Returning Individual Research Results to Participants

GUIDANCE FOR A NEW RESEARCH PARADIGM

Jeffrey R. Botkin, Michelle Mancher, Emily R. Busta,
and Autumn S. Downey, *Editors*

Committee on the Return of Individual-Specific Research Results
Generated in Research Laboratories

Board on Health Sciences Policy

Health and Medicine Division

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JEFFREY R. BOTKIN (*Chair*), Associate Vice President for Research and Professor of Pediatrics, The University of Utah School of Medicine
PAUL S. APPELBAUM, Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law, Columbia University
SUZANNE BAKKEN, Professor of Biomedical Informatics, Columbia University
CHESTER BROWN, Professor and the St. Jude Chair of Excellence in Genetics for the Department of Pediatrics, University of Tennessee Health Science Center
WYLIE BURKE, Professor Emeritus, University of Washington
RICHARD FABSITZ, Adjunct Faculty, George Mason University
VANESSA NORTHINGTON GAMBLE, University Professor of Medical Humanities, The George Washington University
GREGG GONSALVES, Assistant Professor, Yale School of Public Health
RHONDA KOST, Director, Clinical Research Support Office, Co-Director Community Engaged Research Core, Associate Professor of Clinical Investigation, The Rockefeller University Center for Clinical and Translational Science
DEBRA G. B. LEONARD, Professor and Chair of Pathology and Laboratory Medicine, Robert Larner, M.D. College of Medicine, University of Vermont, University of Vermont Health Network
AMY McGUIRE, Leon Jaworski Professor of Biomedical Ethics, Baylor College of Medicine
JAMES H. NICHOLS, Professor of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine
BRAY PATRICK-LAKE, Director of Stakeholder Engagement, Duke Clinical Research Institute
CONSUELO H. WILKINS, Associate Professor of Medicine, Vanderbilt University Medical Center and Meharry Medical College
BRIAN J. ZIKMUND-FISHER, Associate Professor, University of Michigan

Study Staff

MICHELLE MANCHER, Study Director
AUTUMN S. DOWNEY, Interim Study Director
EMILY R. BUSTA, Associate Program Officer
OLIVIA C. YOST, Research Associate
CAROLINE M. CILIO, Senior Program Assistant
DANIEL BEARSS, Senior Research Librarian
ANDREW M. POPE, Director, Board on Health Sciences Policy

Consultants

REBECCA L. DAVIES, Associate Professor, University of Minnesota
CHRISTI GUERRINI, Assistant Professor, Baylor College of Medicine
E. HAAVI MORREIM, Professor, University of Tennessee Health Science Center

Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

BARBARA E. BIERER, Harvard Medical School and Brigham and Women's Hospital
JULIA GREEN BRODY, Silent Spring Institute
ELLEN WRIGHT CLAYTON, Vanderbilt University Medical Center
BARRY S. COLLER, The Rockefeller University
CRISPIN GOYTIA-VASQUEZ, Mount Sinai Health System
ALBERTO GUTIERREZ, NDA Partners LLC
KATHY L. HUDSON, People-Centered Research Foundation
DEVEN McGRAW, Ciitizen
J. STEPHEN MIKITA, Spinal Muscular Atrophy Foundation
ELLEN PETERS, The Ohio State University
HEIDI REHM, Massachusetts General Hospital
MARK E. SOBEL, American Society for Investigative Pathology
SUSAN M. WOLF, University of Minnesota

BARBARA A. ZEHNBAUER, Emory University School of Medicine
MARK L. ZEIDEL, Harvard Medical School and Beth Israel Deaconess Medical Center

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **LYNN R. GOLDMAN,** The George Washington University, and **JOSHUA M. SHARFSTEIN,** Johns Hopkins Bloomberg School of Public Health. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

There is a long-standing tension in biomedical research arising from a conflict in core values—the desire to respect the interests and desires of research participants by communicating results contrasted with the responsibility to protect participants from uncertain, perhaps poorly validated information. Traditionally, the balance has been tipped toward the latter resulting in what has been termed "helicopter research." The notion here is that investigators drop into communities or people's lives, engage with them in often very personal ways, and then take off, never to be heard from again.

Yet, people are curious about themselves, particularly about their health and their family's health, leaving a sense of frustration and loss when investigators take but do not share. Studies show that many participants want and expect their personal results. They often have these expectations regardless of what the consent discussion promised. Experimental results are often uncertain and disclosure of unvalidated results can, in some circumstances, lead to harmful medical or life decisions. But, of course, investigators are confident enough in experimental results to publish their work, suggesting that individual data points are sufficiently meaningful to contribute to generalizable knowledge. A participant might ask, "If the findings are good enough to publish, why can't my results be shared with me?" This conflict in values is central to this report. In struggling with the complex and competing considerations, we have attempted to achieve a new balance, one that leans toward communication of results while seeking to enhance the quality of results emerging from research laboratories. Our push toward more disclosure, we believe, is part and parcel of the larger cultural transition toward more engagement, collaboration, and transparency between investigators and research participants.

Our committee has had the opportunity to work together for 1 year to produce this report, with strong support from the extraordinary staff at the National Academies of Sciences, Engineering, and Medicine. We have achieved consensus on a number of core issues. We are recommending a transition away from firm rules, such as those embodied in current interpretations of the Clinical Laboratory Improvement Amendments and the Health Insurance Portability and Accountability Act regulations, that stipulate when results must or cannot be disclosed toward a process-based approach. In many circumstances, and on a study-by-study basis, we recommend a peer-review process to assess the risks and benefits of results disclosure with careful attention to laboratory quality. Establishing supporting processes will require motivation, resources, and time.

This report is the product of a wonderful collaboration between a diverse set of committee members who came to the task with divergent viewpoints about core issues. Through extended discussions, mutual respect, and multiple iterations of the language, we achieved a remarkable degree of consensus. This is a testament to the integrity, scholarship, and humility of the dedicated people who agreed to serve on the committee. We were also privileged to work with the outstanding staff of the National Academies who were unfailingly creative and supportive. We are deeply grateful to Michelle Mancher, Autumn Downey, Emily Busta, Caroline Cilio, Olivia Yost, and Andrew Pope for their expertise, hard work, and insights. We also benefited greatly from consultants to the project including Christi Guerrini, E. Haavi Morreim, and Rebecca Davies and to those who testified to the committee and submitted comments to enrich our understanding and deliberations.

Our hopes and expectations are that this report will provide a roadmap toward better and more collaborative and transparent research practices that will benefit participants, investigators and society more broadly.

Jeffrey R. Botkin, *Chair*
Committee on the Return of Individual-Specific
Research Results Generated in Research Laboratories

Acknowledgments

This Consensus Study Report reflects contributions from a number of individuals and groups. The committee takes this opportunity to recognize those who so generously gave their time and expertise to inform its deliberations. To begin the committee would like to thank the individuals who attended and presented at their open-session meetings and webinars and the many individuals and organizations who submitted written comments to the committee (see Appendix A). The committee greatly benefited from the opportunity for discussion with these individuals and is appreciative for their many contributions. The committee also thanks the participants who graciously gave their time, knowledge, and perspectives through interviews with the committee. Their thoughtful remarks enriched the committee's understanding of the complex issues and informed their deliberations (see Appendix B).

Many others provided support to this project in various ways. We thank Paul Bachner, University of Kentucky College of Medicine; Karen Dyer, Centers for Medicare & Medicaid Services; Michael P. Ryan, New York State Department of Health; and David E. Sterry, Clinical and Laboratory Standards Institute, for their technical review. Finally, our gratitude to Casey Weeks for his creative efforts in our graphic design process and Robert Pool for his editorial assistance in preparing this report.

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Acronyms and Abbreviations

ACA	Patient Protection and Affordable Care Act of 2010
ACMG	American College of Medical Genetics and Genomics
AIDS	acquired immunodeficiency syndrome
AV	analytic validity
BRISQ	Biospecimen Reporting for Improved Study Quality
CBPR	community-based participatory research
CDC	Centers for Disease Control and Prevention
CDS	clinical decision support
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments of 1988
CLIAC	Clinical Laboratory Improvement Advisory Committee
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare & Medicaid Services
CSER	Clinical Sequencing Evidence-Generating Research consortium
CTSA	Clinical and Translational Science Awards Program
CU	clinical utility
CV	clinical validity
DNA	deoxyribonucleic acid
DRS	designated record set
DTC	direct-to-consumer
EHR	electronic health record

eMERGE	Electronic Medical Records and Genomics Network
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FHS	Framingham Heart Study
GAP	Genomic Advisory Panel
GINA	Genetic Information Nondiscrimination Act of 2008
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IDE	investigational device exemption
IDIOM	Scripps Idiopathic Diseases of Man Study
IF	incidental finding
IND	investigational new drug
IRB	institutional review board
ISO	International Organization for Standardization
KKI	Kennedy Krieger Institute
LDT	laboratory developed test
MRCT	Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard
NBAC	National Bioethics Advisory Commission
NCI	National Cancer Institute
NDA	new drug application
NGS	next-generation sequencing
NHGRI	National Human Genome Research Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
OCR	Office for Civil Rights
OHRP	Office for Human Research Protections
PCB	polychlorinated biphenyl
PCORI	Patient-Centered Outcomes Research Institute
PGT	personal genetic test
PHI	protected health information
PI	principal investigator

PU	personal utility
QA	quality assurance
QC	quality control
QMS	quality management system
RCT	randomized controlled trial
REVEAL	Risk Evaluation and Education for Alzheimer's Disease
RoR	return of individual research results
SOP	standard operating procedure
VUS	variant of unknown significance
WHO	World Health Organization

Abstract

When is it appropriate to return individual research results to participants? The immense interest in this question has been fostered by the growing movement toward greater transparency and participant engagement in the research enterprise. Yet, the risks of returning individual research results—such as results with unknown validity—and the associated burdens on the research enterprise are competing considerations. A committee of the National Academies of Sciences, Engineering, and Medicine reviewed the current evidence on the benefits, harms, and costs of returning individual research results, while also considering the ethical, social, operational, and regulatory aspects of the practice. The committee's report includes 12 recommendations directed to various stakeholders—investigators, sponsors, research institutions, institutional review boards (IRBs), regulators, and participants—that are designed to help (1) support decision making regarding the return of results on a study-by-study basis, (2) promote high-quality individual research results, (3) foster participant understanding of individual research results, and (4) revise and harmonize current regulations.

SUPPORT DECISION MAKING REGARDING THE RETURN OF RESULTS ON A STUDY-BY-STUDY BASIS

Decisions on whether to return individual research results will vary depending on the characteristics of the research, the nature of the results, and the interests of participants. The justification for returning results becomes stronger as both the potential value of the result to participants and the feasibility of return increase. Investigators should not make assumptions about the kinds of results

that participants may value and should incorporate participant needs, preferences, and values into their decision-making process.

The responsible return of individual research results requires careful forethought and preparation. Thus, the committee recommends that investigators include plans in study protocols that describe whether results will be returned and, if so, when and how and that research sponsors and funding agencies require that applications for funding consistently address the issue. Additionally, institutions and IRBs should develop policies to support the review of plans to return individual research results.

PROMOTE HIGH-QUALITY INDIVIDUAL RESEARCH RESULTS

Confidence in the validity of individual research results is critical to decisions about whether to return results to participants. Requirements established by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) were designed to ensure the quality of results from clinical laboratories and are not appropriate or feasible for all research laboratories. However, no alternative exists that defines basic quality standards for research laboratories in the United States. To promote the quality of results returned and to improve the reproducibility of science, the committee recommends that the National Institutes of Health lead an effort to develop a quality management system (QMS) for research laboratories testing human biospecimens.

When individual research results are intended for clinical decision making in the study protocol, investigators must continue to perform tests only in laboratories that are CLIA certified. However, when results are not intended for clinical decision making in the study protocol, IRBs should permit the return of results under the recommended QMS—once developed—or after determining that the laboratory analysis is sufficient to provide confidence in the result, the value to participants outweighs the risks, and appropriate disclaimer information on the limitations of the validity and interpretation of the individual's result is provided.

FOSTER PARTICIPANT UNDERSTANDING OF INDIVIDUAL RESEARCH RESULTS

Once the decision is made to return individual research results to participants, investigators and institutions should communicate those results in a manner that conveys the key takeaway messages and fosters participants' understanding. Doing so requires providing contextualizing information and explanations that convey what is known and unknown about the meaning and potential clinical implications of the results, including the level of uncertainty in the results' validity. Communications should be appropriate for participants with different needs, capabilities, resources, and backgrounds. The development of evidence-based best practices, which will require the systematic evaluation of the effectiveness of

various approaches, will improve the quality of the process of returning individual research results.

REVISE AND HARMONIZE CURRENT REGULATIONS

As currently written and implemented, the regulations governing access to research laboratory test results are not harmonized: they afford inconsistent and inequitable access for participants, and regulatory conflicts create dilemmas for laboratories, investigators, and institutions. For example, the Centers for Medicare & Medicaid Services (CMS) prohibits the return of results from laboratories that are not CLIA certified, but in some circumstances the Health Insurance Portability and Accountability Act of 1996 (HIPAA) may require the return of results requested by a participant, regardless of whether they were generated in a CLIA-certified laboratory. Accordingly, the committee recommends that regulators revise and harmonize the relevant regulations in a way that respects the interests of research participants in obtaining individual research results and appropriately balances the competing considerations of safety, quality, and burdens on the research enterprise. For example, CMS should revise CLIA regulations to allow for the return of results from non-CLIA-certified laboratories when results are requested under the HIPAA access right and also when an IRB process determines it is permissible. However, the Office for Civil Rights of the Department of Health and Human Services should limit access to individual research results under HIPAA to those generated in a CLIA-certified laboratory or in a research laboratory compliant with the recommended externally accountable QMS for research laboratories.

Taken together, the recommendations in this report promote a process-oriented approach to returning individual research results that considers the value to the participant, the risks and feasibility of return, and the quality of the research laboratory. The committee expects that adoption of its recommendations will lead to an increase in the return of individual research results over time, but it also acknowledges that this will create new demands on the research enterprise that cannot be addressed overnight. The recommendations in this report are intended to help stakeholders discuss and prepare for these responsibilities and to develop the necessary expertise, infrastructure, policies, and resources. The initial investments will likely be significant, but ultimately the return on those investments in terms of increased participant trust and engagement with the research enterprise and higher-quality standards for research laboratories will be worthwhile.

Summary[1]

Biospecimens from research participants are an essential resource for a broad range of studies, from exploratory, basic science inquiries to clinical trials using well-validated tests. These types of research have been enormously valuable in advancing knowledge about almost every aspect of human health and disease. The conduct of research with human volunteers is dependent on a collaborative, productive relationship between participants who give their time and samples and the investigators and research teams that conduct the research. This complex relationship has many elements, but in the past the communication of individual research results to participants has generally not been one of them.

In the last several decades, questions have been raised about the practice of not returning test results generated in a research study to the study's participants; early on, much of the discussion was focused on returning results from imaging studies, while more recently the focus has moved more to the disciplines of genetics and environmental research. At the same time, the push for increased community and participant engagement across the research study life cycle and the rise of technology-enabled open science and data-sharing movements have added further momentum to the issue. Recent significant changes to federal regulations have promoted transparency and allowed individuals greater access to their clinical and research test results. These changes include the elimination of the laboratory exclusion from the Health Insurance Portability and Accountability Act (HIPAA) privacy rule and revisions to the Common Rule that require prospective participants to be told during the consent process whether clinically

[1] This Summary does not include references. Citations for the discussion presented in this Summary appear in subsequent report chapters.

relevant individual research results will be returned. On the other hand, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) bars laboratories that are not CLIA certified from reporting individual research results. This creates a dilemma when research results that are clinically relevant or otherwise valuable to participants, particularly those that might not otherwise be discovered, are generated in research laboratories that are not CLIA certified. See Box S-1 for a brief description of these federal regulations. (Box 6-1 in Chapter 6, from which Box S-1 is adapted, includes additional laws and regulations relevant to the return of individual research results.)

Over the last couple of decades expert groups have written position statements supporting the return of individual research results and secondary findings[2] under certain conditions, such as when the results are clinically actionable, valid, and reliable. However, participant demand for individual research results is driven not just by the potential benefits that individuals could gain by learning about clinically actionable information, but also by their desire to learn about themselves from information that they would not otherwise obtain. More specific guidance is needed on how stakeholders should consider the benefits, risks, and costs associated with the return of individual research results, including the broad spectrum of results which may not be accurate, medically actionable, or have clear meaning.

Seeking guidance on these issues from a consensus body of experts representing diverse perspectives, the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) asked the National Academies of Sciences, Engineering, and Medicine to conduct a study and generate a report that reviews and evaluates the ethical, societal, regulatory, and operational issues related to the return of individual-specific research results generated from research on human biospecimens. The full Statement of Task for the committee is presented in Box S-2.

SCOPE AND KEY TERMINOLOGY

The topic of the return of research results is exceptionally broad in scope and encompasses all fields of human research (e.g., biomedical, psychological, behavioral). During its first meeting on July 19, 2017, the committee had an opportunity to clarify the scope of the study with representatives of the three sponsoring federal agencies. In the course of that discussion, the study sponsors clarified that the committee was intended to focus on research results that are generated from the analysis of human biospecimens (samples of material collected from the human

[2] Secondary findings are results that are not the primary objective of the research. Such findings are referred to in the literature by a variety of terms, such as "additional," "secondary," "incidental," "ancillary," "supplemental," etc., and these terms can be combined with additional clarifiers such as "unanticipated" and "anticipated."

BOX S-1

HIPAA, CLIA, and the Common Rule

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule: The Office for Civil Rights (OCR) is the authority responsible for implementing and enforcing the HIPAA privacy rule. The privacy rule standards are directed toward protecting individuals' health information "while allowing the flow of health information needed to provide and promote high-quality health care and to protect the public's health and well-being." Since 2000, the HIPAA regulations have recognized the right of individuals to inspect and obtain a copy of their protected health information (PHI)[a] contained within a designated record set (DRS).[b] This right of access is binding on all HIPAA-covered entities,[c] except that before 2014 this right did not apply to HIPAA-covered laboratories.

Clinical Laboratory Improvement Amendments of 1988 (CLIA): Laboratories in the United States that perform tests on human specimens for the purpose of providing information for the diagnosis, prevention, or treatment of a disease or for the assessment of the health of an individual are regulated by CLIA and are required by the Centers for Medicare & Medicaid Services (CMS) to be CLIA certified through a process that ensures that certain quality-control assurances and requirements are in place. CLIA requirements for clinical laboratories ensure the quality and integrity of data, accurate reconstruction of test validation and test performance, and the comparability of test results regardless of performance location.

Federal Policy for the Protection of Human Subjects (the "Common Rule"): A policy adopted by 15 federal agencies that addresses the protection of human participants in research and includes requirements for informed consent and institutional review board (IRB) review of research protocols. The Office for Human Research Protections (OHRP) leads the Department of Health and Human Services' (HHS's) efforts to protect human subjects in biomedical and behavioral research and to provide leadership for all federal agencies that conduct or support human subjects research under the Common Rule. In January 2017, HHS announced its adoption of revisions to the Common Rule, which for the first time require

continued

BOX S-1, CONTINUED

that investigators disclose their plans on whether and under what circumstances "clinically relevant research results, including individual research results," will be returned to participants. The changes are expected to go into effect on January 21, 2019.

[a] PHI is defined as individually identifiable health information, which is any information (including genetic information) that (a) is created or received by a covered entity or employer; (b) "relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual"; and (c) identifies or could be used to identify the individual (45 C.F.R. § 160.103).

[b] A designated record set is defined as a group of records maintained by or for a covered entity that comprises (1) medical records and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) other records that are used, in whole or in part, by or for the covered entity to make decisions about individuals (45 C.F.R. § 164.501). This last category includes records that are used to make decisions about any individuals, whether or not the records have been used to make a decision about the particular individual requesting access.

[c] HIPAA-covered entities include health plans, health care clearinghouses, and health care providers who transmit health information in electronic form in connection with a covered financial or administrative transactions (e.g., billing transactions). Research laboratories are HIPAA-covered entities if they electronically conduct a covered transaction or if they function as part of a larger covered entity (e.g., hospitals, medical centers). HIPAA also extends to business associates of covered entities (45 C.F.R. § 160.103).

BOX S-2

Statement of Task for the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories

The Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine will undertake a study that will review and evaluate the return of individual-specific research results from research laboratories, which are required to be returned in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Currently, any research laboratory that returns individual-specific research results is regulated by CLIA. Research laboratories that do not report patient-specific results are excepted from the CLIA regulations. The committee will

- Review the current evidence concerning the return of individual-specific research results to individuals, including the value to the individual participating in the research and society and the quality challenges particular to research results.
- Review the current regulatory environment, including CLIA and any other applicable laws, for conducting tests and returning individual-specific research results, including the potential regulatory considerations associated with returning such results. In doing so, the committee will assess how the current regulations ensure or fail to ensure minimization of risks (e.g., erroneous or unreliable results) and maximization of the benefits that accrue to individuals and society.
- Review current practices in returning research results and identify what are considered to be best practices, if any, for doing so.
- Identify and assess available evidence of benefits and harm to individuals and society regarding the return of research results generated in research laboratories.
- Make recommendations on the issue of returning individual-specific research results generated in research laboratories that are regulated by CLIA, and also taking into consideration any other

continued

BOX S-2, CONTINUED

applicable laws or regulations. In making recommendations, the the committee will take into account the desires of individuals regarding access to the information, the benefits and harms of returning research results to both the individuals themselves and to individual participation and trust in the research enterprise, the operational requirements and potential vulnerabilities associated with the return of results by research laboratories to the laboratory itself or the parent institution of the laboratory, as well as the need to protect both individuals and public health. In making the recommendations, the committee will consider and address, as appropriate,

- The adequacy of the current CLIA regulations as applied to research laboratories (or subcategories of research testing by such laboratories) that currently return individual-specific results in accordance with CLIA.
- Barriers or perceived barriers that lead research laboratories to refrain from taking the steps necessary to become certified under CLIA.
- Whether there are any operational or other requirements, including regulatory requirements, for research laboratories that may be developed or modified and implemented under CLIA or any other applicable laws to more adequately address the return of individual-specific research results. Additionally, whether there are or may be specific considerations for research laboratories (including any obligations or desires on the part of researchers to fulfill requests for access to research test results and whether they have the appropriate personnel or resources to explain the research results) or for individuals (including protections and ability to receive, store, and understand research results) regarding the return of such results. Also, whether, from a policy perspective, there are specific circumstances under which research results generated in research laboratories should be or should not be returned.
- Whether there are any baseline test characteristics that should be met if individual-specific research results generated in research laboratories were to be returned in accordance with CLIA and any other applicable laws, such as the purpose or

BOX S-2, CONTINUED

potential indication, analytic and clinical validity, and potential clinical relevance of the test.

- Whether the current regulatory requirements and policies are adequate to address returning research results in an appropriate manner and, if not, what new, revised, or alternative policies or regulatory requirements might better address the appropriate return of individual-specific research results generated in research laboratories. Also whether any such new or revised policies would have implications for the continuation of the current regulatory framework.

The committee will not undertake any examination of or deliberation on specific research results to be returned. The committee will also not make recommendations on the return of non-individual-specific results (e.g., results in aggregate form). The committee will also not provide any legal interpretation or analysis regarding the scope or applicability of CLIA.

body, such as urine, blood, tissue, and cells). The committee was not to consider the return of results from imaging, behavioral, or cognitive tests, for example. Of note, the committee's charge was not limited to the return of genetic test results, as many other kinds of research are performed on human biospecimens. These include, for example, basic science studies using tumor biopsies to identify a new biomarker for colon cancer, clinical trials that evaluate blood samples for antibody levels induced by a new malaria vaccine, and epidemiological studies measuring the level of a suspected toxin in urine samples for an environmental exposure study—all of these involve laboratory tests on human biospecimens and are in the scope of this report.

