning results, and how this might detract from other NHANES or National Center for Health Statistics (NCHS) activities, Jarvik said that there are more expensive and less expensive ways to proceed. There are many already-studied roads that could be followed with reasonable efficiency to return high-impact results should they ever be found, she suggested, and there may be an unwarranted level of concern about the frequency of incidental findings. While NHANES does not have genomic expertise, the expertise does exist elsewhere. In her view, NHANES does not need to hire an entire board to

determine what to return, because many groups are working on that issue and their knowledge can be leveraged.

Wolf noted that NHANES is already returning many results and possibly also returning incidental findings or at least worrying about them. If one is scanning, she said, one is likely dealing with incidental findings. Echoing the sentiments of several workshop participants, Wolf found it implausible that NCHS would do a public study and say that it will sit on certain data and not return them to participants. In her opinion, this is a "nonstarter" in view of the fact that NHANES already touts the return of nongenetic results as a benefit of participation. She commented that some of the questions that this workshop has agonized about have been asked and answered already in the design of the study, and that it makes sense to contextualize the genomics issue in light of NHANES policies regarding nongenetic data.

Wolf suggested that NHANES could use a research mechanism to more rigorously ascertain what a population is thinking about return of results and how incidental findings are treated. There may be information to be learned about genetics from other parts of the survey: how the study is handling incidental findings revealed during scans, how participants are handling the return of STD information, and the same for pregnancy information. She further noted that there is a literature about how incidental findings can be both benefit and burden, and suggested this distinction might be highlighted in NHANES communications.

Jeffrey Botkin emphasized that, in his opinion, the NHANES-participant deal may be more complicated. There is the short term, in which well-validated, familiar clinical tests are being used to describe the participants, give a snapshot of their current physiology, and so forth, and he noted the guarantee or promise to return those results directly to people in the context of that short-term relationship around the study recruitment. Then, he continued, there is separate language around long-term research results, in which it is plainly agreed the participants will not receive those results. These two should not be conflated as the same promise. To him, both are part of the deal, and based on the explicit language of the consent form, one can make a distinction between the short-term obligations and the understanding about those results, and whatever obligation one might have longer term with experimental results that may not emerge for years or a decade or more.

ADAPTIVE GOVERNANCE AND COMMUNICATION WITH PARTICIPANTS

The key for NHANES, according to Kelly Edwards, is adaptive governance, an approach to governance that would be dynamic and responsive

to the changing landscape of health research. Edwards stated that to get too focused on the particular—whether there are 56 or 118 actionable variants, or whether one methodology is marginally better than another—is to miss the broader picture.

She said that some changes can be made at an executive board level, some changes require consultation with other advisory boards, perhaps including community advisory boards, and other changes are at a significant enough level that each individual must be asked what they would like to do going forward, as some at the workshop proposed with the re-contact/re-consent approach to the retrospective data collection. A proactive opting into a return-of-results model is a straightforward way of reengaging participants, Edwards observed.

Virginia Cain mentioned that NHANES has considered two approaches to genetic information going forward. One would be to bank the samples and do research in the future, and the other approach is to do gene sequencing up front. She noted that the process around incidental findings involves a level of complexity that would be hard to communicate to people and wondered what participant expectations would be. Wiley Burke mentioned that up-front sequencing poses an interesting communication challenge that, in her view, probably starts by not telling people you will be doing a whole-genome sequence. Any results to report back will be a discrete set of results, which Burke suggested could be explained to people so they know exactly what to expect. Edwards commented there is always a question about the subtleties of what people understand, and one approach is to minimize or match expectations. She mentioned that some projects have developed short animated videos to explain some of these complex concepts. With simple consultation around public education and science literacy, there are ways to describe these concepts that could live on the NHANES Website as videos, and NHANES already has experience with videos for other aspects of health.

Les Biesecker mentioned the issues of familiarity and comfort, and used a doctor visit with a complete history and physical examination as an analogy. Virtually everyone has experienced a visit to a doctor, visits that are always unconsented, are exploratory, have a positive predictive value and a sensitivity for finding things, and may reveal incidental findings that were not looked for. He noted everything about searching a genome is the same as in an exam. What is different about a history and a physical exam, he said, is that people are so used to them and have been undergoing them for so long that they usually do not worry about them anymore. Genomics is new, so, as he said, the hair goes up on the back of people's necks, but the problems and challenges are the same.

PARTICIPANT CONSENT OR RE-CONSENT REGARDING GENETIC DATA

Several presenters mentioned possible changes to the NHANES consent forms. If there ever is any possibility of return of results, this possibility should be talked about at the front end of the consent process, according to Clayton. Weir suggested that consent language should probably say that reporting will occur if and when the results are actionable, and the challenge is to develop language that can explain this to people.

With regard to specimens that have already been collected, Botkin stated that the consent language is determinative. NHANES made an agreement with survey participants about not returning results, and it is perfectly appropriate to honor that consent language, given all the complexities and difficulties around the return-of-results issue. An alternative would be to go back to them and say NHANES has a new understanding and new capabilities, there are circumstances in which to consider returning results, and ask participants if they would be interested in obtaining results under those circumstances. If they were interested and opted in, this would be a perfectly acceptable alternative. These are ethically acceptable alternatives, Botkin said, although the latter is a much more burdensome alternative.

PARTICIPANT UNDERSTANDING OF TRADE-OFFS

According to Botkin, once there is an opportunity to talk with people in any detail about the trade-offs involved with biobanking and use of genomic information and electronic medical records, people understand the need for a trade-off between confidentiality and utility. People expect a high level of protection, he said, but not to the extent that a resource such as NHANES, which is such a valuable one, would become substantially less useful.

Jarvik commented that what is heard most commonly in the clinical setting is that people want their data to have an impact and that they are willing to take some chances. Participant engagement does not only revolve around the return of results. Engagement can tell clinicians, researchers, and biobank curators many things about governance, what kind of consent to have, what sharing policies to have, and what kinds of research participants value most, she said.

SHOULD POPULATION-BASED BIOBANK RESEARCH LIVE BY DIFFERENT RULES?

Several workshop presenters discussed whether NHANES is going to produce data that will generate findings, and whether the science will

produce results that are valid and returnable. Benjamin Berkman posed an intermediate question: Assuming a study will produce valid findings, is there something ethically distinct about population-based biobank research? This question is pertinent not only to NHANES, but also to this class of research, he said. He posed a series of questions: Are there certain characteristics of population-based studies that distinguish them from other kinds of research where a stronger obligation is felt to return incidental findings? Can a line be drawn saying that to the extent there is an obligation to return incidental findings, this obligation only applies to some core set of clinical studies? Can a set of characteristics be defined that would, on a principled justifiable basis, argue that population-based research is just too different and does not have an obligation to report to participants, even if results are going to be generated?