In recent years, this topic has generated immense interest and debate among bioethicists and scientists, particularly in the fields of genetics and environmental exposure research. In the field of genetics, much of the debate has been focused on the return of clinically actionable *secondary findings*—results that were not the primary objective of the research. This is an important issue in the broader context of returning information generated in the course of research to individual

participants, but the sponsors clarified that it was not intended to be a central focus of this committee's report. Instead, in this report the committee uses the term *individual research results* to refer to results that are generated in the course of a study to help answer the research question or otherwise support the study objectives (e.g., to determine clinical trial inclusion/exclusion) and that are specific to one participant. Distinctions can also be made between different types of individual research results according to the kind of information provided—i.e., uninterpreted data versus interpreted findings. In the genetics field there is also an ongoing discussion about the return of sequencing information, which is generally referred to as "raw data." For the purposes of this report, all of these types of information are included in the term "individual research results." Chapter 5 discusses ways to facilitate the understanding of different types of individual research results.

While not a primary focus of the committee's deliberations, there was recognition that secondary findings remain an important part of the discussion about returning research results, given that many sequencing and other "omics" research studies have no primary target. Moreover, the issue of returning secondary findings has a long history (e.g., in the context of returning results from imaging tests), and the committee recognized that the lessons learned from those experiences might be relevant to the committee's task. Furthermore, the committee acknowledged that the recommendations in this report may have impact beyond their application to results generated from biospecimens. In addressing its charge, the committee considered three general scenarios in which consideration of the return of individual research results is relevant:

1. the planned offer of anticipated individual research results to participants,
2. the return of individual research results upon the request of participants, and
3. the offer of unanticipated research results to an individual participant.

For the purposes of this report, *anticipated results* are those results that are actively sought or are expected to arise when using a particular research test on human biospecimens. This includes results that are not the primary objective of the test or study. *Unanticipated results* are those that are unexpected either because they could not have been anticipated given the current state of scientific knowledge or because the research team did not consider the potential of generating them using a particular research test. In designing a study, investigators can anticipate several types of results and possible outcomes that may arise from the tests and analyses used over the course of investigation, and very few results should be unanticipated. However, despite investigators' ability to predict the possible outcomes of their research, unanticipated results cannot be entirely avoided, as the state of the science may change over the course of a study or a participant

may have an unknown or undiagnosed condition that becomes apparent over the course of biospecimen analysis, thus leading to unforeseen results.

Frequently, the considerations that stakeholders will need to take into account for the return of individual-specific research results to research participants for any of the three scenarios described above will be identical. Therefore, throughout the report the committee uses the shorthand phrase "return of results" to refer to the practice of returning individual research results in any of the three scenarios described above when it is not important to make a distinction between them.

During the discussion of the charge at the committee's first meeting, the following additional areas were identified by the study sponsors as falling outside the study scope, although it should be noted that only some of these are explicitly excluded in the Statement of Task:

- Specific assays or test results (i.e., the committee was not asked to generate a list, for example, of specific genes associated with disease susceptibility that, when tested for, should or should not be returned);
- The return of aggregate research data or study-level results;
- The return of results from anonymized or de-identified specimens that investigators cannot link back to the contributing participant, as well as the role or obligation of biobanks that retain identifiers that would enable the return of individual research results generated by investigators using de-identified biobank specimens (e.g., for secondary research);
- The infrastructure and policies needed for the implementation of a system to return results from secondary research; and
- Laboratory developed tests (LDTs) and the associated LDT regulations.

In discussions with the sponsors, the committee also clarified the scope as it applies to CLIA. The sponsors indicated to the committee that it would be appropriate to include in its description of the current regulatory environment for the return of individual research results CMS's current interpretation of the scope and applicability of CLIA, which is that "only those facilities performing research testing on human biospecimens that do not report patient-specific results may qualify to be excepted from CLIA certification." Although CMS's current interpretation has been questioned by some legal scholars, the committee was advised that making any comments, analysis, or conclusions regarding the appropriateness of that interpretation would be beyond what was intended in the Statement of Task. Furthermore, the committee was not asked to make recommendations to Congress regarding changes to the CLIA law. However, recommendations on changes to the CLIA regulations were within the study scope if the committee felt that such changes were needed to better align the regulatory environment with the risks and benefits of the return of research results. Chapter 6 addresses the committee's recommendations on clarifying and revising federal regulations.

BENEFITS AND RISKS OF RETURNING INDIVIDUAL RESEARCH RESULTS

We know from research and shared experience that participants often want and value their individual research results. Participants may benefit from the return of individual research results that inform clinical decision making, life or reproductive planning, and other decisions that may affect health and quality of life. Additionally, results may have personal value to participants by providing a newfound understanding about a health condition. Participants, patients, and their advocates want to be active contributors to the research process and are at the forefront of the movement to get participants involved in the research process from planning to completion. Many advocates consider the practice of withholding results based on concerns about participant welfare to be paternalistic, and they question the notion that participants cannot understand the distinction between clinical results and individual-specific results generated in a research context. Because of its potential to increase public engagement and trust in the research enterprise, the return of individual research results could have multiple positive effects, including possible improvements in the efficiency, generalizability, and participant-centeredness of research. These considerations suggest that the return of individual research results should be an important element of research in this transition toward more transparency and more robust participant engagement in the conduct of research.

On the other hand, important countervailing considerations have been raised concerning whether and how research results should be returned to participants. For instance, research participants do not have the same relationship with investigators as clinicians do with their patients. This means the ethical obligation to return results is less clear (see Appendix D). Furthermore, we know that research participants may conflate the research and clinical care relationships, having what has been termed a "therapeutic misconception." The problem here is that some participants may misinterpret the goals of clinical care (individual benefit) with the goals of research (generalizable knowledge) and mistakenly assume that a research study will yield reliable results with clinical value. By its very nature research often produces results that are of uncertain value and, depending on the stage of research, may not be analytically or clinically valid.[3] The return of uncertain, poorly validated, or poor-quality results poses a risk that participants will make important clinical or life decisions based on information that subsequently proves to be wrong or is misinterpreted.

The risks associated with returning individual research results may be minimized by improving result validity through the adoption of an externally accountable quality system by research laboratories. Furthermore, the use of effective communication strategies can minimize the risk of misinterpretation or

[3] *Analytic validity* indicates how well a test measures the property or characteristic it was intended to measure, whereas *clinical validity* is a measure of how consistently and accurately a test detects or predicts the intermediate or final outcomes of interest.

over-interpretation of research results. However, implementing such strategies may be a significant challenge for many research laboratories, which often operate with little in the way of formal quality assurance processes and often with constrained resources as well. In addition, few investigators have been specifically trained and have the resources needed to communicate results to participants in an effective manner. Clearly, this expanded activity will require additional resources, including resources devoted to planning, ensuring laboratory quality, and the time, effort, and expertise necessary for engaging participants. The cost and feasibility of any additional requirements or expectations on investigators, research laboratories, and institutions is a serious concern, especially when the level of funding for research from government bodies is uncertain. To the extent that additional resources cannot be found to address these costs, a central question is how to balance the value of return of individual research results with the costs, including the opportunity costs, and how to use existing resources. Careful consideration must be given to how the return of individual research results could more broadly affect the research enterprise, health care, and society.

The committee carefully considered the potential benefits, risks, and competing ethical justifications of investigators to return, or not to return, individual research results. Strong justifications can be made for returning results in many circumstances beyond traditional and current practices. The committee identified situations with compelling reasons for the return of individual results to participants, as well as situations with reasons to limit or constrain the returning of results. In determining whether to return results for any given study, ethical principles must be balanced, and the benefits and risks must be carefully considered based on the specific context of the study.

Recommendation 1: Determine the Conditions Under Which Individual Research Results Will Be Returned to Participants.

When conducting research involving the testing of human biospecimens, investigators and their institutions should routinely consider whether and how to return individual research results on a study-specific basis through an informed and thoughtful decision-making process.

Investigators, with oversight from their IRBs and institutions, will ultimately be responsible for making decisions on a case-by-case basis regarding whether and how to return individual research results, as the decisions require the careful consideration of many factors, which are described below. However, research sponsors and funding agencies also have an important role in developing policies to support reasonable consistency across research studies and institutions. Although these oversight mechanisms are no guarantee against harm, the committee believes that at this time institutional review is the most practical and reasonable approach to support decision making regarding the return of individual research results. Chapter 4 presents the committee's framework that can support

investigators and IRBs in their decision making. The committee recognizes that it will be challenging for IRBs to foster the return of results and to assess the risks and benefits of this practice in the near future before experience and an evidence base has fully developed. In the meantime, we encourage IRB professionals to approach the issue reflectively, regularly engage stakeholders, attend to accumulating data and institutional experiences, and share experiences, data, and protocols with colleagues through professional meetings and publications. Current practices and research into the return of results taking place in NIH-funded research like the *All of Us* Research Program, the Clinical Sequencing Evidence-Generating Research (CSER) consortium, and the Electronic Medical Records and Genomics (eMERGE) Network can be used to develop initial guidance for IRBs. NIH could also assist IRBs by convening a workshop or working group with other research funders to examine current practices regarding the return of results from biospecimens and explore lessons learned from biomonitoring programs and other domains such as radiology, imaging, and social and behavioral health research. As the evidence base expands, there may be a further role for government agencies to develop guidance to support investigators and their IRBs in their decision-making process.

GUIDING PRINCIPLES FOR RETURNING INDIVIDUAL RESEARCH RESULTS

The purpose of research is to create generalizable information for the benefit of society, and, unlike clinical care, research is not primarily focused on providing personal benefit for individual participants. Given this perspective, what is the nature of the relationship and expectations between investigators and participants and does our evolving conception of the relationship and expectations require more transparency with respect to individual research results? To what extent should the established ethical obligations to research participants, as codified in international and national guidelines, such as those laid out by the Council for International Organizations of Medical Sciences, the Declaration of Helsinki, the Belmont Report, and the Common Rule, be extended to entail obligations or responsibilities to promote the return of individual research results?

The complexity of these broad questions is substantial because of the sometimes competing, deeply held values involved. The research enterprise has been criticized for its lack of transparency and for the transactional nature of taking from participants without creating value when the results are too often not published or shared. This lack of transparency and true collaboration may factor into the contemporary concerns regarding current difficulties with research participant recruitment and retention, which in turn contribute to the escalating costs of conducting clinical studies. Amid growing consumer expectations for user-centeredness, engagement, and value, these criticisms have led to calls for a paradigm shift. At the same time, the productivity of research in an era of

uncertain resources is dependent on making prudent decisions in the allocation of those resources in the pursuit of valuable ends.

Efforts to transform the culture of the research enterprise involve actions and attitude changes along many fronts. One such change involves important and powerful modifications in terminology. Throughout this report—and consistent with use in the broader research community—the committee refers to human research volunteers as "participants" rather than research "subjects," terminology we recommend for adoption by federal regulators in guidance and new regulations. The use of such language goes beyond semantics; it represents a conceptual move from the passive language of subjects to the active language of participants, it is in accordance with the ethical principles of autonomy and respect for persons, and it reflects the growing movement for participants to be engaged more robustly in the design and conduct of biomedical research.

Two general themes should be evident in this report. First, through its findings, conclusions, and recommendations, the committee is encouraging more frequent return of individual results than is currently the practice in research involving human biospecimens. While careful consideration on a study-by-study basis is important, the committee believes that if the return of individual research results becomes a more common practice, it will demonstrate respect for participants and support transparency and the development of trust with participants, in turn bringing benefits to participants, investigators, sponsors, funding agencies, research institutions, and society. Second, because this is a relatively unfamiliar practice to many investigators, sponsors, funding agencies, and institutions, and because it is a practice that requires the mobilization of resources, we do not expect our recommendations to change standards and practices immediately. We understand that accomplishing the goals articulated in this report will take time and resources and that best practices in terms of when and how to return results will emerge with experience and with new research focused on these very questions. Our hope is that this report will motivate stakeholders in ways that will ultimately transform research practices in parallel with other changes that promote transparency and trust, participant engagement, higher research quality, and improved reproducibility of research findings.

Taking into account the complex ethical and societal considerations underpinning the movement to increase the return of individual research results, the committee formulated the following six principles to help guide its deliberations and the development of the recommendations presented in this report:

- ***Principle 1:*** *Participants bring essential and valuable information to the research enterprise without which research cannot be conducted. Because research results have value to many participants, as a matter of reciprocity, respect, transparency, and trust, the return of results should be routinely considered in the design of research protocols involving human participants.*

- ***Principle 2:*** *Research has significant societal value. The potential value of returning individual research results must be carefully considered along with the trade-offs for research participants, investigators, research institutions, and society.*
- ***Principle 3:*** *When individual research results are offered, participants have the right to decide whether to receive or to share their results.*
- ***Principle 4:*** *When individual research results are returned, the process of communication is important to promote understanding of the meaning, potential uses, and limitations of the information.*
- ***Principle 5:*** *The value of research results to investigators, participants, and society depends on the validity and reliability of the result. High standards of laboratory quality, from the acquisition of specimens to the communication of results, enhance the validity and reliability of the results generated in research laboratories.*
- ***Principle 6:*** *The conduct of high-quality, generalizable, and equitable research involves the inclusion of diverse populations and requires investigators to return individual research results in a manner that accommodates the full spectrum of community needs and preferences, regardless of participant social or economic status. The potential value of results, which is best assessed with input from the participant, community, or trusted proxy, should be considered.*

QUALITY MANAGMEMENT SYSTEMS FOR LABORATORIES TESTING HUMAN BIOSPECIMENS

Establishing laboratory processes to give all stakeholders (investigators, institutions, regulators, and participants) confidence in the validity of the individual research results being returned is critical to ensuring the accuracy of information provided to research participants as well as the quality of the science. However, many research laboratories without CLIA certification currently do not have the systems in place to provide confidence in the validity of individual participants' research results. Certainly, many research laboratories produce high-quality science, but without the documentation of practices under a quality management system (QMS),[4] it is difficult to know which laboratories can generate accurate and reliable individual research results with proper assignment of the individual results to the correct research participants. Questions about validity and thus quality of individual research results pose a barrier to the responsible return of research results to participants. More broadly, the lack of established quality processes poses a problem for the rigor and reproducibility of the science.

[4] Quality management systems (QMSs) are defined by the World Health Organization, the International Organization for Standardization, and the Clinical and Laboratory Standards Institute as "coordinated activities to direct and control a laboratory with regard to result validity and reliability."

When individual research results are intended for use in clinical decision making in the study protocol, tests must be performed in laboratories that are CLIA certified. When the study protocol does not call for individual research results to be used in clinical decision making (see Box S-3), CLIA certification may not always be an appropriate or necessary mechanism to ensure that the quality of the research test results is sufficient to permit the return of results. While CLIA has significantly improved the quality of clinical laboratory results used in clinical decision making, its requirements are not always a good fit with the kinds of testing performed in the research context, such as tests relevant to biomonitoring for environmental contaminants. Moreover, current CLIA regulatory requirements have not kept up with the rapid pace of technological innovation (e.g., genetic sequencing technologies). For example, current CLIA requirements do not address the complexity of the required informatics analyses, interpretation, and reporting required with next-generation sequencing technologies or other omics testing. Furthermore, while the direct cost of CLIA certification may not be prohibitory, meeting the requirements to obtain the certification by compliance with all of the regulatory requirements would come with significant costs for most research laboratories, although the extent of the burden would depend on the infrastructure and processes already in place in the laboratory (see Chapter 3 for more detail).

BOX S-3

Results Not Intended for Clinical Decision Making in the Study Protocol

The committee categorized research test results generated in research laboratories based on how the test results will be used according to the study protocol. Research results intended to inform clinical decision making for study purposes, such as liver function tests that could affect the clinical management of a participant within the study, should be generated under the same quality standard used for clinical tests—i.e., the test should be performed in a CLIA-certified laboratory.

In many circumstances, results will not be used for clinical decision making in a study because they are exploratory and their health implications are unknown or unvalidated. For example, the initial results of a study seeking to identify a new biomarker associated with a disease

continued

BOX S-3, CONTINUED

generally should not be used to influence the clinical management of participants until such findings are independently validated. In other circumstances, a result will have known clinical or health implications for a participant but should not be used for clinical decision making without further evaluation and testing. These types of results may be anticipated by investigators or may arise in a study as unanticipated results. For example, investigators conducting genome sequencing to identify a new variant associated with a disease may also identify a clinically relevant variant that has a known association with another condition. If such testing is not conducted in a CLIA-certified laboratory, the clinically relevant variant should not be used for clinical decision making. If an investigator offers this type of research result to a participant (or returns it upon participant request), the communication must clearly convey that the result should not be used for clinical decision making without further evaluation by a clinician and confirmatory testing (see Chapter 5 for additional discussion on communicating results to participants). In returning the research result with this qualification, the researcher is not providing information for use in clinical decision making on the basis of the research test alone.

The decision about whether further evaluation is warranted based on a research result can only be made through consultation between the participant and a health care provider familiar with the participant's clinical circumstances. For example, the participant's genetic risk status may already be known, or the participant may have co-morbidities that make further evaluation inappropriate. Conversely, confirmation of the result in a CLIA-certified laboratory, as ordered by a physician, might contribute to decision making regarding the participant's care. The investigator often is not in a position to make such follow-up recommendations (unless the investigator also serves as the participant's clinician) and should not be placed in the position of doing so. Rather, the investigator should provide what information he or she can about the potential implications, so that the participant and his or her health care provider can have the necessary information to decide the appropriate next steps.

However, if investigators plan to return individual research results to participants, it is essential that the quality of the laboratory analysis is sufficient to provide confidence in the result to be returned. Currently, there is no accepted QMS for research laboratories that could serve as an alternative to CLIA certification. For these reasons, the committee recommends that NIH lead an effort with the Centers for Disease Control and Prevention, FDA, CMS, and other relevant federal agencies and nongovernmental organizations, including patient and community groups, to develop a QMS with external accountability[5] for research laboratories that perform tests on human biospecimens. Outside the United States, several governmental and nongovernmental organizations are already working in this arena, including ongoing initiatives in Europe aimed at producing guidance and recommendations to assist investigators in meeting quality essentials in laboratory practice. Prior to the development of the recommended QMS for research laboratories, or in the event that results are generated over the course of a study that may be valuable to a participant but were not anticipated by the investigator, IRB review should serve as an alternative pathway for determining if certain conditions have been met and if the return of results not intended for use in clinical decision making is permissible (see Recommendation 3 and Figure S-1).

Recommendation 2: Develop a Quality Management System for Research Laboratories Testing Human Biospecimens.

NIH should lead an interagency effort including nongovernmental stakeholders to develop an externally accountable quality management system for non-CLIA-certified research laboratories testing human biospecimens.

Recommendation 3: Ensure the High Quality of Individual Research Results That Are Returned to Participants.

To provide confidence in the quality of research test results disclosed to participants, institutions and their IRBs should permit investigators to return individual research results if

- **A. testing is conducted in a CLIA-certified laboratory; or**
- **B. results are not intended for clinical decision making in the study protocol (as defined in Box S-3) and testing is conducted under the externally accountable quality management system for research laboratories once established (see Recommendation 2); or**
- **C. results are not intended for clinical decision making in the study protocol (as defined in Box S-3) and the IRB determines that**
  1. **the probability of value to the participant is sufficiently high and the risks of harm are sufficiently low to warrant return;**

[5] External accountability means that a research laboratory's compliance with defined QMS standards is assessed by an entity independent of the laboratory.

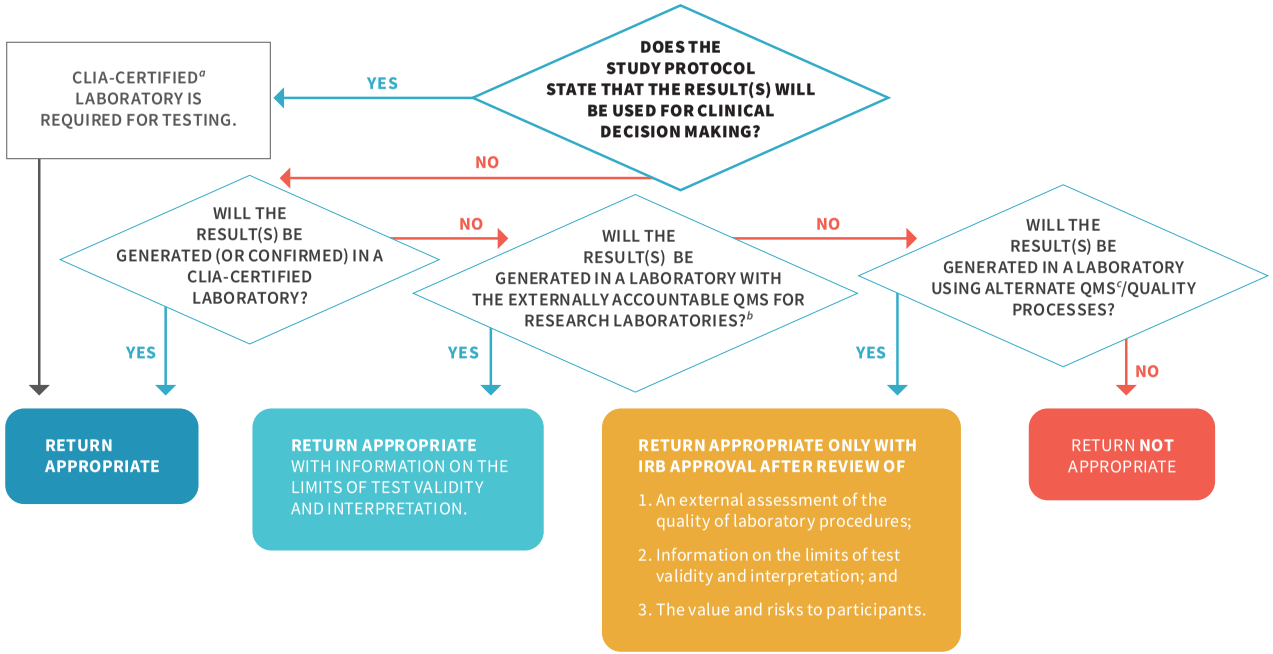

FIGURE S-1 Determining whether laboratory quality is sufficient for investigators to return individual research results.

[a] CLIA-certified includes tests run in a CLIA-certified, -accredited, or -waived laboratory.

[b] See Recommendation 2.

[c] Such as from the International Organization for Standardization, Biospecimen Reporting for Improved Study Quality reporting requirements, or other voluntary QMS (see Chapter 3).

NOTE: CLIA = Clinical Laboratory Improvement Amendments of 1988; DRS = designated record set; HIPAA = Health Insurance Portability and Accountability Act of 1996; NIH = National Institutes of Health; QMS = quality management system.

2. **the quality of the laboratory analysis is sufficient to provide confidence in the result to be returned, as determined by a review process independent of the laboratory; and**
3. **information will be provided to the participant(s) regarding limits on test validity and interpretation (see Recommendation 10).**

B and C will require changes to the CLIA regulations, embodied in Recommendation 12, or changes to the interpretation of the CLIA regulations.

Quality management systems have been shown to make work more efficient, facilitate the training of new staff, improve reproducibility, increase patient safety, and enhance data integrity. However, putting a QMS in place will have multiple impacts on research laboratories, in terms of both their research processes and resource requirements. Adoption of the quality system will likely require changes to the laboratory operations and the training environment. Additional resources may be needed for the analytical and clinical validation of testing procedures, equipment maintenance standards, and more stringent staffing and staff training and competency assessment requirements. To minimize the burden for research laboratories, sponsors, funding agencies, and research institutions need to facilitate access to resources and support quality management system training and the development of the necessary laboratory infrastructure to ensure that human biospecimen testing is performed under high-quality standards. The initial training, cost, and time commitment will likely be significant, but the value added will be considerable, both for participants and for science.

Recommendation 4: Ensure Adequate Resources and Infrastructure to Generate High-Quality Research Results.

Research institutions and funding agencies should develop and provide access to the resources and infrastructure needed to ensure that investigators conducting testing on human biospecimens can meet the necessary standards for quality, so that research test results can be returned to participants (see Recommendation 3). This may include assisting investigators and their research laboratories in

- **A. training and access to resources to prepare for the future adoption of the externally accountable quality management system for research laboratories (see Recommendation 2);**
- **B. adopting the externally accountable quality management system for research laboratories once established for relevant laboratories (see Recommendation 2); or**
- **C. becoming CLIA certified or facilitating access to core, affiliated, or third-party CLIA-certified laboratories for sample testing, retesting, or a confirmatory testing process when research results are for use in clinical decision making in a study protocol.**

A DECISION-MAKING FRAMEWORK FOR THE RETURN OF INDIVIDUAL RESEARCH RESULTS

Decisions about whether and how to return individual research results are influenced by many factors. These include the potential value of the information to the participant; the nature of the relationship, if any, between the participant and investigator; the analytic and clinical validity of the research result; and the feasibility of return. Benefits to the participants and to the research enterprise have to be weighed against risks, including potential harms to individuals, the diversion of resources and investigator efforts from conducting research, liabilities, risks of privacy breach, and discrimination. Furthermore, investigators may be legally required to disclose a result if a participant makes a request under HIPAA, which ensures individuals a right to access any personal health information contained within the DRS of a HIPAA-covered entity.

A small number of well-defined cases present clear and broadly accepted rationales for when the return of results should be obligated or discouraged (see Box S-4). But, for the majority of scenarios, decisions have to be made on a case-by-case basis by weighing several factors. As the potential value of the result to participants and the feasibility of return increase, the justification for returning results becomes stronger (see Figure S-2 for a conceptual framework). *Value* in this context means the value of a result *from the perspective of the participant* and might entail clinical utility or personal utility as well as personal meaning (e.g., lineage information). This participant-centric approach recognizes that the value of a result is not necessarily tied to its use. To clarify, defining value in this way is not meant to imply that each participant needs to be queried regarding the results that would be meaningful to him or her, but it does require the investigator to consider value from the participant perspective rather than from the more traditional clinical perspective. Feasibility is also determined by multiple factors, including potential challenges, the costs and burdens of returning results, whether biospecimens can be linked to a specific participant, and the resources available to communicate the results effectively and appropriately.

Ascertaining Participant Needs, Preferences, and Values

Investigators, institutions, and research sponsors and funding agencies need to be cautious about making assumptions regarding the kinds of results that participants may find meaningful. Expert-identified criteria do not always reflect participant preferences and values, as the value of a research result to participants will be influenced by both their perspectives and the contexts in which they are participating in the research. Incorporating the needs, preferences, and values of community representatives and advocacy groups into decision making regarding the return of individual research results is important for helping investigators to better understand what participants value and to weigh the benefits and risks of disclosure.

BOX S-4

Individual Research Results That Should and Should Not Be Returned to Participants

Results that investigators or laboratories are obligated to return:

- Urgent, clinically actionable results (ethical obligation under duty to warn/rescue)
- Results that are in the designated record set of a HIPAA-covered entity if they are requested by the participant (legal obligation under HIPAA)

Results that investigators should be discouraged from returning:

- Results that cannot be interpreted at the individual level
- Results that have limited value to participants and would entail significant burden (cost or complexity) to return
- Results without established clinical validity for a life-threatening or sensitive health condition
- Results for which there are serious questions regarding validity[a] or identity

[a] The validity of the result depends on both the test that is run and the laboratory environment in which it is conducted. Tests in the development phase (intended either for research use or clinical use) would not generate results that are appropriate for return if validity testing had not yet been performed (see Chapter 3 for additional discussion on establishing analytic validity).

Ascertaining and incorporating participant needs, preferences, and values into decision-making processes regarding whether or not to return individual research results can be undertaken at the study level but also in the development of policy or guidance. Both are critical to advancing a more participant-centric research paradigm. For some kinds of studies—particularly those that will involve significant interactions between researchers and participants—obtaining representative input from relevant and representative community members in

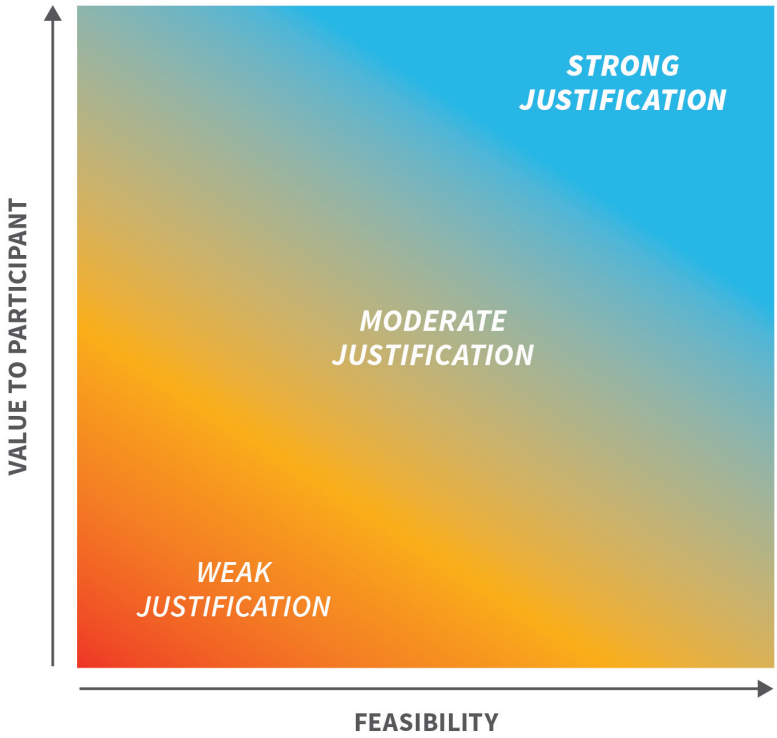

FIGURE S-2 A conceptual framework for decisions on returning individual research results.
NOTES: This figure demonstrates that as the potential value of the result to participants and the feasibility of return increase, the justification for returning results becomes stronger. **Value** in this context means the value of a result *from the perspective of the participant* and might entail clinical utility or personal utility as well as personal meaning. **Feasibility** is determined by multiple factors, including potential challenges, the costs and burdens of returning results, and whether participants' biospecimens are linked to the participant identity as well as the resources available to communicate the results effectively and appropriately.

the study design phase (e.g., through advocacy groups or community advisory boards) can help ensure that decisions on whether and how to return results are aligned with participant values and needs. For other types of studies (e.g., when biospecimens have been de-identified or if investigators can reasonably rely on existing documentation of participant needs, preferences, and values in the literature or from past experiences working with community groups), engagement may not be as important.

Many investigators will be new to participant and community engagement activities and will need to rely on existing models, guidance, and informational resources as they develop study protocols and consider return of individual research results. Investigators may need to be made aware of the existence of these resources or receive training in order to effectively engage participants in discussions of their preferences for the return of individual research results. To minimize the burdens on individual investigators, research sponsors and institutions can help investigators understand the preferences and needs of their prospective participants by leveraging their core resources (e.g., Clinical and Translational Science Awards Program cores, community advisory boards) and by engaging community and participant representatives to develop policies and guidance (see Chapter 4 for additional information on the range of engagement in the return of individual research results).

Recommendation 5: Incorporate Participant Needs, Preferences, and Values in Decision Making About the Return of Individual Research Results.

Research stakeholders should ensure that participant needs, preferences, and values are incorporated into decision making regarding the return of individual research results. To facilitate this,

- **A. investigators should seek information through various mechanisms, including reviewing published literature, leveraging experiences from similar studies, consulting participant or community advisory boards, and engaging community and participant groups and advocacy organizations in the development of the research protocols;**
- **B. research institutions and sponsors should enable and facilitate investigator access to the relevant community and participant networks, resources, and training; and**
- **C. research sponsors should engage community and participant representatives in the development of policy and guidance related to the return of individual research results.**

PLANNING FOR THE RETURN OF INDIVIDUAL RESEARCH RESULTS

The development of a plan at the design phase of a study that addresses whether, when, and how results will be offered to participants as part of the study protocol, or provided in response to a participant request or upon discovery of an unanticipated but potentially valuable result, can help maximize the benefits and prevent or mitigate the potential harms associated with the return of research results. Incorporating the plan into the research protocol ensures transparency and appropriate budgeting, while IRB review ensures that the risks and benefits to participants are carefully considered in a peer-review process.

The planning process should consider the types of results that might be shared (such as routine clinical results generated in the course of research, test results generated in a research laboratory, or urgent findings) and when in the study life cycle they might be shared without threatening the scientific integrity of the study. By requiring and reviewing plans and providing support for the return of individual research results, research institutions and sponsors can help foster a culture in which the return of individual research results is more routinely considered and practiced.

Recommendation 6: Include Plans for the Return of Individual Research Results in Research Protocols.

For all studies using human biospecimens, investigators should routinely address their plans regarding the return of individual research results in their funding application or research protocol. The investigator's plan should describe

- **A. whether individual research results will be offered to participants and, if so, when and how. The plan should also provide the rationale for these decisions, including how participant needs, preferences, and values were considered;**
- **B. how the consent process will reflect transparency and effective communication with participants regarding whether and, if so, how individual results will be offered;**
- **C. how investigators and their institutions will respond if participants request their results, including how information in the designated record set will be released to participants when they have a right to access their individual research results under HIPAA; and**
- **D. the budget and resources for the return of individual research results, when appropriate.**

Recommendation 7: Ensure Planning for the Return of Individual Research Results in Applications for Funding.

Research sponsors and funding agencies should ensure that investigators are considering whether and how individual research results will be returned to participants, by

- **A. requiring that applications for research funding consistently address the return of individual research results, indicating whether, and if so, when and how individual research results will be offered to research participants, as well as the rationale for these decisions;**
- **B. including in the scientific review process for funding applications an assessment of plans for the return of individual research results; and**
- **C. building funding into grants and contracts or providing administrative supplements for the return of individual research results.**

Recommendation 8: Develop Policies and Procedures to the Support Review of Plans Regarding the Return of Individual Research Results.

Research institutions and their IRBs should develop policies and procedures that support the assessment of plans for the return of individual research results. Policies and procedures should ensure that

- **A. the IRB has, or has access to, the necessary expertise to review the return of individual research results plans;**
- **B. appropriate consideration has been given to participant needs, preferences, and values (see Recommendation 5);**
- **C. the research teams have access to the appropriate expertise (e.g., a scientific review committee) to consider the factors relevant to decisions on returning individual research results, including analytic validity, clinical validity, and the value of the results to participants;**
- **D. the consent process is aligned with the return of individual research results plan (see Recommendation 9); and**
- **E. the investigators have access to the necessary resources (e.g., core resources) and expertise to enable the communication of individual research results in an effective manner (see Recommendation 10).**

EFFECTIVELY COMMUNICATING INDIVIDUAL RESEARCH RESULTS TO PARTICIPANTS

The return of individual research results to participants is relatively uncommon in the research enterprise. As a result, few standardized practices or even guidance on how to accomplish this challenging communication task have been developed. Different communication approaches may be appropriate in different contexts and may be associated with different costs or burdens to investigators. Given the scientific community's general lack of experience with returning individual research results to participants, as well as the complexity and uncertainty inherent in results generated through research, the development of guidance and best practices may help address inconsistency in practices and minimize the risk of harm from the return of research results.

To establish an empirical evidence base for the development of best practices, the research community will need to develop a learning system in which processes for returning research results are evaluated for benefits and harms and communication practices are refined. This will require the accumulation of experience over time. In the absence of such empirically derived best practices, applying existing principles for clear communication, such as considering audience characteristics and needs and having a clearly defined communication objective, represents a clear strategy for improving the quality of return-of-results practices now. Being clear and transparent during the consent process regarding whether, under what circumstances, and how investigators will offer and return research results

can help to set appropriate expectations and build trust. The use of established communication principles is also important in order to enhance the likelihood of participants understanding research results and the appropriate use of that information.

The ability of participants to understand and make use of research results depends on the provision of relevant contextual information that clarifies what is known or unknown about the meaning of a specific result. When relevant contextual information (such as reference standards) for a result is not known, studies should weigh the benefits and risks of return and consider whether the return of only aggregate results would be more appropriate than the return of individual results. Understanding is also facilitated by providing a clear takeaway message that includes a statement regarding actionability. For more complex studies, it can be challenging to effectively communicate to research participants the degree of uncertainty that the research results entail, especially in contrast to the more familiar context of clinical testing. As a result, the return of individual research results should often be accompanied by caveats and qualifiers that address potential inaccuracies and uncertainties.

The appropriate return of individual research results requires investment and careful forethought regarding the necessary contextualizing information, takeaway messages, and caveats. It also requires a consideration of the need to communicate in ways appropriate for participants with different needs, resources, and backgrounds. However, upfront investments to improve investigator access to resources, training, and expertise can be scalable, and the development of best practices over time will improve the consistency and quality of the process of returning individual research results.

Recommendation 9: Ensure Transparency Regarding Return of Individual Research Results in the Consent Process.

In the consent process, investigators should communicate in clear language to research participants

- **A. which individual research results participants can access, if requested, including any results participants have a legal right to access under HIPAA, and how to request these results; and**
- **B. which individual research results, if any, will be offered to participants and why, and the participant's option to decline to receive their research results.**
- **C. If results are going to be offered the following elements should also be communicated during the consent process:**
  1. **the risks and benefits associated with receiving individual research results;**
  2. **conditions under which researchers will alert participants of urgent results;**

3. **at what time and through what process results will be communicated to participants;**
4. **whether the results will be placed in the participant's medical record and whether the results will be communicated to the participant's clinician; and**
5. **when relevant to the research protocol, the participant's option to have results shared with family members in the event the participant becomes incapacitated or deceased.**

Recommendation 10: Enable Understanding of Individual Research Results by Research Participants.

Whenever individual research results are communicated to participants, investigators and institutions should facilitate understanding of both the meaning and the limitations of the results by

- **A. ensuring that there is a clear takeaway message and necessary reference information to convey what is known and not known about both the meaning of the result and potential clinical implications;**
- **B. communicating effectively the level of uncertainty in the result validity;**
- **C. providing mechanisms for participants to obtain additional information and answers to questions when appropriate and feasible;**
- **D. providing guidance for follow-up actions/consultations when appropriate;**
- **E. aligning the communication approaches to the particular needs and preferences of the participants and the context of the study;**
- **F. providing a written summary of the results and other information communicated to participants for future reference by participants and investigators; and**
- **G. leveraging existing and emerging health information technologies to enable tailored, layered, and large-scale communications when appropriate.**

Recommendation 11: Expand the Empirical Evidence Base Relevant to the Return of Individual Research Results.

To expand the empirical evidence base relevant to the return of individual research results, sponsors and funding agencies should support additional research to better understand the benefits and harms of the return of results as well as participant needs, preferences, and values and to enable the development of best practices and guidance.

When it comes to funding empirical research for the return of individual research results, NIH is the obvious, and likely primary, sponsor who would fund such an endeavor. However, this responsibility should not fall to NIH alone.

The return of research results will soon become an integral part of the research enterprise—it is a global endeavor and all sponsors of research using human biospecimens should direct resources to addressing the needs of investigators and participants through the funding of empirical research in the practice. The development of unified guidance on returning individual research results will help prevent dramatic variability in practice between institutions and will aid IRBs in making informed decisions. Funding agencies have a responsibility to ensure that processes for return are both feasible and implemented appropriately.

RESHAPING THE REGULATORY ENVIRONMENT

The legal and regulatory requirements and restrictions pertaining to the return of individual results are currently uncertain, thus causing variable interpretation and action across IRBs and research sites. As currently written and implemented, the laws and regulations governing access to laboratory results, both clinical and research, are not harmonized; they afford inconsistent and inequitable access for participants to their individual research results, and regulatory conflicts create dilemmas for laboratories. Specifically, CMS's interpretation of CLIA blocks any laboratory from returning a test result if the laboratory is not CLIA certified, but HIPAA requires the return of results upon a request by the patient if the results are part of their DRS. In some cases regulations are too restrictive, while in others they are not restrictive enough, allowing for the return of results of poor or unsubstantiated quality without appropriate caveats or context. Moreover, the regulations governing the protection of human participants do not address the return of results, meaning that the guidance available to research participants and investigators in inadequate. Overall, the current regulatory environment for the return of individual research results is not well aligned with the benefits and risks associated with the practice.

The current absolute prohibition of the return of results from non-CLIA-certified laboratories fails to account for several factors, including the high quality maintained by some research laboratories, the value that many participants place on results despite uncertain validity, and the access rights afforded by HIPAA to individual results regardless of quality standards. Additionally, there is little evidence of harm from the return of research results, although the overall body of evidence is limited and may reflect a lack of evidence rather than conclusive evidence of a lack of effect. Accordingly, the committee believes that, in certain circumstances, results can be provided to participants when laboratories have not achieved CLIA certification. However, the committee is cognizant of the potential harms to participants and the research enterprise if laboratory quality systems are not in place in research laboratories or if loopholes are created that can be abused to perform clinical testing in a research laboratory without CLIA certification. Therefore, the Office for Civil Rights of the Department of Health and Human Services should limit access to individual research results under HIPAA to those

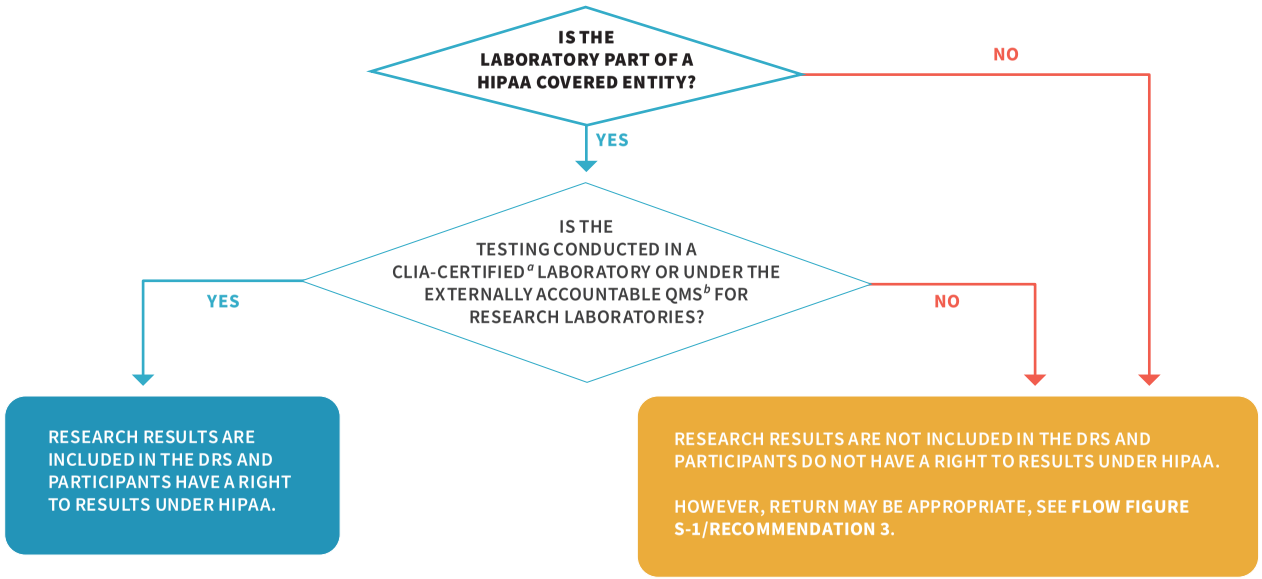

FIGURE S-3 Determining whether participants have the right to access their individual research results under HIPAA.

[a] CLIA-certified includes tests run in a CLIA-certified, -accredited, or -waived laboratory.

[b] See Recommendation 2.

NOTE: CLIA = Clinical Laboratory Improvement Amendments of 1988; DRS = designated record set; HIPAA = Health Insurance Portability and Accountability Act of 1996; NIH = National Institutes of Health; QMS = quality management system.

generated in a CLIA-certified laboratory or in a laboratory that has adopted the QMS for research laboratories recommended by the committee (see Figure S-3). Through its recommendations, the committee promotes an approach that requires high-quality standards when investigators plan to return results, but also supports a thorough peer review and approval process for the potential return of valuable results generated in laboratories not meeting CLIA requirements.

Recommendation 12: Revise and Harmonize Regulations to Support the Return of Individual Research Results.

Regulators and policy makers should revise and harmonize the relevant regulations in a way that respects the interests of research participants in obtaining individual research results and appropriately balances the competing considerations of safety, quality, and burdens on the research enterprise.

Specific actions that should be taken include the following:

- **A. Because the designated record set (DRS) is intended to include information used to make decisions about individuals, those decisions should be based on test results that are of sufficient quality to be valuable for decision making. Accordingly, the Office for Civil Rights (OCR) of the Department of Health and Human Services (HHS) should define the DRS to include only individual research results generated in a CLIA-certified laboratory or under the externally accountable quality management system for research laboratories (see Recommendation 2);**
- **B. OCR should require all HIPAA-covered entities that conduct research on human biospecimens to develop a plan that is reviewed and approved by the IRB for the release of individual research results in the designated record set to participants in a responsive manner when requested under HIPAA;**
- **C. CMS should revise CLIA regulations such that when there is a legal obligation under the HIPAA access right to return individual research results, a laboratory will not be considered in violation of CLIA and need not obtain CLIA certification before satisfying this legal obligation;**
- **D. CMS should revise CLIA regulations to allow research results to be returned from a non-CLIA-certified laboratory when they are not intended for clinical decision making in the study protocol (as defined in Box S-3) and the laboratory conducts its testing under the quality management system with external accountability or the IRB has approved the return of results (as described in Recommendation 3);**
- **E. CMS and OCR should harmonize the definitions of the following terms, providing a clear explanation and justification for any**

differences or discrepancies: "test report" and "completed test report" (CLIA), and "PHI in the designated record set" (HIPAA);

F. OCR, OHRP, and NIH should harmonize the definitions of the following terms, providing a clear explanation and justification for any differences or discrepancies: "de-identified" (HIPAA), "non-identified" (Common Rule), and "identifiable sensitive information" (21st Century Cures Act regarding certificates of confidentiality);

G. HHS (including CMS, FDA, NIH, OHRP) should ensure that all regulations, policies, and guidance relevant to human research refer to research "participants" rather than research "subjects," in accordance with the ethical principles of autonomy and respect for persons; and

H. FDA should clarify and provide additional guidance that if a device is not exempt from investigational device exemption (IDE) regulations, disclosure of results in many circumstances, including to healthy volunteers, will not necessarily entail significant risk, and FDA should clarify when it will consider the return of individual research results to entail significant risk. Additionally, FDA should provide guidance to IRBs on how to determine significant risk if the device is not exempt from IDE regulations.