One key step toward the answers, Berkman suggested, is to determine how difficult it would be to return results and whether an institutional review board (IRB) would approve a no-return approach given a high degree of difficulty. If it is true that returning findings will impact research in such a way that one will be unable to answer fundamental questions and will somehow impinge on the ability to do core parts of one's mission, Berkman said that argument can be used to justify a no-return policy or a very-high-bar return policy. Data suggest that IRBs do consider arguments about core capacity to accomplish a scientific mission, he said, if in fact that capacity is limited by allocating resources to a return-of-results policy. Some IRBs are willing to approve a no-return paradigm. According to Berkman, the disagreement among workshop participants about return of incidental findings underlines the fact that this is still a field in flux, and there should be room for different positions with regard to research that does not look at all like clinical research.

Burke noted that there seems to be strong support within the field for the notion that secondary uses of biobank specimens may generate less concern, obligation, sense of duty, or even ability to return results, which is a very important distinction. But, as Jarvik argued, highly actionable genetics findings should be returned in keeping with the fact that other highly actionable medical findings are returned to human subjects. It is difficult for the NHANES study to step through the secondary-use-of-data exception, she said.

The return-of-results discussion has implications for the research enterprise more broadly, according to Botkin. He stated there is no doubt that if one does a research scan and sees a tumor, one has to respond to that. On the other hand, if investigators' responsibility to return data is expanded, the line between research and clinical care may be blurred. In Botkin's view, there is no clear upper limit in terms of what the researchers' obligations are, both in terms of what to return and how often to

review their data to find out which data points may have changed from Bin Two to Bin One. This could enormously complicate the research enterprise in a way that may not end up benefiting the overall welfare of the public, because so many resources would be diverted.

FURTHER CLARIFICATIONS FOR NCHS

NCHS staff raised several questions during the final discussion. The NHANES program is grappling with the issue of which guidelines it should adopt when considering the return of genetic results. When study participants need advice about glucose levels, the American Diabetes Association has guidelines, and the National Cholesterol Education Program has useful guidelines for cholesterol thresholds. In the same vein, Kathryn Porter asked, what is the best place to look for guidance on Bin One variants? Burke noted that while the American College of Medical Genetics and Genomics (ACMG) recommendations (the 56-gene list) have received the most attention, several workshop presenters identified other lists such as the one described by Jarvik (see also Fabsitz et al., 2010). But as Les Biesecker stressed, the important point is that any list is just a starting point. He said such a list is not a how-to manual for dealing with every single variant in every situation, and it is not about research; it is only a starting point for constraining one's problem to a greater degree than it might otherwise be.

What a list does not do, Biesecker continued, is answer the pragmatic questions about how one evaluates the results, which ones should be CLIA validated, and which ones should go back to participants or patients. It will not work to have external guidelines, he said, because as this workshop has shown, there is no single commonly accepted formulation. Issues have to be worked on in-house with expertise from people who are following the debates, who know the range of recent literature, who can weigh the medical and genetic pros and cons, and who can help decide that variant X meets one's criteria for these good reasons and variant Y does not.

A "Returning Results Board," a third party, could be extremely useful, suggested Edwards. She pointed out that an analogy that occurs in clinical settings is end-of-life decision making, where one has a living will or an advance directive and has tried to think through every worst-case scenario but may end up in a different ambiguous scenario that the written wishes did not anticipate. A list or policy that is too specific about which results will or will not be returned is destined to miss the mark, according to Edwards, because results will often be rare and circumstances will evolve. A body of people with the requisite expertise

to help make decisions in real time seems like a necessary component of NHANES.

Another topic of discussion involved the NHANES DNA data bank, which currently is closed to new research proposals and tests. Porter explained that any past tests that have been done are available for secondary analysis, but new genetic tests are not permitted because the IRB said there is no way of determining whether results would need to be reported to participants. Madans noted that the NCHS would like to open the bank to new proposals, and asked if, leaving aside issues of re-consent and consent going forward, new proposals could be entertained given the consent currently in place.

Burke said in her view, feedback at the workshop from most participants suggested that it would be ethically acceptable to generate genomic data, even genomic data that met some criteria of reportability, and not report back for samples that were collected under a consent that said no return of results. One could also consider a re-consent process to return, Burke suggested. Several participants suggested that going forward, as future samples are collected and there is an anticipation of additional genomic research being done, it would be most appropriate to change the consent form so that return of results is possible. Accompanying that could be a very careful process that defines the criteria for the threshold of return, which likely would be very high, Burke said.

Weir said that because genetic analyses are done by third parties who come to NHANES to use the samples, the onus is on the researchers to say what they are going to look at and what the reportability is. To him, NHANES would then have the obligation to communicate the results and the information. No one who runs large population studies can possibly stay on top of all the curation that is needed to know about what markers matter and for which people, he observed.

One participant wondered whether NCHS could argue to its IRB that results of tests on already-stored samples do not have to be reported. Jarvik said she thought yes, because the samples in the DNA bank were not extracted under the standard practices that are now used when data are going to be returned. The same consideration would apply to genotypes that were generated in outside non-CLIA labs, she asserted, because the samples do not have the tracking that would generally be used for a valid test result. Madans commented that a first step for NHANES would be to reevaluate if results from existing samples would be reportable from a quality point of view. This has not yet been done.

Botkin suggested a layered argument can be made. In his view, the no-return consent is sufficient, and concerns about sample integrity can be layered on top to strengthen that argument. Another layer he identified

is the policy that NHANES has already adopted; that is, not to support or permit studies that are likely to develop incidental findings or findings on so-called Bin One conditions. The unlikelihood of finding other Bin One conditions (not currently in the bin) further reduces the probability that this would ever be an issue. Weir agreed, adding that the consent used was state of the art then and is still state of the art in much of the rest of the research community, even if standards are evolving.

References

Appelbaum, P.S., Roth, L.H., and Lidz, C. (1983). The therapeutic misconception: Informed consent in psychiatric research. *International Journal of Law and Psychiatry*, *5*(3-4), 319-329.

Belsky, L., and Richardson, H.S. (2004). Medical researchers' ancillary clinical care responsibilities. *British Medical Journal*, *328*(7454), 1494-1496.

Berg, J.S., Amendola, L.M., Eng, C., Van Allen, E., Gray, S.W., Wagle, N., Rehm, H.L., DeChene, E.T., Dulik, M.C., Hisama, F.M., Burke, W., Spinner, N.B., Garraway, L., Green, R.C., Plon, S., Evans, J.P., Jarvik, G.P., 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.

Berg, J.S., Khoury, M.J., and Evans, J.P. (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.

Botkin, J.R. (2014). *Statistical Agency Considerations in Releasing DNA Test Results*. Presentation at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC. Available: http://sites.nationalacademies.org/DBASSE/CNSTAT/DBASSE_086008 [June 2014].

The Cochrane Collaboration. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. J.P.T. Higgans and S. Green (Eds.). Available: http://handbook.cochrane.org/ [February 2014].