FINAL THOUGHTS

The recommendations in this report, if followed, will result in substantial and potentially controversial changes to the research regulations and the research enterprise involving research with human biospecimens. The opportunity for change has arisen in response to the evolving relationship between investigators and participants and is supported by an assessment of the potential benefits and risks of returning individual research results. The need for higher standards of quality in many research laboratories is clearly illustrated in this report (see Chapter 3). Yet, despite the inherent limitations in the validity and interpretability of some research results, our assessment is that the risks associated with the communication of results have been overstated, particularly for the many research projects that are unlikely to yield highly sensitive or clinically meaningful results. Furthermore, the potential benefits of results disclosure to individual participants and to the research enterprise have been understated.

Therefore, we are recommending that the current absolute standard—that all disclosed results must be generated in a CLIA-certified laboratory—should be replaced with a process-oriented standard, meaning that a peer-review process can be used in some circumstances to weigh competing considerations regarding the return of individual results. We recommend that such a process take into account, on a case-by-case basis, the values of the participants, the risks and benefits of the return of particular results, the quality of the research laboratory and test

performance, and the feasibility for investigators to pursue this course. There are risks to moving away from an absolute standard, but we believe that the risks can be mitigated through improvements in laboratory quality, a case-by-case assessment of the risks and benefits, and the promotion and development of communication strategies to help place results in the proper context for participants. The committee believes that the benefits of this more nuanced approach will greatly exceed the adverse impacts and costs.

The committee is well aware that more frequent return of individual research results will create new demands on the research enterprise. Many institutions and researchers currently lack the experience and resources to return individual research results in a deliberate and effective manner. The committee does not expect that a more widespread return of results will happen immediately. However, the committee foresees an evolving set of responsibilities and offers recommendations that it believes will help stakeholders prepare for these added responsibilities and develop the necessary expertise over time.

At a broader level, the justification for fundamental changes in the research landscape can be found in our changing understanding of the ethics of human participant research as well as in our recognition that failures to support transparency and to earn respect and trust from individuals in the community are hampering the conduct of science. The vision is that a dedicated commitment to collaboration will better honor participants, benefit science, and promote the welfare of society. While the standards and practices related to the return of individual results are but one set of elements in this evolving landscape, the return of research results is a tangible, measurable piece that we know is valued by participants and is feasible in many more circumstances than are reflected in current practice. Our hope is that this report will promote the practice through selected changes in research regulations, the use of quality management systems that ensure the quality of research results, and the commitment of all stakeholders (see Table S-1) to innovative, collaborative processes in the planning and conduct of research.

TABLE S-1 Recommendations by Stakeholder[a]

STAKEHOLDER	RECOMMENDED ACTION
HHS	**RECOMMENDATION 12G** – Chapter 6 Refer to research volunteers as *participants*, not *subjects* in all regulations relevant to human research
CMS	**RECOMMENDATIONS 12C and D** – Chapter 6 Revise CLIA regulations to allow for the return of individual research results from non-CLIA-certified laboratories when results are requested under the HIPAA access right and when the quality of results has been established and they are not intended for use in clinical decision making
	RECOMMENDATION 12E – Chapter 6 Work with OCR to harmonize definitions of key terms relevant to the return of individual research results in the federal regulations
FDA	**RECOMMENDATION 12H** – Chapter 6 Clarify and provide additional guidance regarding how the return of individual research results affects IDE requirements for research studies
NIH	**RECOMMENDATION 2** – Chapter 3 Lead an interagency effort with nongovernmental stakeholders to develop standards for a quality management system for research laboratories testing human biospecimens

continued

TABLE S-1, Continued

	RECOMMENDATION 12F – Chapter 6 Work with OCR and OHRP to harmonize the definitions of key terms relevant to the return of individual research results in the federal regulations
OCR	**RECOMMENDATION 12A** – Chapter 6 Revise the definition of the designated record set (DRS)
	RECOMMENDATION 12B – Chapter 6 Require HIPAA-covered entities that conduct research on human biospecimens to develop a plan for the release of individual research results in the DRS when requested under HIPAA
	RECOMMENDATIONS 12E and F – Chapter 6 Work with CMS, OHRP, and NIH to harmonize definitions of key terms relevant to the return of individual research results in the federal regulations
OHRP	**RECOMMENDATION 12F** – Chapter 6 Work with OCR and NIH to harmonize definitions of key terms relevant to the return of individual research results in the federal regulations
Research sponsors and funding agencies	**RECOMMENDATION 4** – Chapter 3 Ensure adequate resources and infrastructure to generate high-quality individual research results
	RECOMMENDATION 5 – Chapter 4 Engage community and participant representatives in the development of policy and guidance related to the return of individual research results

	RECOMMENDATION 7 – Chapter 4 Ensure planning for the return of individual research results in applications for funding
	RECOMMENDATION 11 – Chapter 5 Support research to expand the empirical evidence base relevant to the return of individual research results
Research institutions	**RECOMMENDATION 1** – Chapter 2 Consider whether and how to return individual research results on a study-specific basis
	RECOMMENDATION 3 – Chapter 3 Ensure the high quality of individual research results that are returned to participants
	RECOMMENDATION 4 – Chapter 3 Ensure adequate resources and infrastructure to generate high-quality research results
	RECOMMENDATION 5 – Chapter 4 Enable and facilitate investigator access to relevant community and participant networks, resources, and training
	RECOMMENDATION 8 – Chapter 4 Develop policies and procedures that support the assessment of plans for the return of individual research results, and ensure that IRBs and research teams have or have access to the necessary expertise and resources to assess plans.

continued

TABLE S-1, Continued

Research institutions	**RECOMMENDATION 10** – Chapter 5 Enable the understanding of individual research results by research participants
IRBs	**RECOMMENDATION 3** – Chapter 3 Ensure the high quality of individual research results that are returned to participants
	RECOMMENDATION 7 – Chapter 4 Review the return-of-results plan and ensure the consent process aligns with it
Investigators	**RECOMMENDATION 1** – Chapter 2 Consider whether and how to return individual research results on a study-specific basis
	RECOMMENDATION 5 – Chapter 4 Seek information on participant needs, preferences, and values related to return of individual research results
	RECOMMENDATION 6 – Chapter 4 Include plans for return of individual research results in research protocols
	RECOMMENDATION 9 – Chapter 5 Ensure transparency regarding return of individual research results in the consent process

	RECOMMENDATION 10 – Chapter 5 Enable understanding of individual research results by research participants
Participants	**RECOMMENDATION 5 –** Chapter 4 Engage researchers to ensure that participant needs, preferences, and values are incorporated in decision making about the return of individual research results

[a] An interactive version of this table can be found at http://resources.nationalacademies.org/ReturnofResults/index.html (accessed August 13, 2018).

1

Introduction

Conducting biomedical research involving human participants often entails the generation of laboratory test results associated with individual research participants—results that in the past have not been routinely shared with the individuals participating in the research. In recent years, however, that has begun to change. The research enterprise has begun to take steps to become more participant-centric, acknowledging the importance of increasing the engagement of and transparency with research participants across all phases of research. And one particular aspect of the relationship between investigators and participants that increases transparency and engagement is the return of individual research results to research participants (Ohayon et al., 2017). Engaging participants more broadly in research has been shown to improve participants' trust in the research enterprise and to encourage individuals to participate in future research (CTSA Community Engagement Key Function Committee Task Force on the Principles of Community Engagement, 2011; Domecq et al., 2014; Holzer et al., 2014). Thus, as part of the broader movement to make the research enterprise more participant-centric, there has been an increasing push to return individual research results to participants. This push is the product not only of transformation in the research enterprise but also of the changing expectations of the research participants themselves. There is a growing demand by research participants to gain access to their individual results—a demand that is driven not just by the potential benefit that individuals could gain by learning about clinically actionable information, but also by participants' desire to learn about themselves from information that they would not otherwise obtain (Facio et al., 2013; Sanderson et al., 2016).

However, the return of individual research results generated in research laboratories presents a number of challenges. Research by its very nature often produces results that are of uncertain value and, depending on the stage of research, may not be analytically or clinically valid.[1] One overarching challenge is determining how to weigh the potential benefits and harms of returning results which may not be accurate or have clear meaning. Additionally, many research laboratories do not currently have the personnel or quality procedures in place to ensure result validity (Ambulos, 2013) or have the requisite knowledge and experience to effectively return individual research results (Rigby and Fernandez, 2005; Thorogood et al., 2014). Complicating matters is the fact that current interpretations of two federal regulations established to protect individuals' health and health information—the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA)—conflict in their requirements for and limitations on the return of test results to individuals.

Over the last several decades, consensus has been growing in certain research domains that some types of research results or secondary findings[2]—specifically, those that are clinically actionable and valid—can be and, when certain conditions apply (e.g., immediate clinical action is warranted), should be returned to participants (see the section "Past Expert Group Recommendations on the Return of Individual Research Results"). As a result, some research projects have begun to offer research results as part of their study plan (Brody et al., 2014; Fullerton et al., 2012; Jarvik et al., 2014; Kullo et al., 2014). Still, a number of questions remain, and these have generated considerable debate among investigators, research participants, research sponsors, and legal scholars. These questions include

- Under what circumstances is it appropriate for investigators to offer individual research results to participants? Are there circumstances under which the return of individual-specific results should be obligated, encouraged, or discouraged?
- Do participants have a right (either ethically or legally) to receive any or all of their results if they request them from the investigator?
- If individual research results are returned, what should the expected standards be for investigators to adequately communicate the meaning and level of confidence or uncertainty in their results to participants? Do best practices for the return of individual research results exist as a guide for investigators?

[1] *Analytic validity* indicates how well a test measures the property or characteristic it was intended to measure, whereas *clinical validity* is a measure of how consistently and accurately a test detects or predicts the intermediate or final outcomes of interest (IOM, 2012).

[2] *Secondary findings* are results that are not the primary objective of the research (PCSBI, 2013). Such findings are referred to in the literature by a variety of terms, such as "additional," "secondary," "incidental," "ancillary," "supplemental," etc., and these terms can be combined with additional clarifiers such as "unanticipated" and "anticipated" (Tan et al., 2017).

- Are the current regulatory requirements adequate to address returning individual research results in an appropriate manner and, if not, what new, revised, or alternative policies or regulatory requirements might better address the appropriate return of individual research results?

To address these issues, the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) requested that the National Academies of Sciences, Engineering, and Medicine (the National Academies) convene a committee to consider whether and under what circumstances individual research results generated in research laboratories ought to be returned to study participants, considering participant preferences and investigator obligations, current practices, and the available evidence on potential benefits and harms as well as the regulatory environment for returning individual research results to participants. The full Statement of Task for the committee is presented in Box 1-1. This report presents the findings, conclusions, and recommendations of the National Academies committee empaneled to respond to this request.

STUDY SCOPE AND KEY TERMINOLOGY

The topic of the return of research results is exceptionally broad in scope and encompasses all fields of human research, including biomedical, psychological, and behavioral research. During the committee's first meeting on July 19, 2017, its members had an opportunity to clarify the scope of the study with representatives of the three sponsoring federal agencies, each of whom presented the charge to the committee and took part in a subsequent question-and-answer period. In the course of that discussion, the study sponsors clarified that the committee was intended to focus on research results that are generated from the analysis of human biospecimens, i.e., samples of material collected from the human body, such as urine, blood, tissue, cells, and protein (NCI, 2018). The committee was not to consider the return of results from imaging, behavioral, or cognitive tests, for example. However, the committee acknowledged that the recommendations in this report may have broader impact beyond their application to results generated from biospecimens.

Of note, the committee's charge was not limited to the return of genetic test results, as many other kinds of research are performed on human biospecimens. Such research may include, for example, basic science studies using tumor biopsies to identify a new biomarker for colon cancer, clinical trials that evaluate blood samples for antibody levels induced by a new malaria vaccine, and epidemiological studies measuring the level of a suspected toxin in urine samples for an environmental exposure study; all of these types of research involve laboratory tests on human biospecimens and are in the scope of this report.

BOX 1-1

Statement of Task for the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories

The Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine will undertake a study that will review and evaluate the return of individual-specific research results from research laboratories, which are required to be returned in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Currently, any research laboratory that returns individual-specific research results is regulated by CLIA. Research laboratories that do not report patient-specific results are excepted from the CLIA regulations. The committee will

- Review the current evidence concerning the return of individual-specific research results to individuals, including the value to the individual participating in the research and society and the quality challenges particular to research results.
- Review the current regulatory environment, including CLIA and any other applicable laws, for conducting tests and returning individual-specific research results, including the potential regulatory considerations associated with returning such results. In doing so, the committee will assess how the current regulations ensure or fail to ensure minimization of risks (e.g., erroneous or unreliable results) and maximization of the benefits that accrue to individuals and society.
- Review current practices in returning research results and identify what are considered to be best practices, if any, for doing so.
- Identify and assess available evidence of benefits and harm to individuals and society regarding the return of research results generated in research laboratories.
- Make recommendations on the issue of returning individual-specific research results generated in research laboratories that are regulated by CLIA, and also taking into consideration any other applicable laws or regulations. In making recommendations, the committee will take into account the desires of individuals

BOX 1-1, CONTINUED

regarding access to the information, the benefits and harms of returning research results to both the individuals themselves and to individual participation and trust in the research enterprise, the operational requirements and potential vulnerabilities associated with the return of results by research laboratories to the laboratory itself or the parent institution of the laboratory, as well as the need to protect both individuals and public health. In making the recommendations, the committee will consider and address, as appropriate,

- The adequacy of the current CLIA regulations as applied to research laboratories (or subcategories of research testing by such laboratories) that currently return individual-specific results in accordance with CLIA.
- Barriers or perceived barriers that lead research laboratories to refrain from taking the steps necessary to become certified under CLIA.
- Whether there are any operational or other requirements, including regulatory requirements, for research laboratories that may be developed or modified and implemented under CLIA or any other applicable laws to more adequately address the return of individual-specific research results. Additionally, whether there are or may be specific considerations for research laboratories (including any obligations or desires on the part of researchers to fulfill requests for access to research test results and whether they have the appropriate personnel or resources to explain the research results) or for individuals (including protections and ability to receive, store, and understand research results) regarding the return of such results. Also, whether, from a policy perspective, there are specific circumstances under which research results generated in research laboratories should be or should not be returned.
- Whether there are any baseline test characteristics that should be met if individual-specific research results generated in research laboratories were to be returned in accordance with CLIA and any other applicable laws, such as the purpose or

continued

BOX 1-1, CONTINUED

potential indication, analytic and clinical validity, and potential clinical relevance of the test.

- Whether the current regulatory requirements and policies are adequate to address returning research results in an appropriate manner and, if not, what new, revised, or alternative policies or regulatory requirements might better address the appropriate return of individual-specific research results generated in research laboratories. Also whether any such new or revised policies would have implications for the continuation of the current regulatory framework.

The committee will not undertake any examination of or deliberation on specific research results to be returned. The committee will also not make recommendations on the return of non-individual-specific results (e.g., results in aggregate form). The committee will also not provide any legal interpretation or analysis regarding the scope or applicability of CLIA.

In recent years, the topic of the return of individual research results has generated immense interest and debate among bioethicists and scientists, particularly in the fields of genetics (Fabsitz et al., 2010; Green et al., 2013; Holm et al., 2014; Jarvik et al., 2014) and environmental exposure research (Brody et al., 2007; Haines et al., 2011; Haynes et al., 2016; Sly et al., 2009). In the genetics context, much of the debate has been focused on the return of clinically actionable *secondary findings*—results that are not the primary objective of the research (PCSBI, 2013).[3] This is an important issue in the broader context of returning information generated in the course of research to individual participants, but the sponsors clarified that it was not intended to be a central focus of this committee's report. Instead, in this report the committee uses the term "individual research results" to refer to results that are generated in the course of a study to help answer the research question or otherwise support the study objectives (e.g., to determine clinical trial inclusion/exclusion) and are specific to one participant

[3] It is important to note that for some types of studies with narrow and clearly defined targets, it is very easy to distinguish individual research results from secondary findings, but for other studies (e.g., hypothesis-generating research) that have no primary target, there is no clear dividing line.

(PCSBI, 2013). There was, however, a recognition that secondary findings remain an important part of the discussion, given that many sequencing and other "omics" research studies have no primary target. Moreover, it should be noted that the issue of returning secondary findings has a long history (e.g., in the context of returning results from imaging tests), and the committee recognized that the lessons learned from those experiences might be relevant to the committee's task. Distinctions can also be made between different types of individual research results according to the kind of information provided—i.e., uninterpreted versus interpreted findings. In the genetics context, there is also an ongoing discussion about the return of sequencing information which is generally referred to as raw data. For the purposes of this report, all these types of information are included in the term "individual research results." Chapter 5 discusses ways to facilitate the understanding of different types of individual research results.

In addressing its charge, the committee considered three general scenarios in which consideration of the return of individual research results is relevant:

1. the planned offer of anticipated individual research results by investigators to participants,
2. the return of individual research results upon the request of participants, and
3. the offer of unanticipated individual research results to participants.

For the purposes of this report, *anticipated results* are those results that are actively sought or are expected to arise when using a particular research test on human biospecimens. This includes results that are not the primary objective of the test or study. *Unanticipated results* are those that are unexpected either because they could not have been anticipated given the current state of scientific knowledge or because the research team did not consider the potential to generate them using a particular research test. In designing a study, investigators can anticipate several types of results and possible outcomes that may arise from the tests and analyses used over the course of investigation, and very few results should be unanticipated. However, despite investigators' ability to predict the possible outcomes of their research, unanticipated results cannot be entirely avoided as the state of the science may change over the course of a study or a participant may have an unknown or undiagnosed condition that becomes apparent over the course of biospecimen analysis, thus generating unforeseen results.

Frequently, the considerations that stakeholders will need to take into account when deciding on the return of individual-specific research results to research participants will be the same for all of the three scenarios described above. Therefore, throughout the report, the committee uses the shorthand phrase "return of results" to refer to the practice of returning individual research results in any of the three scenarios described above when it is not important to make a distinction among them.

During the discussion of the charge at the committee's first meeting, the following additional areas were identified by the study sponsors as falling outside the study scope, although it should be noted that only some of these are explicitly excluded in the Statement of Task:

- Specific assays or test results (i.e., the committee was not asked to generate a list, for example, of specific genes associated with disease susceptibility that, when tested for, should or should not be returned);
- The return of aggregate research data or study-level results;
- The return of results from anonymized or de-identified specimens that investigators cannot link back to the contributing participant, as well as the role or obligation of biobanks that retain identifiers that would enable the return of individual research results generated by investigators using de-identified biobank specimens (e.g., for secondary research);
- The infrastructure and policies needed for the implementation of a system to return results from secondary research; and
- Laboratory developed tests (LDTs) and the associated LDT regulations.

In discussions with the sponsors, the committee also clarified the scope as it applies to CLIA. The sponsors indicated to the committee that it would be appropriate to include in its description of the current regulatory environment for the return of individual research results CMS's current interpretation of the scope and applicability of CLIA, which is that "only those facilities performing research testing on human biospecimens that do not report patient-specific results may qualify to be excepted from CLIA certification" (CMS, 2014). Although CMS's current interpretation has been questioned by some legal scholars (Burke et al., 2014; Evans, 2014; Prince et al., 2015), the committee was advised that making any comments, analysis, or conclusions regarding the appropriateness of that interpretation would be beyond what was intended in the Statement of Task. Furthermore, the committee was asked not to make recommendations to Congress regarding changes to the CLIA law. However, recommendations on changes to the CLIA regulations were within the study scope if the committee felt that such changes were needed to better align the regulatory environment with the risks and benefits of the return of research results. Chapter 6 addresses the committee's recommendations on clarifying and revising federal regulations.

STUDY CONTEXT

A number of societal drivers have brought the issue of returning individual research results to participants to the forefront of public debate. First, participants have expressed the desire to receive their results, and in the growing movement toward participant-centered research, research sponsors and investigators are increasingly listening to them (Brody et al., 2014; Dunagan et al., 2013; Jarvik et al.,

2014; Ohayon et al., 2017). Most notably, NIH made a commitment to return research results to participants enrolled in the *All of Us* Research Program (discussed in Box 1-3). Second, expert groups have come to some consensus concerning the general principles for returning certain types of results, although investigators, sponsors, and institutional review boards (IRBs) are given little concrete guidance on how to weigh the benefits and risks of returning research results that may not be accurate, clinically actionable, or have clear meaning, and, more broadly, there has been insufficient exploration of the benefits, burdens, and costs to the research enterprise of returning results. Third, the conflicting CLIA and HIPAA regulations regarding the circumstances under which laboratories are obligated to return research results—or prohibited from returning them—upon a participant's request have created confusion among investigators and their institutions, resulting in calls for guidance from federal agencies on how to apply the law. The sections below further explore these drivers and the impetus for this study.

The Evolution of the Participant Role in Research and Implications for Return of Results

The issue of returning individual-specific research results is one facet of a growing movement to engage research participants more substantively in the design and conduct of biomedical research (see Box 1-2). The roles of research participants, patients, family members, advocacy organizations, and community representatives have undergone a significant transformation in the past few decades as representatives of these groups have voiced their desire to be engaged in all stages of the research process, from planning and design to execution, interpretation, and dissemination. The increased focus by the research enterprise on engagement has been in part motivated by the recognition that health is socially determined and that addressing the health needs of diverse communities requires the involvement of those most affected, enabling them to be the beneficiaries of the research.

In 21st-century research, patient groups have catalyzed a growing array of sophisticated, innovative initiatives, including launching patient registries and conducting natural history studies, funding translational and early phase clinical research programs, designing trials, developing novel trial infrastructure, using venture philanthropy to drive therapy development, and conducting policy advocacy aimed at the evolving regulatory environment (CTTI, 2015). Additionally, participant-centric technologies and digital health applications have changed the way consumers interact with their own data, creating a new system in which data are being both generated and controlled by participants. As a result, recent years have seen the establishment of a number of initiatives that are moving the research enterprise to a more participatory model of research. The Patient-Centered Outcomes Research Institute, for example, requires that investigators engage stakeholders representing the population of interest in the

BOX 1-2

The Imperative for Participant-Centered Research in Name and Action

Historically, the role of patients and community members in research has been as passive "subjects"—a term connoting individuals on whom research was to be conducted and thus to be seen as representatives of some group or class of humans under study and not as individuals with personal needs, interests, and preferences. Given this state of affairs, investigators had little expectation that those who volunteered to take part in research should have a voice in its design or execution. Moreover, the research "subject" construct suggests a power and knowledge differential between the investigator and subject along with an associated vulnerability in the subject, the implications of which are that investigators have an ethical responsibility to ensure the well-being of human subjects and that protective mechanisms are needed to prevent their exploitation (Bromley et al., 2015). While cases of egregious human experimentation in the past demonstrated the need for protections for research participants and prompted the establishment of cornerstone ethical principles for human research, such as those laid out in the Nuremburg code, the Declaration of Helsinki, and the Belmont Report, dissatisfaction has been growing with the notion of research participants as subjects—a characterization that many find demeaning (Corrigan and Tutton, 2006) and reflective of research policies and regulatory systems that are paternalistic (Miller and Wertheimer, 2007). The role of subject is associated with passivity and, for some, exploitation (Bromley et al., 2015), a perception that may contribute to public distrust in the research enterprise and to the challenges that many investigators face in the recruitment and retention of research participants. High-profile historical examples of research participants and their families pushing back on this dynamic and demanding a more active role in research involving their biospecimens include the Henrietta Lacks story and the gene patent legal suit (Skloot, 2010),[a] which both resulted in public controversy and litigation (Colaianni et al., 2010). Consequently, a national movement is reframing the role of research participants in such a way that they are not the objects of research, but rather collaborators in the research process.