Daack-Hirsch S., Driessnack, M., Hanish, A., Johnson, V., Shah, L., Simon, C., and Williams, J. (2013). "Information is information": A public perspective on incidental findings in clinical and research genome-based testing. *Clinical Genetics*, *84*(1), 11-18.

Dorschner, M.O., Amendola, L.M., Turner, E.H., Robertson, P.D., Shirts, B.H., Gallego, C.J., Bennett, R.L., Jones, K.L., Tokita, M.J., Bennett, J.T., Kim, J.H., Rosenthal, E.A., Kim, D.S., National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project, Tabor, H.K., Bamshad, M.J., Motulsky, A.G., Scott, C.R., Pritchard, C.C., Walsh, T., Burke, W., Raskind, W.H., Byers, P., Hisama, F.M., Nickerson, D.A., and Jarvik, G.P. (2013). Actionable, pathogenic incidental findings in 1,000 participants' exomes. *American Journal of Human Genetics, 93*(4), 631-640.

Evans, P.P., and Rothschild, B.B. (2012). Return of results: Not that complicated? *Genetics in Medicine*, *14*(4), 358-360.

Fabsitz, R.R., McGuire, A., Sharp, R.R., Puggal, M., Beskow, L.M., Biesecker, L.G., Bookman, E., Burke, W., Burchard, E.G., Church, G., Clayton, E.W., Eckfeldt, J.H., Fernandez, C.V., Fisher, R., Fullerton, S.M., Gabriel, S., Gachupin, F., James, C., Jarvik, G.P., Kittles, R., Leib, J.R., O'Donnell, C.O., O'Rourke, P.P., Rodriguez, L.L., Schully, S.D., Shuldiner, A.R., Sze, R.K.F., Thakuria, J.V., Wolf, S.M., and Burke, G.L. (2010). Ethical and practical guidelines for reporting genetic research results to study participants: Updated guidelines from a National Heart, Lung, and Blood Institute working group. *Circulation Cardiovascular Genetics*, *3*(6), 574-580.

Facio, F.M., Eidem, H., Fisher, T., Brooks, S., Linn, A., Kaphingst, K.A., Biesecker, L.G., and Biesecker, B.B. (2013). Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. *European Journal of Human Genetics*, 21(3), 261-265.

Goddard, K.A.B., Whitlock, E.P., Berg, J.S., Williams, M.S., Webber, E.M., Webster, J.A., Lin, J.S., Schrader, K.A., Campos-Outcalt, D., Offit, K., Feigelson, H.S., and Hollombe, C. (2013). Description and pilot results from a novel method for evaluating return of incidental findings from next-generation sequencing technologies. *Genetics in Medicine*, *15*(9), 721-728.

Green, M.J., and Botkin, J.R. (2003). "Genetic exceptionalism" in medicine: Clarifying the differences between genetic and nongenetic tests. *Annals of Internal Medicine*, *138*(7), 571-575.

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

Green, S., Higgins, J.P.T., Alderson, P., Clarke, M., Mulrow, C.D., and Oxman, A.D. (2008). *Cochrane Handbook for Systematic Reviews of Interventions: Part 1 Cochrane Reviews*. Available: http://media.wiley.com/product_data/excerpt/15/04706995/0470699515.pdf [May 2014].

Hausman, D.M. (2004). Polling and public policy. *Kennedy Institute of Ethics Journal*, *14*(3), 241-247.

Institute of Medicine. (2012a). *Future Uses of the Department of Defense Joint Pathology Center Biorepository*. Washington, DC: The National Academies Press.

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

Johnston, J.J., Rubinstein, W.S., Facio, F.M., Ng, D., Singh, L.N., Teer, J.K., Mullikin, J.C., and Biesecker, L.G. (2012). Secondary variants in individuals undergoing exome sequencing: Screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. *American Journal of Human Genetics, 91*(1), 97-108.

Kaufman, D., Murphy, J., Scott, J., and Hudson, K. (2008). Subjects matter: A survey of public opinions about a large genetic cohort study. *Genetics in Medicine*, *10*(11), 831-839.

Khoury, M. (2014). *Issues for the NHANES.* Presentation at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC. Available: http://sites.nationalacademies.org/DBASSE/CNSTAT/DBASSE_086008 [June 2014].

Kohane, I.S., Mandl, K.D., Taylor, P.L., Holm, I.A., Nigrin, D.J., and Kunkel, L.M. (2007). Reestablishing the researcher-patient compact. *Science*, *316*(5826), 836-837.

Lunshof, J.E., Church, G.M., and Prainsack, B. (2014). Raw personal data: Providing access. *Science*, *343*(6169), 373-374.

Madans, J.H. (2014). *Statistical Agency Considerations in Releasing DNA Test Results.* Presentation at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC. Available: http://sites.nationalacademies.org/DBASSE/CNSTAT/DBASSE_086008 [June 2014].

McGuire, A.L., Joffe, S., Koenig, B.A., Biesecker, B.B., McCullough, L.B., Blumenthal-Barby, J.S., Caulfield, T., Terry, S.F., and Green, R.C. (2013). Ethics and genomic incidental findings. *Science*, *340*(6136), 1047-1048.

McQuillan, G.M., Pan, Q., and Porter, K.S. (2006). Consent for genetic research in a general population: An update on the National Health and Nutrition Examination Survey experience. *Genetics in Medicine*, *8*(6), 354-360.

Merritt, M.W., Taylor, H.A., and Mullany, L.C. (2010). Ancillary care in community-based public health intervention research. *American Journal of Public Health*, 100(2), 211-216.

Murphy, J., Scott, J., Kaufman, D., Geller, G., LeRoy, L., and Hudson, K. (2008). Public expectations for return of results from large-cohort genetic research. *American Journal of Bioethics, 8*(11), 36-43.

National Human Genome Research Institute. (2012). *ClinSeq: A Large-scale Medical Sequencing Clinical Research Pilot Study*. Available: http://www.genome.gov/clinseq/ [March 2014].

National Research Council. (2010). *Conducting Biosocial Surveys*. R.M. Hauser, M. Weinstein, R. Pool, and B. Cohen (Eds.). Washington, DC: The National Academies Press.

Presidential Commission for the Study of Bioethical Issues. (2013). *Anticipate and Communicate. Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*. Available: http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf [March 2014].

Richardson, H.S., and Cho, M.K. (2012). Secondary researchers' duties to return incidental findings and individual research results: A partial-entrustment account. *Genetics in Medicine*, *14*(4), 467-472.

Sankar, P., Cho, M.K., Wolpe, P.R., and Schairer, C. (2006). What is in a cause? Exploring the relationship between genetic cause and felt stigma. *Genetics in Medicine*, *8*(1), 33-42.

Sapp, J.C., Dong, D., Stark, C., Ivey, L.E., Hooker, G., Biesecker, L.G., and Biesecker, B.B. (2014). Parental attitudes, values, and beliefs toward the return of results from exome sequencing in children. *Clinical Genetics*, *85*(2), 120-126.

Williams, M.S. (2014). *What Data Are Returnable?* Presentation at the Workshop on Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens, February 10-11, National Research Council, Washington, DC. Available: http://sites.nationalacademies.org/DBASSE/CNSTAT/DBASSE_086008 [June 2014].

Wolf, S.M. (2013). Return of individual research results and incidental findings: Facing the challenges of translational science. *Annual Review of Genomics and Human Genetics*, *14*, 557-577.

Wolf, S.M., Annas, G.J., and Elias, S. (2013). Patient autonomy and incidental findings in clinical genomics. *Science, 340*(6136), 1049-1050.

Wolf, S.M, Crock, B.N., Van Ness, B., Lawrenz, F., Kahn, J.P., Beskow, L.M., Cho, M.K., Christman, M.F., Green, R.C., Hall, R., Illes, J., Keane, M., Knoppers, B.M., Koenig, B.A., Kohane, I.S., LeRoy, B., Maschke, K.J., McGeveran, W., Ossorio, P., Parker, L.S., Petersen, G.M., Richardson, H.S., Scott, J.A., Terry, S.F., Wilfond, B.S., and Wolf, W.A. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genetics in Medicine*, *14*(4), 361-384.

World Health Organization. (2014). *Genomic Resource Centre: Genetic Stigmatization.* Geneva, Switzerland: Author. Available: http://www.who.int/genomics/gender/en/index3.html [July 2014].

Zipf, G., Chiappa, M., Porter, K.S., Ostchega, Y., Lewis, B.G., and Dostal, J. (2013). National Health and Nutrition Examination Survey: Plan and operations. *Vital and Health Statistics*, *1*(56).

Acronyms

ACMG	American College of Medical Genetics and Genomics
Add Health	National Longitudinal Study of Adolescent Health
BMI	body mass index
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
ClinSeq	a large-scale medical sequencing clinical research pilot study (sponsored by the National Human Genome Research Institute)
CSER	Clinical Sequencing Research Project
dbGaP	database of Genotypes and Phenotypes (developed by the National Center for Biotechnology Information)
DNA	deoxyribonucleic acid, a molecule that encodes genetic instructions
EGAPP	Evaluation of Genomic Applications in Practice and Prevention Initiative Working Group
eMERGE	electronic MEdical Records and GEnomics Network
GENEVA	Gene Environment Association Studies consortium

GIFs	genetic incidental findings
GWAS	genome-wide association study that examines many common genetic variants in different individuals to see if any variant is associated with a trait
HapMap	the International HapMap Project is a multicountry effort to identify and catalog genetic similarities and differences in human beings
HIV	Human Immunodeficiency Virus, a slowly replicating retrovirus that causes the acquired immune deficiency syndrome
HRS	Health and Retirement Study
IOM	Institute of Medicine
IRB	institutional review board
NCHS	National Center for Health Statistics
NCS	National Children's Study
NHANES	National Health and Nutrition Examination Survey
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NRC	National Research Council
NSHAP	National Social Life, Health, and Aging Project
PEER	Genetic Alliance's Platform for Engaging Everyone Responsibly
PRIM&R	Public Responsibility in Medicine and Research consortium
SNPs	single nucleotide polymorphisms, the most common type of genetic variation among people.
WLS	Wisconsin Longitudinal Study

Appendix A

Workshop Agenda

Guidelines for Returning Individual Results from Genome Research Using Population-Based Banked Specimens

National Academy of Sciences
2101 Constitution Ave, NW
Washington, DC
Lecture Room

February 10-11, 2014

Day One–February 10

8:15-8:45 am **Registration (East Court)**
Continental breakfast available from 8:15 am

8:45-9:00 am **Welcome and Opening Remarks**
- Wylie Burke, *University of Washington*, Workshop Chair
- Connie Citro, *NRC Committee on National Statistics*
- Virginia Cain, *National Center for Health Statistics*

9:00-10:00 am **Genomics in Population-Based Data Collection: The Example of the National Health and Nutrition Examination Survey (NHANES)**
Session chair: Wylie Burke, *University of Washington*
- Overview of NHANES (30 min.)—Kathryn Porter, *National Center for Health Statistics*
- Discussion (30 min.)

10:00-11:00 am **Perspectives on Returning Genome-Based Research Results**

Session chair: Jeffrey Botkin, *University of Utah*

- Role-based obligations (15 min.)—Henry Richardson, *Georgetown University*
- The case for a stringent approach to returning results (15 min.)—Steven Joffe, *University of Pennsylvania*
- The case for broad return (15 min.)—Susan Wolf, *University of Minnesota*
- Discussion (15 min.)

11:00-11:15 am **Break**

11:15 am-12:30 pm **Framing the Discussion**

Session chair: Ellen Clayton, *Vanderbilt University*

- The evolution of genomic technology and clinical utility (20 min.)—Gail Jarvik, *University of Washington*
- Ethical frameworks (20 min.)—Benjamin Berkman, *National Human Genome Research Institute*
- Discussion (35 min.)

12:30-1:15 pm **Lunch**

1:15-3:15 pm **How Is NHANES Similar to/Different from Other Population-Based Studies?**

Session chair: Eileen Crimmins, *University of Southern California*

- National Longitudinal Study of Adolescent Health (Add Health) (15 min.)—Carolyn Halpern, *University of North Carolina*
- Health and Retirement Study (15 min.)—David Weir, *University of Michigan*
- National Social Life, Health, and Aging Project (15 min.)—Martha McClintock, *University of Chicago*
- Wisconsin Longitudinal Study (15 min.)—Robert Hauser, *National Research Council*
- National Children's Study (15 min.)—John Moye, *National Institute of Child Health & Human Development*
- Illumina (15 min.)—Tina Hambuch, *Illumina*
- Discussion (30 min.)

3:15-3:30 pm **Break**

3:30-5:00 pm **Issues for NHANES**
Session chair: Adam Berger, *Institute of Medicine*
- The scientific value of incorporating genomic data collection into NHANES (20 min.)—Sharon Kardia, *University of Michigan*
- Panel on "Determining what data are returnable" (30 min.)
  1. Marc Williams, *Geisinger Genomic Medicine Institute*
  2. Muin Khoury, *Centers for Disease Control and Prevention*
- Survey participants' attitudes and preferences (20 min.)—Laura Beskow, *Duke University*
- Discussion

6:30 pm **Dinner** (Steering Committee and Invited Speakers)

Day Two–February 11

8:30-9:00 am **Registration (East Court)**
Continental breakfast available from 8:30 am

9:00-10:45 am **The Logistics of Returning Genomic Results from NHANES**
Session chair: Wylie Burke, *University of Washington*
- Kathryn Porter, *National Center for Health Statistics* (20 min.)
- Retrospective versus prospective samples (20 min.)—Kelly Edwards, *University of Washington*
- Practical issues/aspects of returning results (20 min.)—Barbara Biesecker, *National Human Genome Research Institute*
- Discussion (45 min.)