BOX 1-2, CONTINUED

The degree of appropriate participant engagement in research can be thought of as a continuum. In some cases, the appropriate action may simply be to keep participants informed—for example, by explaining research protocols and providing aggregate study results. In other cases, it may be the case that participants should play a more active role, which could take the form of providing input and feedback to investigators or even working collaboratively with them in the design and conduct of research. Throughout this report, and consistent with use in the broader research community (American Psychological Association, 1973; Boynton, 1998; Bromley et al., 2015), the committee refers to human research volunteers as "research participants" rather than "research subjects," in accordance with the ethical principles of autonomy and respect for persons and to reflect their changing role in the research enterprise.

[d] *Greenberg v. Miami Children's Hosp. Research Inst., Inc.,* 264 F. Supp. 2d 1064, 2003 U.S. Dist. LEXIS 8959, 121 A.L.R.5th 687, 16 Fla. L. Weekly Fed. D 417 (S.D. Fla. May 29, 2003).

research it funds to ensure that studies address questions that are important to patients and other stakeholders and that the outcomes that are measured are those patients and other stakeholders find meaningful (Frank et al., 2015). In this new paradigm of participant-centered and community-partnered research, community members, patients, and their advocates have a seat at the table (for example, through membership on community advisory boards) and are increasingly included in the development of research protocols.

This increasingly common role of participants as research collaborators and partners, combined with the ethical principle of respect for participants, has led to calls for general study results (i.e., aggregate results) and lay summaries of the research to be shared with participants, regardless of whether the study conclusions are negative or the study is ultimately published. This practice, which may also bolster engagement and trust in the research enterprise (Beskow et al., 2012), has been endorsed and promoted by NIH, FDA, and other federal and nonfederal research sponsors, although its adoption is still in the early stages, and it has not yet become routine practice (*Federal Register*, 2016; IOM, 2015). Arguments similar to the ones for returning general study results to study participants have also

been made for returning individual-specific research results. Furthermore, some advocates have argued that once participants have access to their results, they will be able to pool and share their data to help advance the science and guide more participant-centered research (Open Humans, 2018). Current literature shows support from participants and investigators for the return of results to individuals (as discussed further in Chapter 2), and, notably, maximizing participants' access to information about themselves was adopted as a key goal of the Precision Medicine Initiative (NIH, 2018) (see Box 1-3).

Past Expert Group Recommendations on the Return of Individual Research Results

The question of whether and when to return individual-specific research results has been considered by several expert groups, and a number of recommendations and position statements have been released supporting the return of results and secondary findings under specific conditions (Bookman et al., 2006; Fabsitz et al., 2010; Green et al., 2013; Jarvik et al., 2014; MRCT Center, 2017; National Bioethics Advisory Commission, 1999; PCSBI, 2013; SACHRP, 2016; Wolf et al., 2008). If one examines the publications, certain themes emerge:

- research participants have a right to refuse results that are offered to them;
- the result, whether a research test result or a secondary finding, should be analytically and clinically valid if it is to be returned;
- the result should be important to the individual's health, although there is not universal agreement on whether results relevant to reproductive decisions should be returned;
- the result should be "actionable," in that a meaningful intervention is available that can prevent or at least ameliorate the disease course to an extent that would not likely otherwise occur;
- investigators do not have a duty to use limited research funds to hunt for actionable results, such as genomic findings (Berg et al., 2013; Green et al., 2013; Kalia et al., 2016);[4]
- IRBs should require investigators' study proposals to include documentation of whether and how individual research results will be returned; and
- the obligations of investigators to return results generally ends with the completion of the research project.

[4] In contrast, the American College of Medical Genetics and Genomics has recommended that all clinical laboratories that conduct genetic sequencing should seek out and report pathogenic mutations for 56 specified genes (Green et al., 2013).

BOX 1-3

Precision Medicine

Access to data from a large number of participants is critical for the research that will generate the clinical knowledge to address health questions for individuals. This is addressed in the Precision Medicine Initiative Cohort Program (now named the *All of Us* Research Program) launched by President Barack Obama in 2015. The goal of the *All of Us* Research Program is to gather clinical, contextual, environmental, and genetic data as well as biological samples from at least 1 million volunteers to more precisely predict disease risk, improve diagnosis, and select effective treatment strategies (Genetics Home Reference, 2018). The inclusion of participants' data beyond their genomic and health care information will be critical in understanding the underlying mechanisms of cancers and other diseases, and it will require vast amounts of data sharing among participants, providers, and research organizations. The *All of Us* Research Program is designed to share health information and its research results with the enrolled participants. In a 2015 blog post, Francis S. Collins, director of NIH, emphasized the important role of participants in the research endeavor and how implementing this project will require a shift in the traditional perceptions concerning research participants. "Equally important, the Precision Medicine Initiative Cohort Program will change the way we do research," he wrote. "Participants will be partners in research, not subjects, and will have access to a wide range of study results. What we're doing with the Precision Medicine Initiative cohort is intersecting in a synergistic way with other fundamental changes in medicine and research to empower Americans to live healthier lives" (Bresnick, 2015).

Despite this general level of consensus, there is little evidence that sponsors, investigators, IRBs, or research institutions have taken active measures to routinely promote the return of individual research results. Beyond these general principles, more specific guidance is needed on how stakeholders should consider the benefits and risks of returning individual research results to participants in different circumstances and also on the infrastructure, expertise, and resources that would be needed to enable this endeavor.

The Current Legal and Regulatory Environment

Historically, the federal government has clearly separated regulations related to clinical care from those related to research. FDA, for example, regulates tests used for clinical purposes, but it largely delegates decisions on tests used for research purposes to IRBs, except for FDA oversight of investigational new drug and investigational device exemption research. However, the increasing focus on translational research and the emergence of the learning health system model (IOM, 2013) have highlighted how, in some contexts, the traditional distinctions between clinical and research activities break down.

The growing practice of returning individual-specific research results exemplifies the increasing interconnectedness of research and clinical care (Wolf et al., 2018). With the rise of next-generation or massively parallel sequencing, which allows the sequencing of most of an individual genome, along with other "omics" methods, biomedical investigators are increasingly finding themselves in positions where the analysis of biospecimens using cutting-edge methods and techniques—which may or may not yet be validated for clinical use—generates results with potential clinical significance, leaving some investigators with the desire or sense of obligation to share those results with the research participant. This poses various challenges, particularly in the current regulatory environment, which has been slow to adapt to the growing interconnectedness of clinical care and research, and this in turn has led to calls for modernizing the regulations to better support this interconnected world.

CLIA was put in place to help protect patients by requiring that any laboratory in the United States that performs tests for the purpose of providing information for the diagnosis, prevention, or treatment of a disease or for the assessment of the health of an individual be CLIA-certified through an accreditation process that is designed to ensure that certain quality-control assurances and standards are used by the testing laboratory. CLIA does not apply to laboratories that conduct tests on human biospecimens for research purposes (e.g., academic and industry laboratories) and that do not report patient-specific results. However, if laboratories do report patient-specific results, CMS (the agency that administers CLIA) has interpreted the regulations to mean that those laboratories must be CLIA certified, even if they otherwise only perform research functions. This creates a dilemma when clinically actionable research results, particularly those that are urgent and might not otherwise be discovered, are generated in research laboratories that are not CLIA certified (Burke et al., 2014; Dressler et al., 2012).

Moreover, HIPAA regulations give patients full right of access to their medical information in the designated record set maintained by any HIPAA-covered entity.[5] The designated record set is defined as the group of records maintained by

[5] HIPAA-covered entities include health plans, health care clearinghouses, and health care providers who transmit health information in electronic form in connection with covered financial or administrative transactions (e.g., billing transactions). HIPAA also extends to business associates of covered entities (45 C.F.R. § 160.103).

or for an institution or other entity covered by HIPAA, including medical records, billing records, health plan enrollment payment, and claims adjudication, which are used to make decisions about individuals (45 C.F.R. § 164.501). This definition does not clarify whether research results are or are not part of the DRS.[6] Prior to 2014, laboratories had a specific exception to this rule, which allowed them to refuse to provide test result information. However, a 2014 amendment to the regulation removed this exception. Consequently, laboratories that are not CLIA certified but are covered under HIPAA may be in the position of, on the one hand, being required under HIPAA to provide patient-specific results upon request and, on the other hand, being barred by CLIA from doing so (Barnes et al., 2015). Additional legal and regulatory challenges associated with the return of individual-specific research results are discussed further in later chapters, but the moral dilemma faced by investigators and the CLIA/HIPAA conflict highlighted here demonstrate the need for clarifying guidance from federal agencies on how investigators and research laboratories should proceed—as well as providing a critical analysis as to whether current regulations appropriately address the risks and benefits of participants having access to their research results.

STUDY APPROACH

To respond to its charge, the National Academies convened a 15-member committee composed of individuals with expertise in bioethics, legal and regulatory practice, research and laboratory practice, health communication, health literacy, decision science, and patient and community advocacy. Biographies of the committee members can be found in Appendix E.

The committee deliberated from July 2017 to May 2018. During this time period, the committee met in person five times (July, September, October, and December 2017, and February 2018), and the first four meetings included information-gathering sessions that were open to the public. A 2-day workshop was conducted in conjunction with the September 2017 meeting and covered participant and community perspectives on the return of individual research results, the perspectives of investigators and institutions, applicable laws and regulations, the institutional infrastructure and oversight needed to enable the appropriate return of results, and communication practices used in returning results. Additional perspectives from investigators and from participants were sought during the public sessions held during the October and December meetings, respectively. In addition, the committee held a Web-based meeting in December 2017 to further explore laboratory standards for regulated and non-regulated biomedical research laboratories. Open session agendas for all meetings are provided in Appendix A.

Members of the public were given opportunities to comment on the committee's task at the September and October in-person meetings. The committee

[6] 45 C.F.R. § 164.501—Definitions.

also proactively solicited written comments from stakeholders and the public to ensure that a diverse sample of perspectives was captured and considered in its deliberations.

Throughout the study process, the committee reviewed publicly available peer-reviewed and gray literature to inform its findings, conclusions, and recommendations. The committee also drew on two commissioned papers (see Appendixes C and D) to obtain additional background information and supporting evidence. One paper described the legal and regulatory landscape relevant to the return of individual research results, and the second provided a critical analysis of the ethical principles commonly used to justify disclosure or non-disclosure as well as of the philosophic literature on the relationship between the research participant and the investigator or research institution and the implications of that analysis for the return of results.

Additional detailed information on the committee's methodology, including its literature search strategies and processes for the solicitation of public comments, is provided in Appendix A.

ORGANIZATION OF THE REPORT

This report is organized into six chapters that collectively describe a path forward for the responsible return of individual research results. Following this introduction, Chapter 2 presents the relevant ethical principles and the societal considerations for the return of individual research results, including the potential risks and benefits to individuals and the research enterprise. The chapter ends by listing the committee's guiding principles. Chapter 3 describes the quality management system and infrastructure needed to ensure the quality, reproducibility, and validity of test results produced in research laboratories. Chapters 4 and 5 address the "how" of returning individual research results appropriately. Chapter 4 provides a framework for weighing the competing considerations in study-specific decisions on whether and when individual research results should be returned and also describes the advance planning needed to minimize risks and maximize benefits. Chapter 5 describes best practices for communicating with participants in order to set appropriate expectations and to effectively deliver results in such a way that their meaning and limitations can be understood. Finally, Chapter 6 describes the changes to the regulatory landscape that will be needed to achieve the vision articulated by the committee in this report.

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2

Principles for the Return of Individual Research Results: Ethical and Societal Considerations

Biomedical research has a high value to society because of its potential to improve population health by generating important knowledge about the physiology and pathology of disease and the safety and efficacy of novel and existing treatments or public health interventions. In addition, such research provides information about clinical practice that can be used to improve the delivery of high-quality health care. Resources for biomedical research, therefore, are precious and require careful and responsible stewardship. The return of individual research results necessarily requires the diversion of some research resources from the primary goal of the research, which is to contribute to generalizable knowledge (Williams et al., 2012). At the same time, it is critical to the biomedical research endeavor to have the voluntary participation of individuals who donate their time, often accept risks to their welfare, and share with investigators their biospecimens, health and health care information, and personal information. When done in a careful and thoughtful way so as to avoid unnecessary risk, providing participants with information about themselves that has been uncovered in the course of the research is one possible means (although certainly not the only one) of demonstrating respect and gratitude for their contributions, and this provision of information may lead to greater trust and engagement in the research enterprise, much to society's benefit. This chapter examines the ethical and societal considerations surrounding the question of whether the return of individual research results is appropriate or even obligatory as well as issues concerning the potential harms and benefits to individuals, the research enterprise, and society at large. The chapter concludes with a set of guiding principles that the committee developed to inform its thinking on the questions addressed throughout the remaining

chapters of this report—specifically, whether, when, and how individual research results should be returned to research participants.

ETHICAL CONSIDERATIONS FOR THE RETURN OF INDIVIDUAL RESULTS IN HUMAN PARTICIPANT RESEARCH[1]

One of the more difficult ethical research challenges to emerge recently concerns what an investigator's obligations are—if any—to share information with those who volunteer to participate in his or her research. The recognition is growing that, for many clinical studies, aggregate study results should be shared with the research participants and presented in such a way that the results can be understood by members of the general public. This is consistent with the ethical principles widely used to guide clinical research, which hold that study participants should be treated with respect, acknowledged for the important role they play in advancing science, protected from harm to the extent possible, and receive the maximum possible benefit from their participation (CIOMS, 2016; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). As discussed below, these same ethical principles are often invoked in discussions about the return of individual research results.

Ethical Principles Relevant to the Return of Individual Research Results

Historically, institutional review boards (IRBs) have actively discouraged the disclosure of research results to individual participants apart from a few exceptional circumstances (Fernandez et al., 2003a; Simon et al., 2012). These circumstances primarily referred to the discovery of an unexpected finding (i.e., secondary finding) that had clear medical significance for the research participant. One example of such a finding would be evidence of a clinically silent central nervous system tumor discovered during a brain imaging test in a study comparing different neuroimaging methods. In this case, it might be argued that the research team has a "duty to warn"[2] or a "duty to rescue"[3] the participant as he or she is in a position to prevent serious harm at little or no personal cost and the participant might otherwise not discover the condition in time to change its

[1] This section draws on a paper commissioned by the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories: Haavi Morreim, The return of individual-specific research results from research laboratories: Perspectives and ethical underpinnings (see Appendix D).

[2] The "duty to warn," for instance, comes from the age-old principle that, if one person sees that another is unwittingly about to enter a high danger that quite likely he or she would not voluntarily embrace, then the person seeing the danger has an obligation to warn the other. (See Appendix D for a more in-depth discussion.)

[3] "Duty to rescue" is based on the premise that, when confronted with a clear and immediate need, an individual who is in a position to help must take action to try to prevent serious harm when the cost or risk to self is minimal" (Beskow and Burke, 2010, p. 1).

course. The "duty to warn" and the "duty to rescue" were originally legal concepts, but they have been applied to discussions on the return of individual results, and they are now also seen as referring to an ethical obligation to notify participants when presumably reliable results suggest imminent danger (i.e., death or significant morbidity) (Beskow and Burke, 2010). For those uncommon cases when secondary findings with medical significance arise, expert working groups have developed recommendations for reporting secondary findings and referring participants for follow-up evaluations (Wolf et al., 2008).

More recently, the discussion on the return of individual results has moved beyond incidental or secondary findings to results that are the focus of the research study. Although questions pertaining to the return of individual research results apply to many kinds of studies, it is genomic research in particular that has brought this issue to the forefront over the past couple of decades. Rapid technological advances (e.g., genome sequencing) have enabled the generation of genetic information on an unprecedented scale, and even outside of the context of an investigator's duty to warn or rescue study participants, many investigators and research participants have argued that participants should have access to such information about themselves. Additionally, the rise of community-based participatory research (CBPR), a gold standard model of community engagement valuing the co-ownership of data, co-learning, and the sharing of knowledge to equalize power, provides a framework that encourages the return of research results (Brody et al., 2007; Morello-Frosch et al., 2009; Wallerstein et al., 2017) (see Box 4-2 in Chapter 4 for additional discussion on CBPR).

Published commentaries on the return of individual research results commonly refer to a number of different ethical principles that the authors suggest support an argument for or against returning individual research results to participants. These principles, which are described in the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979), were established to guide the practice of clinical research, and include

- respect for persons/autonomy;
- beneficence/non-maleficence; and
- justice.

Respect for Persons/Autonomy

The principle of respect for persons calls for the recognition of participants' autonomy (i.e., their freedom as individuals to determine their own actions). For participants who are capable of self-determination, this means that investigators should respect the participant's informed choices (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). The requirement for informed consent in clinical research follows from this ethical

principle and ensures that participants are not treated as a means to an end and coerced, deceived, or misled into participating in the research.

Shalowitz and Miller (2005) argue that sharing results with interested participants demonstrates respect for these persons in several ways. It respects their integral role in research and the generation of the data. The authors write, "It would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information about themselves derived from their participation in research" (p. 738). Furthermore, it offers participants the opportunity to incorporate the information into personal decision making. However, the fact that a participant may wish to have access to his or her results does not necessarily confer on the investigator an obligation to return them (Clayton and McGuire, 2012; Fabsitz et al., 2010; MRCT Center, 2017b). Respect for persons can still be demonstrated through the consent process by clearly informing participants that individual results will not be returned, thereby enabling them to decide whether to participate in the research. When results will be offered, respect for autonomy implies that the participants should have the choice as to whether they want to receive the results (i.e., participants have a right *not* to know). In addition, the sharing of general, aggregate study results is a demonstration of respect for the participants.

Beneficence/Non-Maleficence

According to the ethical principle of beneficence, investigators have an obligation to promote and safeguard the well-being of research participants (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). The age-old maxim from medical ethics, "First, do no harm," can be applied in the research context to mean that investigators should not knowingly cause harm to research participants in order to advance science (non-maleficence). Thus, the health of participants should take precedence over the interests of the research (MRCT Center, 2017b). This is not to say that it is inappropriate to expose individuals to risk, as learning what may cause harm could itself entail risk, but such actions require forethought by investigators, institutions, and research sponsors in the design and planning of the research in order to maximize the possible benefits and minimize possible harms. Judgment must be applied (often by an IRB) to determine when the ratio of potential benefits to potential harms is sufficiently favorable to ethically justify the research.

This ethical principle has been invoked as justification both for and against the return of individual research results. Research has the potential to uncover information that could be beneficial to participants in their health management, life planning, or psychological well-being (Ravitsky and Wilfond, 2006). In keeping with the principle of beneficence, some argue that investigators have an ethical obligation to return results that have value to the participants, except where disclosure might compromise the research or a participant's well-being (for instance,

in cases of misattributed paternity). Others maintain that returning results could cause undue distress and may even prompt unwarranted medical intervention, so that, with a few exceptions involving immediate and severe threats to life and health, the risks of return outweigh the potential benefits (Ashida et al., 2010; Bemelmans et al., 2016; Dixon-Woods et al., 2011; Lorimer et al., 2011).

Justice

The principle of justice holds that there should be fairness in the distribution of the benefits and burdens of research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). This does not necessarily mean that all participants must be treated equally, as a distribution on the basis of need, effort or contribution, and merit can be justified. However, it is not acceptable to exclude groups and individuals from the opportunity to participate in research or to deny an individual a benefit to which he or she is entitled without a valid reason. Individuals in similar situations should be treated similarly (Darnell et al., 2016). The challenges encountered in engaging certain disenfranchised groups and any concerns related to a lack of resources (e.g., access to follow-up health care) are not justifiable reasons for excluding individuals or groups from research or for denying potential benefits from the return of results.

The challenges in ensuring fairness with regard to the return of individual results have been noted and may argue against the practice or, alternatively, for the establishment of guidelines and infrastructure to enable greater consistency in the return of results. One author observed, for example, that there is a "very real possibility that research participants in studies with larger budgets are more likely to receive results than those in studies with less room for such expenditures" (Meltzer, 2006, p. 29).

Role of the Investigator–Participant Relationship in Obligations to Return Individual Results

Although some ethical arguments for returning results, such as the duty to warn, are largely independent of any relationship between the investigator and the participant, from both a legal (discussed in Chapter 5) and an ethical perspective the nature of this relationship can be a factor in determining whether the disclosure of individual research results is an obligation. The relationship between an investigator and a participant does not necessarily represent the kind of fiduciary relationship that exists between a health care provider and a patient—i.e., the investigator's primary concern is not the best interests of the participant, but rather the integrity and societal benefit of the research (Burke et al., 2014). Generally, however, a deeper relationship between the investigator and participant gives rise to a greater responsibility to share results that may be of value to the participant.

Several conceptualizations have emerged of the role that the investigator–participant relationship plays in obligations regarding the return of individual research results. Richardson and colleagues note that research participants who volunteer for medical research entrust certain aspects of their health (e.g., confidential medical information, the permission to collect biospecimens) to clinical investigators. As a result of this "partial entrustment," the authors argue, the investigators assume a moral obligation to provide the participants with ancillary care beyond that required to ensure the safety and validity of the study. The scope of the obligation to provide this ancillary care depends on the specific permissions that needed to be obtained during the consent process, Richardson and colleagues argue, and the strength of the claim is influenced by a number of contextual factors, including the degree of participant vulnerability, the participant's dependence on the investigators for care, and the depth of the participant–investigator relationship (Richardson, 2008; Richardson and Belsky, 2004; Richardson and Cho, 2012; Richardson et al., 2017). The resulting duties stemming from these moral obligations may include returning any secondary findings or individual research results, depending on the importance of the results to the participant's health (Beskow and Burke, 2010; Richardson and Cho, 2012).

In contrast to Richardson and colleagues, who base the obligation to return individual results on the specific relationship between the physician investigator and participant, Miller, Mello, and Joffe offer an alternative relationship-based rationale in which the ethical obligations for returning secondary findings stem from the principle of beneficence applied in the context of a professional relationship more generally[4]—one that does not necessarily have to be a physician–patient relationship (2008b). They assert that research participants entrust private health-related information to investigators who are professionals with enhanced capacities to recognize the significance of secondary findings. The privileged access to information by those with the competence to interpret it gives rise to a moral responsibility to disclose results that are indicative of a risk to the participant's health (Miller et al., 2008b). The authors note that the same argument could be used to rationalize the return of individual research results, but they emphasize that such results, in contrast to secondary findings, should be anticipated and that their return is supported by the principle of respect for persons in addition to the principle of beneficence.

[4] The authors define a professional as "a person who possesses specialized knowledge, whose work involves the frequent exercise of discretion, and who can claim membership in a learned profession with a regulatory structure and ethical code of conduct. The hallmarks of a professional relationship are that the professional is entrusted by another with access to private information and/or other domains of individual privacy, such as the home or the body. Professional relationships are often, though not always, characterized by a service role, and may, but do not necessarily, involve a fiduciary relationship" (Miller et al., 2008b, p. 274).

Limitations of Obligations to Return Individual Research Results Arising from Ethical Imperatives

Following a review of a critical analysis of the competing philosophical positions on the issue which are briefly described above and further explored in Appendix D,[5] the committee concluded that the return of individual research results is consistent with, but not mandated by, the ethical principles for human research discussed above, except for the rare occasion when presumably reliable results are of significant clinical import and there is a risk of imminent harm to the participant if they are not disclosed. A variety of other mechanisms can be used to recognize the contribution of participants and respect their autonomy. These include

- setting appropriate expectations in the consent process so that prospective participants can make informed decisions about whether to participate in a study,
- offering financial compensation for time and effort,
- returning aggregate study results (which also fosters transparency and trust), and
- exercising the utmost good stewardship and ensuring the careful management of the participant's entrustment.