10:45-11:00 am **Break**

11:00 am-12:00 pm **Special Considerations for Reporting of Results in NHANES and Similar Surveys**
Session chair: Les Biesecker, *National Human Genome Research Institute*
- Statistical agency considerations in releasing DNA results (15 min.)—Jennifer Madans, *National Center for Health Statistics*

- Genetic exceptionalism in NHANES? (15 min.)—Jeffrey Botkin, *University of Utah*
- Discussion (30 min.)

12:00-1:00 pm **Lunch**

1:00-3:00 pm **Summary of Presentations and Discussion**
Session chair: Wylie Burke, *University of Washington*

- Reports from Steering Committee members and selected speakers (10 min. each)
- Group discussion
- Wrap-up and next steps

3:00 pm **Adjourn**

Appendix B

List of Registrants

Jacob Adetunji
U.S. Agency for International Development

Aimee Alexander
Centers for Disease Control and Prevention

Laura Amendola
University of Washington

Yutaka Aoki
National Center for Health Statistics

John Aquino
Bloomberg BNA

Christine Benally
Indian Health Service

Adam Berger
Institute of Medicine

Benjamin Berkman
National Human Genome Research Institute

Lew Berman
ICF International

Laura Beskow
Duke University

Barbara Biesecker
National Human Genome Research Institute

Leslie G. Biesecker (*Steering Committee*)
National Human Genome Research Institute

Marianna Bledsoe
George Washington University School of Medicine and Health Sciences

Stephen Blumberg
National Center for Health Statistics

Jeffrey Botkin (*Steering Committee*)
University of Utah

Wylie Burke (*Steering Committee Chair*)
University of Washington

Charlisse Caga-Anan
National Cancer Institute

Virginia Cain
National Center for Health Statistics

Charlotte Carlson
University of Michigan

Heather Carroll
Social & Scientific Systems, Inc.

Sarah Carter
J. Craig Venter Institute

Kee Chan
Boston University

Danyang Chen
Pennsylvania Department of Health

Mildred Cho (*Steering Committee*)
Stanford University School of Medicine

Yoonjoung Choi
U.S. Agency for International Development

Winnie Chung
Centers for Disease Control and Prevention

Constance Citro
CNSTAT, National Research Council

Ellen Wright Clayton (*Steering Committee*)
Vanderbilt University

Nancy Conrad
Conrad Foundation

Elizabeth Cooksey
Ohio State University

Deborah Cool
Medical student

Dana Crawford
Vanderbilt University

Lauren Creamer
National Center for Health Statistics

Eileen M. Crimmins (*Steering Committee*)
University of Southern California

Carla Cuthbert
Centers for Disease Control and Prevention

Daniel Day
Avalere Health

Nancy Dole
University of North Carolina at Chapel Hill

Nicole Dowling
National Center on Birth Defects and Developmental Disabilities

Jennifer Dreyfus
Dreyfus Consulting LLC

Aaliyah Eaves-Leanos
Food and Drug Administration

Kelly Edwards
University of Washington

Anna Ettinger
National Children's Study

Altovise Ewing
Johns Hopkins Center to Reduce Cancer Disparities

Margaret Farrell
National Cancer Institute

Colleen Gallagher
MD Anderson Cancer Center

Rosella Gardecki
CHRR at Ohio State University

John Gardenier
Retired (formerly National Center for Health Statistics)

Turkan Gardenier
Pragmatica Corp.

Jeremy Garrett
Children's Mercy Bioethics Center

Nina Gold
Harvard Medical School

John Greco

Marisa Greenberg
Pennsylvania State University

Hermann Habermann
National Research Council

Carolyn Halpern
University of North Carolina at Chapel Hill

Tina Hambuch
Illumina Clinical Services Laboratory

Melissa Hamilton
Virginia Department of Health

Jennifer Harris
Norwegian Institute of Public Health

Sumaira Hassan
Dow University of Health Sciences

Barrie Hayes
University of North Carolina at Chapel Hill

Robert Hauser
DBASSE, National Research Council

Jeannine Helm
National Institute of Dental and Craniofacial Research/ National Institutes of Health

Ingrid Holm
Boston Children's Hospital

Juell Homco
University of Oklahoma

Julie Hunter
IBM

Galina Inzhakova
Kaiser Permanente

Chazeman Jackson
Office of Minority Health, Department of Health and Human Services

Gail Jarvik
University of Washington

Steven Joffe
University of Pennsylvania

Sharon Kardia
University of Michigan

Dave Kaufman
Johns Hopkins University

Eimear Kenny
Icahn School of Medicine at Mount Sinai

Muin Khoury
Centers for Disease Control and Prevention

Sangmi Kim
Georgia Regents University

Corinna Koebnick
Kaiser Permanente

Steven Kornblau
University of Texas MD Anderson Cancer Center

Ellen Kramarow
National Center for Health Statistics

David Lacher
National Center for Health Statistics

Liz Langlois
Tulane University

Mariana Lazo
Johns Hopkins University

Marie Leahy
National Center for Health Statistics

Jung Lee
Genesis Strategic Solutions, Inc.

Johanne Levesque
Statistics Canada

Rongling Li
National Human Genome Research Institute

Neranga Liyanaarachchi
Postgraduate Institute of Medicine, Colombo

Nicole Lockhart
National Human Genome Research Institute

Amy Lossie
National Institutes of Health

Susan Lukacs
National Center for Health Statistics

Andrea Mackay
National Center for Health Statistics

Jennifer Madans
National Center for Health Statistics

Jennifer Malinowski
Vanderbilt University

Cathy McCarty
Essentia Institute of Rural Health

Martha McClintock
University of Chicago

Jean McEwen
National Human Genome Research Institute

Jenna McGwin
American Psychological Association

Scott Mclean
Statistics Canada

Geraldine McQuillan
National Center for Health Statistics

Lori Merrill
Westat

Danielle Metterville
Partners Center for Personalized Genetic Medicine

Julia Milton
Consortium of Social Science Associations

John Moye
National Children's Study

Mugo Muita
United Nations High Commissioner for Refugees

Edgar Munoz
University of Texas Health Science Center

Carolyn Neal
National Center for Health Statistics

F. Javier Nieto
University of Wisconsin–Madison

Miki Nguyen
Kaiser Permanente Southern California

Sangeeta Panicker
American Psychological Association

Roxanne Parrott
Pennsylvania State University

Donald Patrick
University of Washington

Kathryn Porter
National Center for Health Statistics

Tabitha Powledge
Science writer and editor

Sandra Prucka
Eli Lilly and Company

Susan Queen
Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services

Kate Reed
The Jackson Laboratory

Teresa Rhodes
ALI

Henry Richardson
Georgetown University

Jeanne Rivard
National Research Council

Victor Rosa
PC

Gabriel Rosenfeld
National Cancer Institute

Lainie Ross
University of Chicago

Paul Scanlon
National Center for Health Statistics

Sheri Schully
National Cancer Institute

Murat Sincan
National Human Genome Research Institute

Julia Slutsman
National Institute of Child Health & Human Development

Teresa Solomon
The Rockefeller University

Edward Sondik
National Center for Health Statistics (retired)

James Sorace
Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services

Colleen Spees
Ohio State University

Erica Spotts
National Institutes of Health

Sylvia Trujillo
American Medical Association

Alicia Vargas
DC Cancer Registry, Department of Health

Christine Vaupel
Genoptix Medical Laboratory

Caer Rohrer Vitek
Mayo Clinic

Berna Watson
California Department of Public Health

Carol Weil
National Cancer Institute

David Weir
University of Michigan

Karen Whitaker
National Center for Health Statistics

Marc Williams
Geisinger Genomic Medicine Institute

Saba Wolday
Howard University

Susan Wolf
University of Minnesota–Minneapolis

Joseph Woodring
Centers for Disease Control and Prevention

Amber Worthington
Pennsylvania State University

Melanie Young
Environmental Protection Agency

Nicholas Zill
Independent psychologist

Oliver Zill
University of California, San Francisco

Shonia Zollicoffer
Centers for Disease Control and Prevention

Appendix C

Biographical Sketches of Steering Committee Members and Presenters

WYLIE BURKE (*Steering Committee Chair*) is professor and chair of the Department of Bioethics and Humanities at the University of Washington. She is also adjunct professor of medicine and epidemiology and a member of the Fred Hutchinson Cancer Research Center. Previously, she was associate director of the Internal Medicine Residency Program and founding director of the Women's Health Care Center at the University of Washington. She has been a visiting scientist at the Centers for Disease Control and Prevention and an international fellow at the National Health Service in Cambridge, United Kingdom. Her research addresses the social, ethical, and policy implications of genetic information. She is a member of the Institute of Medicine and the Association of American Physicians and a past president of the American Society of Human Genetics. She has a Ph.D. in genetics and an M.D. from the University of Washington, where she also completed a residency in internal medicine.

BARBARA BIESECKER is head of the Genetic Services Research Unit and an associate investigator in the Social and Behavioral Research Branch of the National Human Genome Research Institute. She also is director of the Johns Hopkins University/National Human Genome Research Institute Genetic Counseling Training Program. Her research addresses how genetic counseling can improve people's decision-making and coping strategies, and is focused on the role of uncertainty in adapting to the lack of a diagnosis for a rare condition, using genomic sequence information, distinguishing predictors of decision making to enhance informed choice,

and assessing models of informed consent to undergo exome sequencing. She has an M.S. from the University of Michigan and a Ph.D. from King's College, London.

LESLIE G. BIESECKER (*Steering Committee Member*) is chief and senior investigator of the Genetic Disease Research Branch at the National Human Genome Research Institute and director of the institute's physician scientist development program. His research focuses on understanding the relationship of genomic variation to health and disease, and his lab is currently engaged in studies of rare disorders of development and growth and of new approaches to hypothesis-generating clinical genomics research and clinical genome sequencing research. He has served on the board of directors of the American Society of Human Genetics and on the advisory board for both the World Trade Center 9/11 victim identification project and the Hurricane Katrina victim identification project. He has a B.S. from the University of California, Riverside, and an M.D. from the University of Illinois College of Medicine. He was trained in pediatrics at the University of Wisconsin and in medical genetics at the University of Michigan and is board certified in both of these specialties.

BENJAMIN BERKMAN is deputy director of the bioethics core at the National Human Genome Research Institute and a faculty member in the Department of Bioethics at the National Institutes of Health. He was formerly the deputy director of the O'Neill Institute for National and Global Health Law at Georgetown Law School, where he continues to serve as an adjunct professor. His current work focuses on the legal and ethical issues associated with genomic research, genetic information privacy, public health emergency preparedness, and research involving vulnerable populations. He has worked with the World Health Organization and the Centers for Disease Control and Prevention. He has a bachelor's degree in the history of science and medicine from Harvard University and a J.D. and an M.P.H. from the University of Michigan.

LAURA BESKOW is an associate professor in the Duke Clinical Research Institute. She is also a faculty associate in the Trent Center for Bioethics, Humanities & History of Medicine, and a member of the ethics core of the Duke Translational Medicine Institute. Previously, she was associate director of the Stanford University Program in Genomics, Ethics, and Society, and a career development awardee in Office of Genetics and Disease Prevention at the Centers for Disease Control and Prevention. Her work focuses on ethics and policy issues in research, particularly human subject issues in large-scale genomic and translational research. She is a member of the Subpart A Subcommittee of the Secretary's Advisory Com-

mittee for Human Research Protections at the U.S. Department of Health and Human Services and a member of the editorial advisory board for the *Journal of Empirical Research on Human Research Ethics*. She has a B.S. in nutrition from Iowa State University, an M.P.H with a concentration in health law from Boston University, and a Ph.D. in health policy and administration, with a minor in epidemiology, from the University of North Carolina at Chapel Hill.

JEFFREY BOTKIN (*Steering Committee Member*) is professor of pediatrics and adjunct professor of human genetics at the University of Utah, where he is chief of the Division of Medical Ethics and Humanities in the Department of Internal Medicine. He is also the university's associate vice president for research integrity. His research and publications are focused on the ethical, legal, and social implications of genetic technology with a particular emphasis on research ethics, genetic testing for cancer susceptibility, newborn screening, and prenatal diagnosis. Formerly, he was chair of the Committee on Bioethics for the American Academy of Pediatrics and a member of the Secretary's Advisory Committee on Human Research Protections at the U.S. Department of Health and Human Services (DHHS). He currently is a member of the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children at DHHS. He chairs the Embryonic Stem Cell Working Group at the National Institutes of Health and is a member of the Pediatric Ethics Advisory Committee of the Food and Drug Administration. He is an elected fellow of the Hastings Center. He has a B.A. from Princeton University, an M.D. from the University of Pittsburgh, and an M.P.H. from Johns Hopkins University.

MILDRED K. CHO (*Steering Committee Member*) is professor of pediatrics in the Division of Medical Genetics of the Department of Pediatrics at Stanford University, associate director of the Stanford Center for Biomedical Ethics, and director of the Center for Integration of Research on Genetics and Ethics. Previously, she was an assistant professor of bioethics in the Center for Bioethics and the Department of Molecular and Cellular Engineering at the University of Pennsylvania School of Medicine. Her current research examines ethical and social issues in research on the genetics of behavior, the human microbiome, human genetic variation and natural selection. She is a member of the national advisory boards of the National Human Genome Research Institute and the Genome X-Prize and on the board of reviewing editors of *Science*. She has also served as a member of the working group on synthetic genomes for the U.S. Department of Energy. She has a B.S. in biology from the Massachusetts Institute of Technology and a Ph.D. from the Stanford University Department of Pharmacology.