In some cases, aggregate study results will be the most appropriate information to share with participants, and some aggregate results may have individual-level implications. For example, Fernandez et al. (2003b) discuss the hypothetical case "of a childhood cancer survivor who was not informed that the research in which she had participated as a child had revealed an elevated lifetime risk of cancer for survivors such as herself, and who had therefore failed to manage her risk" (Miller et al., 2008c). However, returning aggregate results does not absolve investigators of the responsibility to consider returning individual-specific research results as well. As discussed further in Chapter 4, investigators will need to consider participant needs, preferences, and values. Some participants, such as those engaged in research to identify treatments for rare diseases, may prefer not to receive individual research results if there is a trade-off in terms of diverting resources from the primary research aim and slowing research progress[6] and may instead prefer that investigators reciprocate in other ways.

[5] The committee commissioned Haavi Morreim, J.D., Ph.D., to draft a paper on the philosophical perspectives and ethical underpinnings for the return of individual-specific research results from research laboratories (see Appendix D).

[6] Testimony of Ellen Wagner of Parent Project Muscular Dystrophy at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

CONCLUSION: Except in cases where reliable research results suggest the participant is in imminent danger, an investigator's decision not to return results does not necessarily violate the ethical principles for human research, as long as the consent process indicated that results would not be returned. No single ethical principle sufficiently justifies an unrestricted obligation to return individual results to participants, but neither does any ethical principle completely absolve investigators from doing so.

To this point this discussion has focused primarily on the ethical obligations arising from a relationship between investigators and participants, or potential participants, who have decision-making capacity. Our analysis suggests that offering to return results can be an important means of fostering transparency, demonstrating respect for the contributions of the participant, and providing benefit to those who volunteer for research. But what about research participants who do not have decision-making capacity or lose that capacity during the research project? This includes younger children, adults and older children who have never had decision-making capacity, and those who lose capacity through disease progression, injury, or death during the conduct of the research. There has been excellent scholarship on these issues in recent years (Anastasova et al., 2013; Beskow and O'Rourke, 2015; Chan et al., 2012; Groisman et al., 2012; Holm et al., 2014; Wolf et al., 2015) and a full exploration of the ethical and legal issues relevant to these participants was not feasible in the time available to the committee. In brief, however, when competent participants express an informed choice regarding results disclosure to family members or others but then lose capacity during the conduct of the study, respect for their autonomy suggests that their preferences should be respected (Wolf et al., 2015). Indeed, for competent participants the optimal approach to this issue is to encourage them to consider at the time of consent how they would want their results to be handled if they are subsequently unable to make a competent choice.

For participants who are not competent at the time of study entry, whether by virtue of minority or cognitive impairment, or who lose competence during the course of the study and have not previously indicated their preferences, we conclude that any ethical responsibility that investigators have to return results to participants is grounded in considerations of beneficence. The return of results may be appropriate when those results have significant health or welfare implications for the participant. Such results generally will be provided to the participant's legally authorized representative, who in turn will be in a position to decide—if the results suggest risk to other family members—whether to share them with those relatives. When a participant dies without having previously indicated his or her preferences regarding the sharing of results with significant health implications for family members, the analysis is more complex. Investigators cannot be said to have a binding duty of beneficence to people who are not enrolled in the study. However, given the moral value of promoting health whenever possible, it will generally be preferable to share information about serious

conditions for which interventions are possible with potentially affected family members. Countervailing considerations in specific cases will include the privacy of the deceased research participant and the burden on the research team. The implications of this ethical foundation relevant to those who lack decision-making capacity will be explored in Chapter 4.

SOCIETAL CONSIDERATIONS FOR THE RETURN OF INDIVIDUAL RESULTS IN HUMAN PARTICIPANT RESEARCH

Although a clear ethical obligation to return individual research results may, as discussed above, be restricted to a small number of cases involving imminent risk to a participant's well-being, there are other societal considerations that suggest the need for a re-evaluation of the circumstances under which returning individual research results to participants may be appropriate. In addressing its task, the committee considered a broad set of stakeholder perspectives and arguments for and against the return of individual research results, including the potential to maximize benefits and minimize risks to participants, the research enterprise, and society as a whole.

Considerations for Research Participants

Individual research results are commonly not returned to participants despite a growing body of literature demonstrating that many participants are interested in receiving their results (Bollinger et al., 2014; Murphy et al., 2008). Participants are particularly interested in receiving results when the results have direct relevance to their health or that of a loved one or are actionable (Long et al., 2016; Murphy et al., 2008). This theme appears to be increasingly consistent across many studies, although participant preferences for receiving results vary widely (Terry, 2016). Some participants have expressed a desire to receive all of their results, while others have indicated that they volunteered in order to advance the research and do not expect to receive individual results but may like to know the key findings from the study. In some cases, participants may even consider individual-specific results to be a burden (Bollinger et al., 2014).[7]

Benefits to Participants from Receiving Individual Research Results

Research results may have significant informational value to participants, and in some cases such information might not otherwise be obtained. Participants may benefit from the return of individual research results that inform clinical decision making, life planning, and other actions that may affect health and the quality of life.

[7] Testimony of John Molina of Native Health at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 11, 2017.

Research results that are clinically actionable—i.e., those that may guide decisions on preventive interventions or treatments or other actions (including surveillance for early detection) that may change the course of a disease or health condition (MRCT Center, 2017a)—have received the greatest attention in arguments for disclosure (Bookman et al., 2006; Fabsitz et al., 2010; National Bioethics Advisory Commission, 1999). However, the committee identified several other important ways that participants may benefit from the return of individual research results. Reproductive planning, for example, may be influenced by results indicating that a participant is a carrier for a recessive or X-linked disorder or that the person may have difficulties carrying a pregnancy to full term, as in the case, for example, of balanced chromosomal translocations (Kavalier, 2005). For participants with certain health conditions (or the caregivers of such individuals), research results may inform other aspects of life planning, such as making insurance (e.g., long-term care) coverage decisions (Caselli et al., 2014; Zick et al., 2005) and anticipating changes in lifestyle (Vernarelli et al., 2010). For example, one parent of a child with a rare degenerative disease spoke to the committee about research results that could predict disease progression, allowing families to plan for the child's transition to the use of a wheelchair.[8] Research results may also inform or help drive individual-level risk reduction efforts, such as taking steps to limit exposure to an environmental contaminant identified in a human biomonitoring study (Ohayon et al., 2017) or changing health behaviors (e.g., exercise, nutrition) to reduce risk factors associated with a disease to which one is found to be at increased risk (Caselli et al., 2014; Chao et al., 2008), though such changes may often not be pursued or sustained (Hollands et al., 2016). In some cases, individual research results may have value to participants even when there is no action to be taken. For example, an individual with a family history of a severe disorder may experience relief in learning that he or she is negative for a susceptibility biomarker (Romero et al., 2005), particularly in cases where no clinical test is yet available. Relief may also result from finally identifying a cause for a heretofore undiagnosed health condition—ending the so-called "diagnostic odyssey"—even if no other resultant clinical action is possible beyond the cessation of diagnostic testing (Beaulieu et al., 2014). Some participants are simply interested in learning more about themselves (Bunnik et al., 2014; SACHRP, 2016).

The benefits of returning individual research results may also extend to others besides the research participant. Some results may have implications for family members, partners, or even whole communities. For example, the genetic results for hereditable conditions, if shared, may lead to cascade testing for family members,[9] and individual biomonitoring results may foster activism aimed at

[8] Testimony of Ellen Wagner of Parent Project Muscular Dystrophy at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[9] Testimony of Adam Buchanan of Geisinger Health System at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

driving community-level changes to reduce exposures (Ohayon et al., 2017). In some such cases, however, decisions will need to be made regarding with whom results should be shared. Generally participants have the discretion to decide with whom to share their results, but this valuation of autonomy is not universal (Smith-Morris, 2007). In some tribal communities, for example, the tribe retains ownership over the biospecimens submitted by tribe members (and the results generated from them) rather than the research institution (Chadwick et al., 2014; Mohammed et al., 2012) and may have the corresponding expectation that the results belong to the tribe, not to the individual.[10]

The committee also heard from multiple research participants that the act of sharing of individual research results can, in and of itself, be beneficial for participants. One participant indicated that the lack of reciprocity in clinical research can reinforce negative experiences with the medical enterprise. "When I go into a clinical setting, I lose a great deal of identity, and I almost become anonymous. Because I've had so much trauma around hospitals, I feel like I don't have a voice." Returning individual research results in a way that makes them meaningful, this participant said, is a way to create a more level playing field and to help participants feel appreciated for their contribution to the research study.[11]

Potential Risks to Participants from Receiving Individual Research Results

The potential benefits discussed above suggest that there are many reasons to consider expanding the return of individual research results beyond the current practice. However, it is also important to consider the potential risks to participants who choose to receive results. The most commonly cited risks are possible adverse psychosocial effects from receiving results with serious health implications or that have uncertain meaning. Some survey-based data have suggested that the disclosure of such results has the potential to do harm. For example, a study using hypothetical questions to assess the possible risks of harm from presymptomatic testing for Alzheimer's disease reported that more than 10 percent of respondents agreed with a statement that they would seriously consider suicide if results indicated they were positive for the ε4 allele of apolipoprotein E (APOE-ε4)[12] or had a non-genetic biomarker (Caselli et al., 2014). However, there is significant uncertainty regarding the translation of hypothetical scenarios to real-world experiences. Only a limited number of studies have empirically evaluated post-disclosure stress or the onset of a psychological disorder (e.g., anxiety, depression), and to date there is little empirical evidence to support

[10] Testimony of John Molina of Native Health at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 11, 2017.

[11] Testimony of Stephen Mikita of Aspirin in Reducing Events in the Elderly (ASPREE) study at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 11, 2017.

[12] The APOE-ε4 genotype is associated with an increased risk of developing Alzheimer's disease.

concerns about serious adverse effects (Ashida et al., 2010; Bemelmans et al., 2016; Bradbury et al., 2015; Calzone et al., 2005; Christensen et al., 2011; Green and Farahany, 2014; Green et al., 2004, 2009; Jenkins et al., 2007). The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) studies, for example, evaluated the psychological and behavioral effects of disclosing genetic biomarker results to participants who were first-degree relatives of an Alzheimer's disease patient (Roberts et al., 2005). Although the disclosure of the APOE-ε4 carrier status was associated with a transient increase in test-related distress, no statistically significant differences in post-disclosure levels of anxiety or depression were observed among three groups of participants: those who were APOE-ε4 carriers, those who were negative for APOE-ε4, and those who were in a non-disclosure group (Green et al., 2009). Similarly, Bradbury and colleagues reported that for a study population of breast cancer patients, the receipt of individual genetic testing research results was not associated with significant increases in anxiety and distress when participants received genetic counseling (Bradbury et al., 2015). In the context of biomonitoring studies, investigators have reported that returning exposure results has resulted in increased concerns and worry among participants but did not generate the harmful levels of worry and panic (Emmett et al., 2009; Ohayon et al., 2017; Ramirez-Andreotta et al., 2016) that some members of the study's IRB believed could result from the disclosure (Ohayon et al., 2017). Indeed, worry can be a productive force when it stimulates preventive or corrective action (Ohayon et al., 2017).

Still, proceeding with caution is prudent, given that little is known about the effects of participant characteristics, beliefs, and past experiences (e.g., a family history of disease, a history of a psychological disorder) on outcomes following disclosure. Some limited data suggest that receiving test results may affect participant expectations and perceptions about themselves, which in turn can have effects on functioning. In the REVEAL study, APOE-ε4-negative participants who received their results reported higher memory function than APOE-ε4-negative participants who did not receive their results. More concerning was a decrease in subjective and objective measures of memory function in APOE-ε4 carriers who received their results as compared with APOE-ε4 carriers who did not learn their genotype (Lineweaver et al., 2014). Prognostic pessimism—negative feelings about the future course of an individual's disorder, including feelings of hopelessness and lack of agency—has been associated with beliefs regarding a genetic or biological predisposition to stigmatizing conditions, such as depression or substance abuse disorder (Lebowitz and Appelbaum, 2017; Lebowitz et al., 2013) and is another potential adverse outcome of receiving research results that indicate an increased risk for some health conditions.

Although similar types of concerns have been raised about the psychological effects of disclosing potentially worrying or disturbing test results in both clinical and research contexts (e.g., when such results are not clinically actionable), some investigators and IRBs have apprehension about the return of individual research

results because of the uncertainty that is often inherent in a research result and because of a lack of confidence in the validity of the result. When results are inaccurate, misleading, or over-interpreted, harm can result from an inappropriate action (e.g., prophylactic surgery for someone whose results falsely indicated an increased risk of breast cancer) or from inaction (e.g., failure to get proper screenings when the results were negative for a susceptibility factor). The committee did not find many real-world examples of harm to individuals involving inaccurate or misinterpreted research results that had been returned to participants, but a recent case of unwarranted prophylactic surgery involving the misinterpretation of clinical genetic testing results demonstrates the potential risk (Bever, 2017). It should also be noted that so far in the genetics context, research has focused mostly on the return of results from clinically valid, commercially available tests. Thus, it cannot yet be determined whether examples of additional harms may arise from the return of research results that have not been validated for clinical use.

In addition to the potential physical and psychological harms, social consequences may also occur after the return of individual research results to participants (Bookman et al., 2006; Smith-Morris, 2007); these social consequences may include stigmatization, economic impacts, and adverse effects on relationships with others, including family members (e.g., in cases of misattributed paternity) and communities. For example, individuals participating in a personal exposure study expressed concerns about the effects of the results on their property values if the results indicated a contamination problem (Ohayon et al., 2017). Reporting research results to individuals may also risk affecting community norms in Native American communities that practice tribal decision making and community self-determination (Smith-Morris, 2007). Commonly reported concerns of participants include breaches of privacy and exposure to the risk of discrimination associated with individual research results (Ohayon et al., 2017). As discussed further in Chapter 6, some legal protections are in place to prevent discrimination on the basis of genetic test results in employment, educational opportunities, and health insurance, but gaps in protections have been noted.[13] For example, federal protections through the Genetic Information Nondiscrimination Act of 2008 do not apply to life, disability, or long-term care insurance (Arias and Karlawish, 2014).

Overall, little is known regarding the actual (versus potential and perceived) risks associated with returning individual research results, but the committee emphasizes that the current state of knowledge reflects a lack of evidence, not conclusive evidence of a lack of effect. Clearly, more research is necessary to better understand the risks associated with results disclosure, including whether certain subsets of individuals are more vulnerable to adverse impacts. What is clear is that many participants want access to their research results and are willing to assume

[13] In the case of environmental exposure research, the lack of legal protections and potential legal liabilities for participants that receive results on household exposure has been raised (Goho, 2016).

the risks. Many argue that withholding results on the basis of the potential risks discussed above is overly paternalistic (Bredenoord et al., 2011; Fernandez, 2008; Townsend et al., 2013).

Considerations for the Research Enterprise

Opinions within the research enterprise are mixed on the appropriateness and value of returning individual research results (Meulenkamp et al., 2012). Although few argue that all research results should be returned, a growing number of investigators believe that participants should, at the very least, have access to any of their test results that were generated in the course of research (Burke et al., 2014; Green et al., 2013; Jarvik et al., 2014; Ohayon et al., 2017; PCSBI, 2013; Wolf et al., 2008), and some institutions have developed standardized processes for decision making on when and how such results should be returned.[14] Some have argued that the one-way flow of information from research participant to scientist is outdated and paternalistic (Johnson, 2014; Lunshof et al., 2014). In much the same way as prospective participants, report investigators are more likely to support the return of results that have clear implications for the prevention or treatment of a health condition (Meulenkamp et al., 2012). Despite the increased interest from investigators in returning individual results to research participants, countervailing concerns have been raised about the risks to participants, the legal liabilities, and the burdens placed on the research enterprise (Bredenoord et al., 2011; Klitzman et al., 2013; Ohayon et al., 2017).

Research sponsors and funding agencies also appear to have conflicting perspectives. As discussed in Chapter 1, the National Institutes of Health has moved toward policies supporting the return of results in a broader set of circumstances than has traditionally been practiced. It has indicated that "as the biomedical research enterprise increasingly moves to a more participatory model of research, where research participants are treated more as partners than passive subjects, we can expect greater emphasis on returning individual-level results of research to participants" (NIH, 2017). It is not clear that private-sector sponsors are equally persuaded on this issue. In comments submitted to the committee, for example, a Merck representative indicated that although it has no proprietary reason not to make results accessible, it currently does not return results from "research-grade" assays even when they are performed in laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[15] The reasoning provided by Merck is consistent with commonly cited concerns from other research system

[14] Memorial Sloan Kettering Cancer Center, 2017. Comment provided to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, October 20. Available by request through the National Academies' Public Access Records Office.

[15] Comment by Julie Anne Zawiska to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, October 19, 2017. Available by request through the National Academies' Public Access Records Office.

stakeholders, which are explored in the section below. On its website, Pfizer indicates that it has allowed clinical trial participants in select studies to access their individual-level results by using the Department of Health and Human Services Blue Button technology, which "enables the secure electronic delivery of medical information gathered in a study directly to trial participants and allows integration into electronic medical records"; the website does not indicate whether results from "research-grade" assays are offered to participants (Pfizer, 2018).

Risks and Burdens for the Research Enterprise from Returning Individual Research Results

To mitigate the risks of returning research results, investigators will need to provide participants with sufficient information and deliver results in ways that enable participants to make informed decisions. From its review of the literature and from input solicited from research system stakeholders, the committee identified several consistent themes regarding the potential risks and burdens to the research enterprise that are associated with the return of research results.

First, the individual-level analysis of research results (e.g., to determine meaning for an individual participant) may differ from the analysis of aggregate results and can be a challenging task for investigators, particularly when the results are generated using novel, cutting-edge technologies and techniques.[16] The inherent uncertainty related to research results makes some investigators uncomfortable with the interpretation and return of results, given the risk for misinterpretation by the participant; this is a particular issue when there are no established health guidelines relevant to the result, as is the case in some environmental exposure studies (Hernick et al., 2011). In some cases, interpretation will require medical expertise and even a knowledge of the participant's medical and family history. Investigators may not always have a relationship with the participant who contributed the biospecimen and, therefore, may not be familiar with that individual's history; however, as is discussed in Chapter 5, in many cases results can be returned without such individual-level interpretation.

Cost is frequently identified as an argument against returning individual research results because of the potential burdens it could generate for an investigator. These burdens include both financial costs and the potential for lost research productivity caused by the diversion of research team efforts (Bredenoord et al., 2011; Budin-Ljøsne et al., 2016; Christensen et al., 2011; Fernandez et al., 2004; Resnik, 2011).[17] The effort involved in re-contacting participants and

[16] Comment by Julie Anne Zawiska to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, October 19, 2017. Available by request through the National Academies' Public Access Records Office.

[17] Comment by Mark E. Sobel to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, August 18, 2017. Available by request through the National Academies' Public Access Records Office.

returning results in ways that are responsible and likely to be useful to them can be significant, particularly when disclosure may involve the services of medical professionals (e.g., genetic counselors) or when the results become available after a trial or study has ended. Additional costs may stem from requirements for confirmatory testing or from instituting other processes to ensure the quality of research results returned to participants (Black et al., 2013) (discussed further in Chapter 3). Although the opportunity costs are not well understood, it is clear that meeting the needs of participants and investigators will require substantial investments in infrastructure and training at individual laboratory and institutional levels. The effects of such measures may extend beyond the issue of resources to also include effects on the laboratory culture and training environment. The likely diversion of resources from the conduct of research, particularly at a time when research funding is uncertain, raises concerns that policies requiring investigators to more routinely return individual research results will unduly burden the research enterprise and hinder progress in biomedical research (Black et al., 2013; Bollinger et al., 2014; Resnik, 2011).

Another commonly cited risk is that the routine disclosure of individual research results could conflate or confuse the purposes of research and clinical care (Bredenoord et al., 2011; Clayton and Ross, 2006; Meltzer, 2006). While there is broad agreement that the return of research results should not be a substitute for clinical care and cannot compensate for inadequate health care access, participants sometimes enroll in studies with the intent of accessing testing or care that they cannot otherwise obtain.[18] Some argue that the return of individual research results may promote therapeutic misconception, leading participants to mistakenly assume that a research study will yield reliable results with clinical value when, in reality, the clinical implications of research results will only rarely be clear (Clayton and McGuire, 2012). Participants themselves have indicated that the return of clinically relevant genetic results blurs the distinction between research and clinical services, although the significance is not always clear to them (Miller et al., 2008a). Proper consent procedures are important to help mitigate the risks associated with participants' unrealistic expectations (Appelbaum and Litz, 2008). When participant expectations are not met, it may undermine motivation to volunteer for research studies in the future. The increased connectedness between research and health care delivery should not necessarily be considered a risk, and in some circumstances better integration may be appropriate and beneficial to participants, the research enterprise, and health care (Darnell et al., 2016; Faden et al., 2013; Kullo et al., 2014; Wolf et al., 2018). As one scholar stated, "Research and clinical care are connecting along a translational continuum. Instead of a wall between the two, we now have a permeable membrane. The return

[18] Comment by Leslie Biesecker provided to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, September 7, 2017. Available by request through the National Academies' Public Access Records Office.

of results is a debate about how to structure the flow of information through that membrane" (Wolf, 2013, p. 573).

Finally, legal risks also influence investigator and institution decisions about returning individual research results. Perceptions regarding legal risks relate both to regulatory compliance issues (Barnes et al., 2015) and to fears that imposing obligations to return individual research results to participants will open the door to greater legal liability for investigators (Clayton and McGuire, 2012). Legal liability for negligence may arise from results that are returned—e.g., if those results are found to be inaccurate—or from a failure to return results (McGuire et al., 2014). However, investigators have traditionally not been viewed by the courts as having a fiduciary relationship with participants (Meltzer, 2006; Pike et al., 2014), and so far there are no examples where ethics-based recommendations from expert groups have been used to impose legal liability (Wolf, 2012). Approaches to overcoming legal and regulatory barriers are discussed in more detail in Chapter 6, but, generally, the current confusion surrounding the regulatory environment and the paucity of legal precedent are impediments to a more widespread adoption of return-of-results practices.

Benefits to the Research Enterprise from Returning Individual Research Results

Although commentaries on the return of individual research results often focus on the expected burdens to investigators, there could be benefits to investigators as well. In particular, if the return of results leads to increased trust and public engagement in the research enterprise, it could have multiple positive effects, including possible improvements in the efficiency, generalizability, and participant-centeredness of research.