ELLEN WRIGHT CLAYTON (*Steering Committee Member*) is the Craig-Weaver professor of pediatrics and professor of law at Vanderbilt University, where she cofounded and directed the Center for Biomedical Ethics and Society. Her research has focused on the ethical, legal, and social issues (ELSI) raised by genetics and genomics research, genetic testing for children and adults, guidelines to promote the inclusion of children in clinical trials, and the translation of new findings into clinical care. She has served on the National Advisory Council for Human Genome Research, as cochair of the ELSI Working Group of the International HapMap Project, and on the American Society of Human Genetics Social Issues Committee. She was awarded the David P. Rall Medal from the Institute of Medicine in 2013. She has a B.S. in zoology from Duke University, an M.S. in biology from Stanford University, a J.D. from Yale Law School, and an M.D. from Harvard Medical School. She completed a residency in pediatrics at the University of Wisconsin.

EILEEN M. CRIMMINS (*Steering Committee Member*) holds the AARP chair in gerontology at the University of Southern California (USC) and leads the Center on Biodemography and Population Health, a joint activity of USC and the University of California, Los Angeles. Her research focuses on the connections between socioeconomic factors and life expectancy and other health outcomes, on healthy life expectancy in older populations, and on male/female differences in health and mortality, as well as differences by gender in life stresses and strains. She is an elected member of the Institute of Medicine. She has an M.A. and a Ph.D. in demography, both from the University of Pennsylvania.

KELLY EDWARDS is an associate professor in the Department of Bioethics and Humanities at the University of Washington School of Medicine and a core faculty member of the Institute for Public Health Genetics. She serves as director of the Ethics and Outreach Core for the Center for Ecogenetics and Environmental Health, codirector of the Regulatory Support and Bioethics Core for the Institute for Translational Health Sciences (CTSA), and lead investigator with the Center for Genomics and Healthcare Equality, all at the University of Washington. Her special interests include community-based research practices, biobank governance, environmental justice, everyday ethics in research practice, feminist and narrative approaches to bioethics, and the integration of ethics into training programs, public conversations about science, and public policy. She has been a member of the International "Making Connections" consortium, and she cochairs the Biobank Working Group within the CTSA Consortium. She has an M.A. in medical ethics and a Ph.D. in the philosophy of education from the University of Washington, Seattle.

CAROLYN TUCKER HALPERN is professor of maternal and child health in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. She is deputy director/co-investigator of the National Longitudinal Study of Adolescent Health (Add Health) Program and director of the Carolina Population Center training program. Her research interests involve understanding healthy sexual development and the implications of adolescent experiences for developmental and demographic processes into adulthood, particularly as these relate to biopsychosocial models of sexual and romantic relationships. She is the principal investigator of a five-year National Institute of Child Health and Human Development-based project examining sexual trajectories from adolescence into adulthood, and a co-investigator on several National Institutes of Health-funded projects evaluating interventions to reduce HIV risk in adolescents in sub-Saharan Africa. She has a B.S. in psychology and an M.A. and a Ph.D. in developmental psychology, all from the University of Houston–Central Campus.

TINA HAMBUCH is director of clinical services at Illumina. She launched a California-certified clinical genetic molecular biologist scientist training program in which she serves as education coordinator and director. Previously, she was a postdoctoral fellow at the Centers for Disease Control and Prevention (CDC) and was on the faculty of the University of Munich. She is currently active in the development and validation of genetic testing as well as clinical tools for physician support and education. She is a member of the American Society of Human Genetics and serves on clinical genomics working groups for the CDC, Association for Molecular Pathology, and Clinical Laboratory Standards Institute. She has a bachelor's degree from the University of California, Riverside, and a Ph.D. from the University of California, Berkeley. She is board certified by the American Board of Medical Genetics in clinical molecular genetics.

ROBERT M. HAUSER is executive director of the Division of Behavioral and Social Sciences and Education at the National Research Council and Vilas Research Professor and Samuel Stouffer professor of sociology (emeritus) at the University of Wisconsin–Madison. Previously, he directed the university's Center for Demography of Health and Aging, the Institute for Research on Poverty, and the Center for Demography and Ecology, and he has been an investigator on the Wisconsin Longitudinal Study since 1969. His current research interests include statistical methodology, trends in educational progression and achievement among American racial and ethnic groups, the uses of educational assessment as a policy tool, and changes in socioeconomic standing, cognition, health, and well-being across the life course. He is a member of the National

Academy of Sciences, the American Academy of Arts and Sciences, the National Academy of Education, and the American Philosophical Society. He has a B.A. in economics from the University of Chicago and an M.A. and a Ph.D. in sociology from the University of Michigan.

GAIL JARVIK is the Arno G. Motulsky endowed chair in medicine, joint professor of medicine and genome sciences, and head of the Division of Medical Genetics at the University of Washington Medical Center (UWMC). She also is an adjunct professor of epidemiology at UWMC, affiliate member of the Fred Hutchinson Cancer Research Center, and Pew Scholar in the biomedical sciences. She has chaired the Genomics, Computational Biology and Technology study section at the National Institutes of Health. Her research focuses on the inheritance of diseases of complex etiology such as cancer, heart disease, stroke, and immune disorders; genome-wide association studies of phenotypes from clinical electronic medical records; and exomic analysis of lipid disorders in large families. She is a practicing clinician in internal medicine and medical genetics. She has an M.D. from the University of Iowa and a Ph.D. in genetics from the University of Michigan.

STEVEN JOFFE is vice chair of medical ethics, Emanuel and Robert Hart associate professor of medical ethics and health policy, and a pediatric oncologist and bioethicist at the University of Pennsylvania Perelman School of Medicine. He currently directs the Penn Fellowship in Advanced Biomedical Ethics, chairs the Children's Oncology Group Bioethics Committee, and serves as a member of the Pediatrics Ethics Subcommittee of the Food and Drug Administration. His research addresses the roles and responsibilities of principal investigators in multicenter randomized trials, accountability in the clinical research enterprise, children's capacity to engage in research decisions, return of individual genetic results to participants in epidemiologic cohort studies, and the integration of whole-exome sequencing technologies into the clinical care of cancer patients. He has an A.B. in fine arts from Harvard College, an M.D. from the University of California, San Francisco School of Medicine, and an M.P.H in epidemiology from the University of California, Berkeley.