One growing source of pressure on the research ecosystem to evolve is the set of challenges that many investigators face in the enrollment and retention of participants in research studies. This problem has been well documented for clinical trials and large prospective cohort studies (Comerford et al., 2017; Gul and Ali, 2009; Leighton et al., 2018; Watson and Torgerson, 2006). Enrollment delays and participant dropout can increase the length and cost, as well as reducing the power of a research study, which can jeopardize the implementation and validity of the research (Gul and Ali, 2009; Leighton et al., 2018; Watson and Torgerson, 2006). Despite the general support for the conduct of biomedical research observed in surveys, the majority of Americans have low awareness of and levels of participation in clinical trials and other human research (Ohmann and Deimling, 2004; Woolley and Propst, 2005). One reason for this limited participation is inadequate information sharing by investigators to participants regarding many aspects of study participation. A persistent lack of transparency on the part of investigators, coupled with historical abuses, has raised questions in the public's mind regarding the trustworthiness of the research enterprise and has dampened interest in participation (Corbie-Smith et al., 1999; Hiratsuka et al., 2012; Northington Gamble, 2006). This issue of lack of

trust and transparency was brought up during committee discussions with research participants and community representatives, who suggested that returning research results to participants may stimulate greater transparency and interest in contributing to research.[19,20]

Some evidence supports the assertion that returning individual research results to participants could improve enrollment and retention. Survey data have shown that receiving results is a strong incentive for participation in research (Christensen et al., 2011; Kaufman et al., 2008, 2016; Murphy et al., 2008), and participants may prefer individual results over aggregate study results (Halverson and Ross, 2012). Increasing trust and enrollment across all participant groups could increase not only the efficiency of research, but also its generalizability. The lack of diversity (e.g., socioeconomic, racial, ethnic, and gender identity/sexual orientation) in many study populations is well documented and limits the applicability of many research findings to the larger heterogeneous population found within the United States and globally (Duma et al., 2017). It is worth noting, however, that questions have been raised regarding the potential for undue inducement for participation (Bledsoe et al., 2012), particularly if investigators overstate the benefits of enrollment in a study (Meltzer, 2006). Investigators and IRBs can help to guard against this possibility by ensuring accuracy in framing the benefits likely to accrue from the return of results. The promise of receiving individual research results may be a larger incentive for those with fewer resources (e.g., insurance) to get medical testing, which raises additional justice-related concerns[21] that will need to be considered in the development of policy.

Finally, the return of individual research results may help patient and participant communities to better connect, compare results, and work with investigators to develop and help answer questions that matter to those affected by the conditions under study, thereby improving the participant-centeredness of biomedical research.[22] Growing access to data from multiple sources (e.g., mobile technology, patient portals) has empowered patients to take a leadership role in driving precision medicine research (Fliesler, 2015). In the rare disease community, for example, patients and their families are increasingly helping design studies, share data, and leverage social media and digital marketing as recruitment tools (Fliesler, 2015).

[19] Testimony of John Molina of Native Health at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 11, 2017.

[20] Testimony of Stephen Mikita of Aspirin in Reducing Events in the Elderly (ASPREE) study at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 11, 2017.

[21] Testimony of Febe Wallace of Cherokee Health Systems at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[22] Testimony of Ellen Wagner of Parent Project Muscular Dystrophy at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

Patients, their family members, and advocates have found a way to use new technologies and the Internet and its vast array of social media networks to connect to patients like them, in a way that typical clinical trial recruitment does not. The willingness of people to be engaged with their health information, generate their own research questions, and share their data is providing investigators with immense amounts of information that is contributing to precision medicine initiatives and affecting what participants expect from research and the role they want to play in it.

Considerations for the Health Care Enterprise

Clinicians, clinical laboratory directors, and other members of the health care enterprise are important stakeholders whose perspectives need to be considered in the development of policies related to the return of individual research results. Health care and research systems are increasingly intertwined in the conduct of biomedical research. Clinical trials frequently involve the delivery of clinical care, and some have posited that the return of individual results is transforming other forms of research (e.g., genetic epidemiology studies) into quasi-clinical services.

This hybrid of clinical care and research can face challenges when participant expectations regarding the timely receipt of results delivered with the appropriate sensitivity are not met (Miller et al., 2008a). Research laboratories often are not set up to provide participants with medical information or to ensure follow-up. Therefore, as health care professionals emphasized to the committee, when the research results that will be returned have a potential medical impact, it is important to have stringent protocols for the return process and adequate resources to support qualified health professionals who can translate the results into meaningful information for participants and discuss their questions and concerns (Grove et al., 2014).[23] One notable challenge in meeting this need is the short supply of some kinds of medical professionals (e.g., genetic counselors) who have the necessary expertise. Returning results in a scalable way will require paying close attention to the processes for mitigating burdens to the health care system. For example, addressing shortages in genetic counselors could involve removing barriers associated with state licensure restrictions[24] and using video-counseling technologies.[25] Reimbursement is another issue that will need to be addressed for studies operating at the research–clinical care interface (Wolf et al., 2018).

[23] Comment by Mary E. Freivogel to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, October 20, 2017. Available by request through the National Academies' Public Access Records Office.

[24] Testimony of Jessica Langbaum of Banner Alzheimer's Institute at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[25] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

In some cases, clinicians may be the primary investigators (as is often the case in clinical trials) or members of a study team (e.g., clinical geneticists) tasked with communicating with participants about results (Wolf et al., 2018).[26] While having clinicians in these roles helps to ensure that health care professionals are available to discuss medically relevant results with participants, the blurring of lines between research and medical care may be confusing for participants, potentially contributing to therapeutic misconception and challenging the traditional understanding of the doctor–patient relationship (Burke et al., 2014); having doctors in a dual role of both clinician and investigator also has the potential to create conflicts of interest (McGuire et al., 2014). In other cases, physicians who are not associated with the study may be asked to discuss and interpret individual research results for their patients. Some research studies have set up processes and infrastructure to deliver research results to the participants' health care providers. In the Scripps Idiopathic Diseases of Man study, having a physician champion who was willing to work with the research team and return and discuss the genetic results with patients was part of the inclusion criteria for participation (Bloss et al., 2015). However, the committee also heard that clinicians may not want to have the responsibility of explaining results to participants, particularly if they themselves do not have a strong understanding of the test or result.[27] To address these kinds of concerns, some research teams offer support to clinicians in the form of informational packets (e.g., with information about the study).[28,29]

Sometimes physicians with no knowledge of a study may be approached by patients looking for a further explanation of the research results that have been returned to them. This raises concerns regarding the potential burdens on primary care providers and other clinicians, who may feel they have neither the time nor the necessary knowledge to interpret their patients' research results (Terry, 2012).[30]

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[26] Testimony of Nicholas Newman of the University of California Department of Pediatrics at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on October 24, 2017.

[27] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[28] Testimony of Adam Buchanan of Geisinger Health System at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[29] Testimony of Joanne Murabito of Framingham Heart Study at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[30] Testimony of Febe Wallace of Cherokee Health Systems at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

Failure of those clinicians to meet patients' expectations for an explanation could erode confidence and trust in health care providers.[31]

Another contentious issue in the return of individual research results relates to the type of laboratory in which testing is conducted. Research laboratories are not held to the same quality assurance and quality control requirements as clinical laboratories, which means that there is a greater risk of pre-analytic, analytic, and reporting errors (e.g., specimen mix-up) when testing is done in research laboratories. Thus, it was stressed to the committee that any test results that could be used to inform patient care decisions should be generated in CLIA-certified laboratories.[32,33,34] Otherwise, a loophole could be created that would enable the generation of results for clinical decision making in non-CLIA-certified research laboratories without medical oversight.[35]

Another issue relates to the potential for research results to be incorporated into electronic health records (EHRs). The Electronic Medical Records and Genomics (eMERGE) Network, for example, makes it possible for investigators to use EHRs to return clinically relevant genomic research results (e.g., genetic variant and pharmacogenomics results) for use by participants and their health care providers (Kullo et al., 2014). However, some fear that providers who are not aware of the limitations of research results in the EHR may misinterpret the significance of the result for patient care decisions,[36] compromising patient safety and also exposing the provider to liability.

Considerations for Society

The benefits and risks to participants, the research enterprise, and the health care system from the return of individual research results can in many cases be seen as benefits and risks to society. However, some implications of the issues

[31] Testimony of Febe Wallace of Cherokee Health Systems at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[32] Comment provided by the College of American Pathologists to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, September 7, 2017. Available by request through the National Academies' Public Access Records Office.

[33] Comment by Douglas A. Beigel to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, September 27, 2017. Available by request through the National Academies' Public Access Records Office.

[34] Comment by Mark E. Sobel to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, August 18, 2017. Available by request through the National Academies' Public Access Records Office.

[35] Comment provided by the College of American Pathologists to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, September 7, 2017. Available by request through the National Academies' Public Access Records Office.

[36] Comment provided by the College of American Pathologists to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, September 7, 2017. Available by request through the National Academies' Public Access Records Office.

discussed above warrant an explicit mention in the society-level context. In particular, increased public engagement and trust in research has many potential societal benefits, including improved health and science literacy, increased activism related to human and environmental health, greater public advocacy for biomedical research, the acceleration of biomedical discoveries, and an increased likelihood that scientific advances will be translated into policy (Ohayon et al., 2017; Terry, 2012). Informing the public about research can affect policy decision making, particularly for public health funding as occurs in the Canadian system (Jbilou et al., 2013). All of these could have positive effects on public health. If, however, the return of individual results is not done in a thorough, responsible, and equitable manner, there are also risks to public health and society, including creating greater health and health care disparities because of more limited mechanisms to engage certain communities. For example, in the absence of efforts to address barriers to increasing diversity in research participant populations, communities that have been traditionally underrepresented in research studies may not have equal access to the benefits from the return of research results, inadvertently perpetuating existing disparities (Yu et al., 2014). Moreover, if sufficient efforts are not undertaken and checks put in place to ensure that the results returned to participants are valid (discussed further in Chapter 3), there is a potential for the spread of misinformation, public disengagement, and further loss of trust in the research and medical enterprises.

RECOMMENDATION AND GUIDING PRINCIPLES FOR THE RETURN OF INDIVIDUAL RESEARCH RESULTS

The committee carefully considered the competing ethical justifications for the responsibilities of investigators to return, or not to return, individual research results as well as the perspectives of different stakeholders and the many societal considerations. Although no clear philosophical justification exists for an unrestricted obligation to return individual results to participants, strong justifications can be offered for returning some results in many circumstances beyond traditional and current practices. However, caution is warranted, given the potential adverse effects on participants and the research enterprise. The effects of returning individual research results will need to be continuously evaluated to build a stronger empirical evidence base.

CONCLUSION: Considering the full spectrum of ethical and societal considerations for the return of individual research results, it is clear that there are certain circumstances when there are compelling reasons to return individual results to participants and others in which it is appropriate to limit and constrain the return of results. In determining whether to return results for any given study, the various ethical principles must be balanced, and the specific context of the situation must be carefully considered.

Recommendation 1: Determine the Conditions Under Which Individual Research Results Will Be Returned to Participants.

When conducting research involving the testing of human biospecimens, investigators and their institutions should routinely consider whether and how to return individual research results on a study-specific basis through an informed and thoughtful decision-making process.

Investigators, with oversight from their IRBs and institutions, will ultimately be responsible for making decisions on a case-by-case basis regarding whether and how to return individual research results, as the decisions require careful consideration of many factors, which are described below. However, as discussed in Chapter 4, research sponsors and funding agencies also have an important role in reviewing return-of-results plans in funding applications in order to support reasonable consistency across research studies and institutions. Although these oversight mechanisms are not foolproof at preventing harm, and increased responsibilities need to be accompanied by a corresponding increase in resources and training if they are to be effective (Icenogle, 2003), the committee believes that at this time institutional review is the most practical and reasonable approach to support decision making regarding the return of individual research results. Chapter 4 presents the committee's framework that can support investigators and IRBs in their decision making. The committee recognizes that it will be challenging for IRBs to foster the return of results and to assess the risks and benefits of this practice in the near future before experience and an evidence base has fully developed. In the meantime, we encourage IRB professionals to approach the issue reflectively, regularly engage stakeholders, attend to accumulating data and institutional experiences, and share experiences, data, and protocols with colleagues through professional meetings and publications. Current practices and research into the return of results taking place in National Institutes of Health (NIH)-funded research like the *All of Us* Research Program, the Clinical Sequencing Evidence-Generating Research consortium, and the eMERGE Network can be used to develop initial guidance for IRBs. NIH could also assist IRBs by convening a workshop or working group with other research funders to examine current practices regarding the return of results from biospecimens and explore lessons learned from biomonitoring programs and other domains such as radiology, imaging, and social and behavioral health research. As the evidence base expands, there may be a further role for government agencies to develop guidance to support investigators and their IRBs in their decision-making process.

Decisions about whether and how to return individual results will be influenced by many factors that require careful consideration. These include the potential value of the information to the participant; the nature of the relationship, if any, between the participant and the investigator; the analytic and clinical validity of the research result; and the potential risks, challenges, costs, and burdens of returning results as well as the resources available to do so effectively and

appropriately. The benefits to participants and the research enterprise have to be weighed against risks, including potential harms to individuals, the diversion of resources and investigator efforts away from conducting research, liabilities, risks of privacy breach, and discrimination. These factors, along with a framework for a decision-making process and recommendations to provide guidance and support for investigators, IRBs, and their institutions as they navigate this process are discussed in more detail in Chapters 3 and 4. As the committee explored these factors and developed its recommendations, its deliberations were guided by the following six principles:

Principle 1: Participants bring essential and valuable information to the research enterprise without which research cannot be conducted. Because research results have value to many participants, as a matter of reciprocity, respect, transparency, and trust the return of results should be routinely considered in the design of research protocols involving human participants.

The emergence of the participant-centric model for research is changing the paradigm from a system that traditionally focused on minimizing the risks of harms to participants to a system that more fully recognizes the rights and interests of the research participants. Accordingly, there is an emerging obligation to consider the personal values of the people who contribute to the research. Research participants are not disembodied providers of biomedical materials—they should be treated as active collaborators on the research (Kohane et al., 2007; Partridge and Winer, 2002). One means of expressing gratitude and respect is to recognize participants' generosity with appropriate reciprocity (Illes et al., 2006), i.e., by communicating results that may be of value to participants.

Principle 2: Research has significant societal value. The potential value of returning individual research results must be carefully considered along with the trade-offs for research participants, investigators, research institutions, and society.

The purpose of biomedical research is to expand generalizable knowledge in order to advance our understanding of pathophysiology and medicine, with the ultimate goal of improving health outcomes for patients and the public. The return of results presents trade-offs for research stakeholders and requires careful consideration of the potential value, benefits, costs, and harms. The appropriate return of individual research results will entail additional resources, capabilities, and processes by and for the research enterprise. The possibility that these associated costs will lead to less investment in new research and a slowdown in biomedical advances is a potential harm to all research stakeholders—investigators, research institutions, participants, and the public. Similarly, each stakeholder has the potential to benefit from returning research results in terms of increased

participant enrollment and retention in research studies and greater public trust in the research enterprise. Determining the best approach to implementing this practice to balance the potential trade-offs will be context dependent. The return of individual research results (other than life-threatening and emergent results) should only be considered at a time, and by a method, that does not compromise the overall study results. Chapter 4 addresses the factors that go into decision making regarding the return of individual research results on a study-specific basis.

Principle 3: When individual research results are offered, participants have the right to decide whether to receive or to share their results.

By offering research results to participants, investigators are respecting participant needs and preferences in the research process; however, participants retain their choice about whether to receive results. As a matter of respect for participant autonomy, investigators may offer the results of their study to its participants; however, what a participant ultimately decides to receive will be contingent on his or her perspective at the time of offer, even if the participant had previously consented to receiving research results. Additionally, investigators should elicit participants' preferences (and invite participants to designate a representative regarding decisions) for sharing their results with relatives, including health care providers, upon their deaths (Wolf et al., 2015). While surveys have shown that "a majority of participants expected to learn their own genetic research results, would feel obligated to share their results with blood relatives while alive, and would want genetic research results to be shared with relatives after their death" (Breitkopf et al., 2015, p. 10), investigators should not assume this to be the case for all studies or for all participants uniformly. Therefore, decisions to share or not should be handled on a case-by-case basis, and investigators should respect participants' decisions.

Principle 4: When individual research results are returned, the process of communication is important to promote understanding of the meaning, potential uses, and limitations of the information.

Addressing the degree of analytic and clinical validity and being clear about uncertainty in the accuracy or significance of a research result is critical to helping the participant understand the result. Generally speaking, research results are not intended to be used in clinical decision making, although this depends on the specific result and how it was generated, so drawing clinical implications from research results should be done with great caution. Communicating results effectively will require attention to communication skills and strategies and will need to take into account the full context of the result, including the characteristics of the research, the test, the quality of the systems used in the research laboratory,

and the participant. Communication is always a function of the ability of the individual doing the communicating and of the resources at hand. Relevant resources can include trained health communicators working in partnership with investigators or investigators with communication aides such as health information technologies, typed descriptions, or other tools or training.

Principle 5: The value of research results to investigators, participants, and society depends on the validity and reliability of the result. High standards of laboratory quality, from the acquisition of specimens to the communication of results, enhance the validity and reliability of the results generated in research laboratories.

Participants can be misled or harmed by false or inaccurate test results which are more likely to arise when the quality of the testing is not optimal. The validity of research results depends on the quality management system used for testing in the laboratory, which includes sample collection, processing, storage, test method validation, equipment maintenance, personnel training and competency, and other quality standards or criteria that ensure the accuracy of the test result for an individual. To contribute to the generation of valid and reproducible research results, research laboratories that use human biospecimens should use appropriate quality standards, and tests should be performed under a quality management system with external verification of compliance.

Principle 6: The conduct of high-quality, generalizable, and equitable research involves the inclusion of diverse populations and requires investigators to return individual research results in a manner that accommodates the full spectrum of community needs and preferences, regardless of participant social or economic status. The potential value of results, which is best assessed with input from the participant, community, or trusted proxy, should be considered.

Research is enhanced by the broad participation of people of different backgrounds, including those who have been traditionally underserved or have limited resources. Working to recruit a diverse pool of research participants may lead to results that are more generalizable and that can engender trust within disenfranchised communities. Consistent with the principle of justice, investigators must strive for equity in participation, access to research, and value for the participant. Investigators cannot fail to include certain groups in research simply because they are perceived as more difficult to engage or because of other social characteristics, such as insurance status (relevant because many clinical research studies bill research participants or their insurers for standard-of-care services not related to the study) (OHSU, 2018).

It follows then that the return of individual results should not contribute to health disparities and inequities in health care or health research. Research

participants should have the same access to research results regardless of their socioeconomic status or their ability to access follow-up care when results indicate medical attention may be needed. The inclusion of diverse populations will affect the manner in which the return of results is performed, and in formulating the return-of-results plans, investigators should take into consideration the full spectrum of community needs. Great care should be taken to address the preferences and needs of disenfranchised populations, including those for whom English is a second language, individuals without health insurance, racial and ethnic minorities, and those with fewer socioeconomic resources. Investigators will require community or participant input in advance of a study's launch and during the return process in order to appropriately consider the preferences and needs of these populations.

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3

Laboratory Quality Systems for Research Testing of Human Biospecimens

Many expert groups have agreed that if individual research results are to be returned to participants, the test results should have a high level of validity (Bookman et al., 2006; Green et al., 2013; Jarvik et al., 2014; PCSBI, 2013). The validity of a result depends on the test used and the laboratory environment in which the test is conducted. Research using human biospecimens is conducted in a broad range of laboratory types where, due to the nature of the research and regulatory requirements, the quality management systems (QMSs)[1] in place vary significantly. For example, certain types of research settings and questions, such as field-based studies, may require less documentation with respect to pre-analytic, analytic, and post-analytic quality measures and reporting capabilities (see Figure 3-1 for details on what is included in these analytic phases) than required in clinical laboratories. This is because the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulates clinical laboratories (discussed in more detail later in this chapter). Consequently, determining whether the individual results generated over the course of research studies are valid may be challenging because documented evidence supporting result accuracy may not be available. While the committee does not expect all research laboratories to operate under a single quality standard, the lack of certainty about the research result validity is a barrier to the return of research results. Using appropriate quality processes in scientific research will be important to ensure the validity of individual research

[1] Quality management systems (QMSs) are defined by the World Health Organization (WHO), the International Organization for Standardization (ISO), and the Clinical and Laboratory Standards Institute (CLSI) as "coordinated activities to direct and control a laboratory with regard to result validity and reliability" (WHO, 2011).

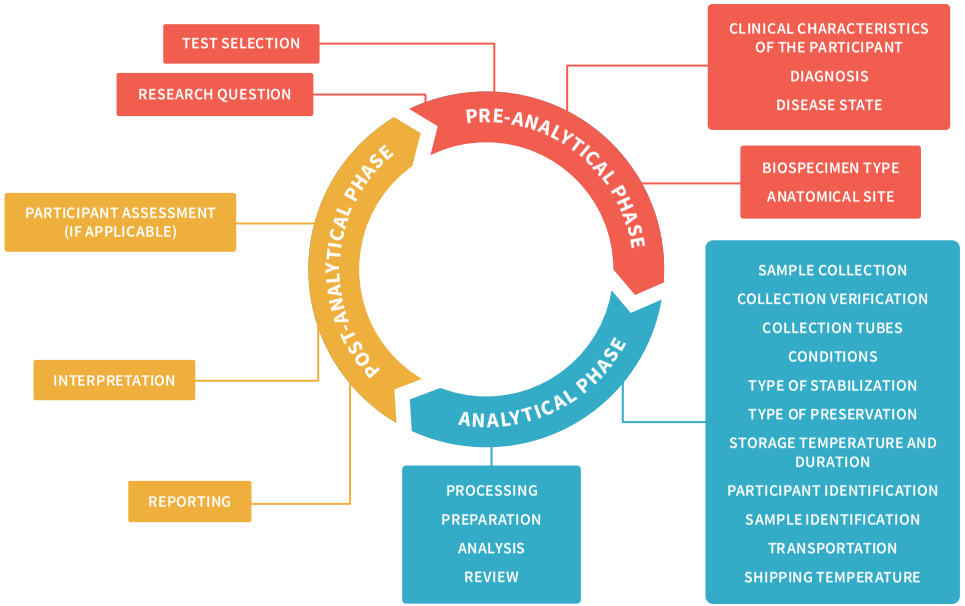

FIGURE 3-1 Diagram of pre-analytic to post-analytic phases of research.
NOTES: This figure adapts the total testing process in clinical research, traditionally separated into the three phases pre-analytical, analytical, and post-analytical (Hawkins, 2012), to the broader range of research settings and questions. It highlights the total research testing process, starting with the identification of a research question followed by an investigator selecting the tests best suited to address the hypothesis; then sample collection, transport, and processing; analysis and interpretation; and finally, showing how the result can influence the development of new hypotheses or even participant care. Rigorous control measures are required throughout the pre-analytical phase to avoid errors associated with specimen handling and identification, which would result in additional errors downstream in the analytical and post-analytic phases (LabCE, 2018).
SOURCE: Figure adapted from Reisner, 2015. © McGraw-Hill Education.

results returned to participants and the integrity and quality of science more broadly. This chapter discusses the need for confidence in the validity of research results that may be returned to participants and describes the associated infrastructure needed to implement the processes to generate high-quality research results.

THE SPECTRUM OF TRANSLATIONAL RESEARCH

Translational research using human biospecimens occurs across a spectrum, ranging from the discovery of basic mechanisms of human physiology and epidemiological associations to first-in-human studies, phase I clinical trials, phase II–IV clinical trials, and implementation studies (IOM, 2013a). There are a variety of laboratory methods used for the research on this spectrum, depending on the samples analyzed and the research questions being addressed. The test methods used and the regulations with which investigators must comply, including the quality processes in place, may vary according to the particular translational phase of the research.