SHARON KARDIA is director of the Public Health Genetics Program and of the Life Sciences and Society Program, professor of epidemiology, and senior associate dean for administration at the University of Michigan. Her main research interests involve the genetic epidemiology of common chronic diseases and their risk factors. She is particularly interested in gene-environment and gene-gene interactions and in developing novel analytical strategies to understand the complex relationship between

genetic variation, environmental variation, and risk of common chronic diseases. Her research utilizes genomic, epigenomic, transcriptomic, and proteomic measures on large epidemiological cohorts. She has an M.A. in statistics and a Ph.D. in human genetics from the University of Michigan.

MUIN KHOURY is founding director of the Office of Public Health Genomics at the Centers for Disease Control and Prevention. He has served the National Cancer Institute (NCI) as senior advisor in public health genomics, and he currently leads the NCI Epidemiology and Genomics Research Program. He is also an adjunct professor in the Department of Epidemiology and the Department of Environmental and Occupational Health at Emory University Rollins School of Public Health, and an associate in the department of epidemiology at the Johns Hopkins University Bloomberg School of Public Health. He has a B.S. in biology/chemistry and a medical degree from the American University of Beirut, Lebanon, and a Ph.D. in human genetics/genetic epidemiology from Johns Hopkins University. He is board certified in medical genetics.

JENNIFER H. MADANS is associate director for science at the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, where she is responsible for the overall plan and development of NCHS's data collection and analysis programs. Her research interests include data collection methodology, measurement of health and functioning, health services, and development of internationally comparable measures of disability and health. She has directed two major national longitudinal studies (the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study and the National Nursing Home Follow-up Study), and participated in the redesign of the National Health Interview Survey questionnaire. She has also served as adjunct associate professor in the Demography and Community and Family Medicine Departments at Georgetown University. She is a fellow of the American Statistical Association and a member of the International Statistical Institute. She has a B.A. from Bard College, and an M.A. and a Ph.D. in sociology from the University of Michigan.

MARTHA MCCLINTOCK is the David Lee Shillinglaw distinguished service professor in psychology at the University of Chicago. She is the founder of the Institute for Mind and Biology, codirector of the Center for Interdisciplinary Health Disparities Research, and she holds joint appointments in the Departments of Psychology and Comparative Human Development. Her current research interests include the interaction between behavior and reproductive endocrinology and immunology, hormonal and neuroendocrinal mechanisms of behavior, and the psychosocial ori-

gins of malignant and infectious disease. She is a member of the Institute of Medicine and the American Academy of Arts and Sciences, as well as a fellow of the American Association for the Advancement of Science, the Animal Behavior Society, American Psychological Society, American Psychological Association, and International Academy of Sex Research. She has a Ph.D. from the University of Pennsylvania.

JOHN (JACK) MOYE is a medical officer with the National Children's Study and a pediatrician with the National Institute of Child Health and Human Development (NICHD). His background is in clinical and laboratory medicine and public health with an emphasis on the prevention and control of communicable and chronic diseases, including sexually transmitted diseases and HIV/AIDS. His research interests include HIV virology and immunology, laboratory quality assurance, and growth and nutrition. He also is involved in clinical trials conducted as part of the NICHD Domestic and International Pediatric/Perinatal HIV Clinical Studies Network, Women and Infants Transmission Study (for which he chairs the Clinical Working Group), and Pediatric HIV/AIDS Cohort Study.

KATHRYN PORTER is director of the Division of Health and Nutrition Examination Surveys (DHANES) at the National Center for Health Statistics. She is responsible for managing the planning and implementation of the ongoing National Health and Nutrition Examination Survey and overseeing the related analytic research activities. She is a captain in the U.S. Public Health Service Commissioned Corps and a former epidemic intelligence service officer and medical officer in the Operations Branch of DHANES. She is a member of the American Medical Association, the American Public Health Association, and the American College of Preventive Medicine, and she is board certified in preventive medicine and public health. She has an M.D. from the Medical College of Virginia and an M.S. in preventive medicine and epidemiology from the University of Maryland.

HENRY S. RICHARDSON is senior research scholar at the Kennedy Institute of Ethics and professor of philosophy at Georgetown University. He has worked principally on the nature of reasoning, both individual and collective. He has twice been a visiting scholar in the Department of Bioethics at the National Institutes of Health, and he has participated in research-ethics training courses organized by that department in Uganda and Tanzania. He was appointed by the director general of UNESCO as a member of the World Commission on the Ethics of Scientific Knowledge and Technology, and he currently serves as the editor of *Ethics*. He has a

B.A. from Harvard College and a J.D., an M.P.P., and a Ph.D. in philosophy, all from Harvard University.

DAVID WEIR is research professor in the Survey Research Center and a research affiliate of the Population Studies Center at the University of Michigan. He is director and principal investigator of the national Health and Retirement Study. His current research interests include the measurement of health-related quality of life, the use of cost-effectiveness measures in health policy and medical decision making, the role of supplemental Medicare health insurance, the effects of health, gender, and marital status on economic well-being in retirement, and the effects of early life experience on longevity and health at older ages. He has a B.A. in history from the University of Michigan and a Ph.D. in economics from Stanford University.

MARC WILLIAMS is a pediatric geneticist and director of the Genomic Medicine Institute for Geisinger Health System in Danville, PA. He is the coprincipal investigator of the Geisinger Electronic Medical Records in Genomics (eMERGE) project, principal investigator of a Patient-Centered Outcomes Research Institute contract on how best to communicate results to patients undergoing whole-genome sequencing for undiagnosed diseases, and medical director of the Geisinger clinical whole-genome sequencing project. He is a director of the board of the American College of Medical Genetics and has been the organization's elected vice-president of clinical genetics. He also is a member of the advisory panel for the American Academy of Pediatrics (AAP) Genetics in Primary Care Institute and a member of the AAP section on genetics and birth defects. He has a B.S. in chemistry and an M.D. from the University of Wisconsin–Madison.

SUSAN M. WOLF is the McKnight Presidential professor of law, medicine, and public policy and the Faegre Baker Daniels professor of law at the University of Minnesota. She is also professor of medicine in the university's medical school and a faculty member in the university's Center for Bioethics. She is the founding chair of the Consortium on Law and Values in Health, Environment and the Life Sciences and the founding director of the joint degree program in law, science, and technology. She is a member of the Institute of Medicine and the American Law Institute and a fellow of the American Association for the Advancement of Science and The Hastings Center. She is faculty advisor to the *Minnesota Journal of Law, Science and Technology* and has served on many editorial boards. She has a B.A. from Princeton University and a J.D. from Yale Law School.

COMMITTEE ON NATIONAL STATISTICS

The Committee on National Statistics was established in 1972 at the National Academies to improve the statistical methods and information on which public policy decisions are based. The committee carries out studies, workshops, and other activities to foster better measures and fuller understanding of the economy, the environment, public health, crime, education, immigration, poverty, welfare, and other public policy issues. It also evaluates ongoing statistical programs and tracks the statistical policy and coordinating activities of the federal government, serving a unique role at the intersection of statistics and public policy. The committee's work is supported by a consortium of federal agencies through a National Science Foundation grant.