In seeking new physiological pathways or novel methodologies, hypothesis-driven basic research is inherently more exploratory than clinical testing and, as such, requires greater flexibility in the standard operating procedures used in the laboratory. In the conduct of such research, investigators may make frequent modifications to the test protocols in order to identify the optimal procedures, and these modifications necessitate frequent revalidations of test performance. As a result, these studies are generally not conducted under a regulated QMS. Procedurally this makes sense; however, it has implications for the reproducibility, interpretability, and validity of test results. Furthermore, as research moves from bench research on participants' biospecimens and into more controlled clinical settings—for example, into clinical trials—human participants play a more involved role. In fact, the testing done in clinical research can affect clinical decision making or generate evidence used to gain Food and Drug Administration (FDA) approval of new drugs or devices, and therefore this testing is often performed in the regulated environment of the clinical laboratory, where protocols are more fixed and laboratory quality assurance processes are more stringent. In some cases, validated clinical tests already used in health care may be conducted during the course of a study—for example, to determine inclusion eligibility for study enrollment.

The progression to more fixed protocols and the prospect of high-quality results generated in the clinical research setting may imply that studies further along the translational spectrum are more amenable to the return of individual research results—or may simply lead to the *assumption* that the closer that research and test results seem to clinical application, the more reasonable it is to return research results. This assumption may also result in part from the belief that investigators conducting clinical research (and some forms of public health

research) have several or even ongoing interactions with the participants, perhaps creating a more robust investigator–participant relationship. However, this is not always the case. Some research will generate long-term relationships with participants through recurring contact and communication with the participants. The contact may occur through additional specimen collection, for instance, or follow-up visits with the trial team (i.e., in longitudinal studies). Some studies, however, may have little or no investigator–participant interaction or communication outside of the collection of a biospecimen (e.g., a one-time specimen collection for an environmental exposure study). In some situations, samples are acquired from a biobank, and, as a result, investigators may have never interacted with the participants who donated the biospecimen. In situations where the biospecimen is anonymized, return will not be possible. Further discussion of anonymized biospecimens or biospecimens acquired from a biobank is beyond the scope of this study.

THE IMPORTANCE OF ANALYTIC AND CLINICAL VALIDITY OF RESEARCH RESULTS

A core concern with the return of research results to participants relates to the potential risks of harm (physical or psychosocial) to the individual if the results are not accurate or were mislabeled and hence are not actually the results for that specific participant. Specimen labeling and handling are critically important quality issues in clinical laboratories, as errors can lead to patient injury from an incorrect diagnosis or treatment (Nakhleh et al., 2011). In research, sample mislabeling can lead to invalid comparisons and problems with reproducibility (Toker et al., 2016). Such sample mislabeling may not affect the overall aggregate results from a research study, as long as the study is powered correctly, but it can have a critical effect in the case of individual research results; if results from mislabeled specimens are provided to the incorrect individual participants, a variety of harms can follow. For example, this can result in unnecessary clinical consultations, medical procedures, and testing that can lead to participant harm. In addition, returning results to the incorrect individual can cause the investigator to miss key information that could inform participant care (Epner et al., 2013). As a result, possible errors in specimen labeling and handling are a central concern in debates on returning individual research results.

This type of risk is ameliorated, although not completely avoided, in the case of clinical test results because of processes in clinical laboratories that are in place to reduce the likelihood of mislabeling or other errors and to otherwise ensure the validity and quality of individual clinical test results (Agarwal, 2014). Specifically, clinical laboratories have requirements for personnel training and ongoing competency, equipment validation and maintenance, testing facility operations (e.g., written document control logs and standard operating procedures), establishing and verifying performance, the specifications of tests across different patient

groups, the retention of records and reports, specimen transport and management, result reporting requirements, and personnel safety.[2] Clinical laboratories must assess and document test precision, reliability, accuracy, sensitivity, and specificity as well as reference ranges and other test characteristics relevant to each test. Together, these requirements form the basis of a quality system that supports the analytic validity of the tests performed in the laboratory.

These quality standards required for clinical laboratories were established by the Centers for Medicare & Medicaid Services (CMS) to protect patients. CMS stipulated that laboratories that report patient-specific test results that will be made available for "the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" are required to meet the CLIA[3] quality standards or an equivalent or superior standard of an approved accrediting organization (Yost, 2003), as discussed further in Chapter 6. These standards help ensure the validity of laboratory test results. The more limited quality-assurance processes in place in many research laboratories pose a problem for the return of research results to participants because the validity of an individual test result may be difficult to assess. The fact that science as a whole is examining its own performance in the area of research rigor and reproducibility and finding itself falling short of its expectations and goals (Baker, 2016; Begley et al., 2015; McNutt, 2014) (as discussed in more detail later in this chapter) lends credence to concerns over the effectiveness of quality procedures in research laboratories in general. Certainly, the relative lack of rigor is not characteristic of all research laboratories. However, the variability that exists from laboratory to laboratory—thanks to the absence of a minimum QMS requirement akin to the requirement that clinical laboratories must meet CLIA standards—creates uncertainty concerning the validity of test results from research laboratories.

A test's analytic validity (AV) and clinical validity (CV) are key considerations in deciding whether to return a research result based on that test (Bookman et al., 2006; Ravitsky and Wilfond, 2006) and may also inform the framing of information that accompanies the research results when they are returned (discussed in more detail in Chapter 5). AV refers to the ability of a test to measure what it is designed to measure (NASEM, 2017a). Results from tests lacking AV may be inaccurate and therefore misleading. Consequently, most expert groups have agreed that it is not appropriate to return results that lack credible evidence demonstrating AV (Fabsitz et al., 2010; Jarvik et al., 2014). CV is a measure of a test's ability to identify or predict accurately and reliably the clinically defined disorder or final health or medical outcomes of interest in an individual (NASEM, 2017a). CV describes, for example, whether a biomarker being tested is associated with a disease, outcome, or response to treatment, and it takes into account clinical sensitivity (the ability to identify those with the disease), clinical specificity (the

[2] 42 C.F.R. § 493.
[3] 42 C.F.R. § 493.

ability to identify those without the disease), and the positive and negative predictive value of the test (NASEM, 2017a). In the context of genetic testing, the National Institutes of Health (NIH) defines CV as "how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease" (NIH, 2018). CMS does not require a demonstration of CV for a laboratory to meet CLIA requirements (Willmarth, 2015). However, FDA, which is concerned with the safety and effectiveness of diagnostic tests, may review the CV of a test to make sure that it identifies, measures, or predicts the presence or absence of a clinical condition or predisposition toward disease in a patient (FDA, 2018; Gottlieb, 2018). If the CV of a test is not established, the meaning of any result from that test for an individual will not be clear, raising questions about how, or whether, the result should be returned. One challenge with research results is that the AV and CV of the tests are not always known, even when the tests are performed under a QMS; indeed, establishing AV or CV may in fact be one of the purposes of a given research study.

Establishing Analytic Validity

Methods for establishing the AV of a test may include (Jennings et al., 2009; NASEM, 2017a)

- comparison to another test measuring the same analyte;[4]
- the use of controls that contain the analyte or biomarker (possibly using controls that contain a specific amount of the analyte if the test is quantitative);
- the use of human samples known to contain the analyte or biomarker; or
- the use of samples which are admixed with a known amount of analyte to simulate a patient sample that contains the analyte.

The demonstration of AV also requires assessing a range of specimens that are known not to contain the analyte—especially specimens from patients with similar diseases who may also be tested in a clinical setting to reach a diagnosis—in order to evaluate the incidence of false-positive results (Jennings et al., 2009). However, obtaining the controls and samples of varying concentrations of analyte for establishing AV can be challenging (IOM, 2012; Mattocks et al., 2010). Some analytes, such as glucose or blood gases, are unstable and can only be accurately measured under strictly controlled specimen collection and handling conditions (Nichols, 2011). Collection, storage, and even the type of preservative used to collect the sample can affect the stability of analytes or the test accuracy. Some

[4] Analyte: any substance or constituent being subjected to analysis or on which the laboratory conducts testing (*Segen's Medical Dictionary*, 2011).

rare diseases make finding positive samples with the relevant analyte a challenge (Jennings et al., 2009; Maddalena et al., 2005). AV must take into account all specimen types that will eventually be used for testing, the cost of analysis, automation, and labor. In addition, assessing the reproducibility of test results that are performed over time, by different technologists, or at different test sites using different instruments is part of the analytic validation of a test (IOM, 2012). Some methods that are highly automated and inexpensive, such as testing for sodium or glucose levels in blood, may be validated using hundreds of samples. However, for tests with more labor-intensive or computationally complex methods, it may be necessary to validate with fewer samples (Jennings et al., 2009). The extent of AV determines how each performance characteristic of the test is known, including its accuracy, precision, linear range, limit of detection, and interference potential (Jennings et al., 2009; Magnusson and Ornemark, 2014). If AV has not been established or if only limited validation studies have been performed, the reliability of the individual results is affected.

The final step of a validation process is to write a standard operating procedure (SOP) that describes all aspects of performing the test (IOM, 2012). This includes detailing the controls to be run with each test or batch; the steps in the testing process, including the exact quantities of reagents and the timing of incubations or other steps; the validation of new lots of reagents; the documentation of testing steps each time that the test is run; and reporting requirements. Other aspects of a QMS ensure that the test SOPs are being followed each time testing is performed (WHO, 2011).

Establishing Clinical Validity

When evaluating the CV of a test, AV is assumed to have been established. As a result, the clinical scenario becomes the important consideration (Jennings et al., 2009; NASEM, 2017a). For example, the CV of a given test can depend on the purpose of the test, such as whether it is diagnostic, prognostic, or predictive. CV is generally established through the testing of positive and negative control samples as well as through testing specimens from the population being studied with and without the disease, biomarker, or analyte that the test detects (Chen et al., 2009). Case control studies and longitudinal cohort studies may be used to establish CV in the diagnostic setting as long as the number of cases is sufficient (NASEM, 2017a). For prognostic and predictive tests, CV can be established with, respectively, longitudinal observational studies and clinical trials. Prognostic CV also can be established with the control arm of a clinical trial. CV can evolve over time, with additional use of the test for purposes or diseases other than those initially assessed during test validation, especially as the test is used in clinical practice and further characterized through additional research (NASEM, 2016).

Implications of Pretest Probability for Test Result Interpretation

The prevalence of a disease in the population being tested determines the predictive value of a positive test (Flyn, 1996; Jennings et al., 2009). The same test may have very good clinical performance in a high-risk population but perform poorly in predicting disease in a low-risk population. For example, a positive HIV test result is more likely to be a true positive for patients in a high-risk sexually transmitted disease clinic than for those in a low-risk population (e.g., a population that is not sexually active), where the same positive HIV test is more likely a false positive (Irwig et al., 2008). Thus, for proper context the interpretation of a test result must consider pretest probability, the patient history, and symptomology. Test results in isolation of a patient's history have a higher probability of being misinterpreted (Flyn, 1996). In the context of clinical care, clinicians order tests because a patient presents with symptoms consistent with or indicative of a particular disease. In the research context, testing is often conducted to prove a hypothesis or to support a study. Testing is not necessarily conducted, or ordered, based on a patient's pretest probability of disease and likelihood of treatment (because actions and treatment are often dictated as part of the trial protocol). Thus, pre-test probability may affect whether a research result is likely to be a true positive for an individual research participant.

LABORATORY QUALITY SYSTEMS TO INCREASE CONFIDENCE IN THE VALIDITY OF RESEARCH RESULTS

Research and clinical laboratories are held to different regulatory standards because of their different recognized purposes (Burke et al., 2014; Clayton and McGuire, 2012). Therefore, research and clinical tests are often conducted in vastly different laboratory environments—although clinical laboratories can also perform research tests.

Many research laboratories are designed to train new researchers, including graduate students and postdoctoral fellows (Bosch and Casadevall, 2017; NASEM, 2017b). They also allow for creativity and flexibility in laboratory protocols in order to foster an environment that can make cutting-edge discoveries. To this end, research laboratories have a more innovative culture with regards to assays and testing protocols. Investigators may make frequent modifications to a testing procedure in order to optimize methodologies (e.g., a novel assay may be developed for more rapid or sensitive detection of a disease) or to answer a specific scientific question. These practices are distinct from those of clinical laboratories, which do not experiment with testing methods and are required to train their staff in quality essentials, process control, documentation, and common sources of pre-analytic and analytic error in order to help maintain specimen control, assay

validity, and reproducibility (American Academy of Family Physicians, 2018).[5] Clinical laboratories are regulated to ensure adherence to more stringent quality standards because their results are designed to be used for clinical decision making. By contrast, the needed flexibility in many research laboratories means that their practices may not align with those required of clinical laboratories.

Research laboratories lacking CLIA certification may still maintain high standards for quality, and in some cases their quality assurance and control processes may even exceed the quality requirements established by CLIA. For example, the committee heard at its public workshop in September 2017 that some genome sequencing results generated by the Clinical Sequencing Evidence-Generating Research (CSER) consortium were less prone to error than results from CLIA-certified laboratories. This was because the CSER laboratory was highly automated and less prone to human error than the CLIA laboratory that was conducting the confirmation testing and not using the same automation.[6] While this laboratory was highly automated with set SOPs, other research laboratories may not have established internal operational standards or may not meet any formal recognized quality standards. The lack of adherence to a formal standard limits investigators' ability to demonstrate the validity of their results.

CLIA

The CLIA requirements for clinical laboratories ensure the quality and integrity of clinical testing, accurate documentation of test validation and test performance, and the comparability of test results regardless of the personnel conducting the testing or the test location.[7] To achieve CLIA certification, laboratories are required to have various systems in place to meet the standards for AV (American Academy of Family Physicians, 2018),[8] but the regulations do not prescribe the design or implementation of those systems. They do not, for example, define specific methods or standards for how to demonstrate the performance characteristics of a test. The laboratory director is required to meet all CLIA regulatory standards for quality and safety and is held accountable to CLIA inspectors who perform on-site assessments of regulatory compliance of

[5] 42 C.F.R. § 493.

[6] Testimony of Rex Chisholm of Northwestern University, eMERGE, at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[7] The enactment of CLIA 1988 and the regulation of clinical laboratories on a national scale followed public outcry in response to scandals reported in *The Wall Street Journal* involving commercial laboratories that had inaccurately analyzed Pap smears resulting in the deaths of several women (Yost, 2003).

[8] 42 C.F.R. § 493.

non-waived testing every 2 years.[9] The laboratory director is also accountable to the physicians and patients who rely on the quality of the laboratory services. This accountability and partnership between the laboratory director and the clinician is critical to protecting patient safety and strengthens confidence in the reliability of any test results used for clinical care.

A laboratory seeking CLIA certification or accreditation must apply for a certificate, pay a biennial fee (which can be as low as $150, but depends on the type of laboratory and tests performed there) (American College of Physicians, 2014), comply with the regulatory requirements of CLIA or another accrediting agency recognized by CLIA, and agree to be inspected at least every 2 years. Depending on the complexity of the test methods used in a laboratory, those checking compliance with the regulatory standards will examine such things as analytic validation of test performance; written SOPs with documentation showing that the SOPs are being followed; staff qualifications, training and ongoing educational requirements, and regular ongoing competency assessments; instrument validation and maintenance; the proper handling and verification of reagents; general laboratory safety; and a QMS to control the handling and processing of samples from test order through collection, transportation to the laboratory, processing, analysis, reporting of test results, and investigation of issues of non-conformance with laboratory SOPs or other errors.[10] In addition, CLIA-certified laboratories performing non-waived testing are required to participate in proficiency testing on a regular basis using specimens sent from an external source approved by CMS (CMS, 2014b). Alternative methods for proficiency testing can be used by clinical laboratories when external proficiency testing is not available. Proficiency testing is required a minimum of twice per year, using multiple samples for each assessment, and must be conducted for each test performed by the laboratory (CMS, 2014b).

Although CLIA has significantly improved the quality of clinical laboratory results used in medical decision making (Ehrmeyer and Laessig, 2004), its requirements are not always appropriate for the kinds of testing performed in the research context, such as tests relevant to biomonitoring for environmental contaminants (NRC, 2006; Ohayon et al., 2017). One investigator noted that "CLIA certification does not cover lab work for the majority of chemicals measured in biological or environmental media samples, but rather is primarily relevant for diagnostic and treatment-related tests such as genetic screening and cholesterol measurements" (Ohayon et al., 2017, p. 144). While laboratories may meet the quality controls and assurance that CLIA mandates, "the lack of well-validated

[9] On-site testing every 2 years is required for laboratory sites performing non-waived testing. Certificate of waiver (COW) laboratories and provider performed microscopy facilities are not routinely inspected or surveyed (CMS, 2014a). More than half of CLIA certificates are for COWs (184,298), sites limited to performing only waived tests. Approximately 16,000 sites have a certificate of accreditation for more complex testing (CMS, 2018).

[10] 42 C.F.R. § 493.

methods for measuring some cutting-edge biomonitoring analytes precludes their ability to be accredited" (Ohayon et al., 2017, p. 144).

Moreover, with the rapid pace of technological innovation (e.g., DNA sequencing technologies), CLIA regulatory requirements are outdated (Ferreira-Gonzalez et al., 2008). For example, CLIA requirements are "inadequate to ensure the overall quality of genetic testing because they are not specifically designed for genetic tests and because they do not give sufficient emphasis to pre- and post-analytic phases of testing" (Task Force on Genetic Testing, 1997). One particular concern is that current CLIA requirements do not address the complexity of the informatics analyses, interpretation, and reporting that are required for next-generation sequencing (NGS) technologies or other omics testing (Gargis et al., 2012). Addressing these gaps has been a focus of several U.S. and international workgroups (Aziz et al., 2014; Euformatics, 2017; Gargis et al., 2012; Rehm et al., 2013; Task Force on Genetic Testing, 1997). However, NGS testing is just one example of how technology, including newer "omics" technology, is rapidly influencing research and health care more broadly. The challenge will be for regulators and their requirements for quality systems to keep pace with the rapidly changing clinical testing environment.

Some organizations that CMS has approved to issue CLIA accreditation have quality standards for NGS tests and other more complex testing methods. CLIA allows CMS-approved organizations to inspect and otherwise ensure that CLIA requirements are met by the clinical laboratories when the requirements of the accrediting organizations are equal to or more stringent than CLIA requirements (CMS, n.d.; Yost, 2003). Accrediting organizations with the authority to certify clinical laboratories under CLIA include the College of American Pathologists, American Association for Laboratory Accreditation, COLA, and others (CMS, n.d.). The College of American Pathologists and the New York State Department of Public Health are two examples of accrediting organizations that have quality standards for NGS tests and other more complex testing methods (Aziz et al., 2014; New York State Department of Health, 2016). Thus, laboratories conducting cutting-edge research and considering pursuing CLIA certification may find more value in certification through an accreditation organization with standards that align with the testing performed in research laboratories rather than with CLIA.

CLIA and the Return of Individual-Specific Research Results

Under the current CMS interpretation of CLIA, if research laboratories return individual research results to participants, the laboratory must be CLIA certified. While the direct cost of CLIA certification is not prohibitory, meeting the requirements to obtain the certification by compliance with all of the regulatory standards would come with significant costs for most research laboratories (Barnes et al., 2015), although the extent of the burden would depend on the

infrastructure and processes already in place in the laboratory.[11] Most research laboratories operate under the direction of a single principal investigator (PI), and many investigators have never worked in a clinical laboratory setting and may not be familiar with the quality procedures, proficiency testing, and software required for CLIA certification. To begin the process of becoming CLIA certified, each PI would likely need to hire a consultant to provide guidance, pre-inspection evaluations, competency evaluations, and laboratory management plans as well as to obtain proper software for logging laboratory samples, reagents, and other processes (Riedl and Dunn, 2013; Robins et al., 2006). To obtain this type of guidance and to assemble the necessary infrastructure for meeting CLIA standards, including laboratory personnel requirements, would require funding and institutional support. This could divert research resources from the conduct of research to the process for CLIA certification. The Secretary's Advisory Committee on Human Research Protections (SACHRP) considered the challenges that would be associated with research laboratories wishing to return results becoming CLIA certified and concluded that it would not be realistic, "as it would impose tremendous, new transaction costs on research and could even lead to the elimination of some research laboratories and the consolidation of others, which would reduce research opportunities overall" (SACHRP, 2015).

Research tests used in clinical decision making, such as some tests conducted in the course of a clinical trial, must be performed in a CLIA-certified laboratory. As alternatives to pursuing CLIA certification, investigators can outsource testing to a CLIA-certified laboratory, can have only those results that will be returned retested in a CLIA-certified laboratory for verification prior to disclosure, or can build or modify an existing laboratory or core facility to make it CLIA compliant. Not all clinical laboratories will have the resources to validate and perform research tests, and sometimes no equivalent test exists, in which case other clinical tests may not be available to assess the significance of the research result. In the latter situation, creating a CLIA-compliant core facility would not be without challenges. For example, the University of Maryland School of Medicine worked to make a genomics core facility CLIA-compliant. A report on that experience concluded that it was "not without difficulty" and offered a list of challenges that anyone taking on such a task could expect to face, including the need for

> (1) a CLIA-qualified director as well as qualified key personnel; (2) appropriate space to allow for a unidirectional work flow separating pre- and post-amplification processes; (3) developing a validation study and implementation for each assay offered and participating in a CLIA-approved proficiency test or sample exchange program; (4) having an experienced quality program manager to oversee the quality program and document management system; (5) having

[11] Testimony of Karen Dyer of CMS at an open session of Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on July 19, 2017.

> the financial resources to invest in developing and operating this unique regulatory environment. (Ambulos, 2013, p. S21)

Given the diversity of research activities that use human biospecimens, it may not be reasonable to expect that all research laboratories performing testing on human biospecimens meet CLIA standards in order to return research results, particularly given the operational challenges of becoming CLIA certified discussed above. If a laboratory plans to return results that are *not* intended for clinical decision making in a study protocol, the laboratory should consider the use of other quality systems (see Box 3-1 on the committee definition of results not intended for clinical decision making in a study protocol). For the purposes of this report, results not intended for clinical decision making in a study protocol include results that have no known or established clinical implications as well as those with potential medical value but which require confirmation prior to a clinical response.

While other recognized laboratory quality standards, such as those from the ISO,[12] allow flexibility in approaches while still supporting technical rigor (Thelen et al., 2015), they generally have requirements that are similar to or even more stringent than those of CLIA (see Table 3-2 at the end of this chapter).[13] Consequently, adopting such standards may present hurdles similar to CLIA certification for investigators who want to return research results. For an investigator or institution considering implementing a recognized laboratory quality standard, many factors should be considered, such as legal obligations to obey state and federal laws, the type of laboratory, the type of testing, cost, institutional support, training, and other variables. Put simply, "one-size quality program does not fit all" (NCI, 2016). In fact, given the variety of laboratory tests, including the use and development of cutting-edge tests and the assessment of novel analytes, the quality systems used by clinical laboratories may not be the most appropriate for research laboratories; however, they may serve as guidance for laboratories considering the adoption of quality practices.

While CLIA is especially critical when results will be used in clinical decision making, many research laboratories are generating results that are not for use in clinical decision making. In these cases, the best way to ensure laboratory quality controls are in place may be through the adoption of a QMS designed specifically with research laboratories in mind and tailored to the nature of the research being conducted. There is a great deal of momentum in this area and immense interest in improving research laboratory rigor and quality, although an alternative quality management system for research laboratories has not yet been established.

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[12] ISO accreditation is not a legally permitted alternative to CLIA certification for laboratories conducting clinical testing in the United States.

[13] Testimony of Randy Querry of the American Association for Laboratory Accreditation at a public webinar of the at the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 7, 2017.

BOX 3-1

Results Not Intended for Clinical Decision Making in the Study Protocol

The committee categorized research test results generated in research laboratories based on how the test results will be used in the context of the study protocol. Research results intended to inform clinical decision making for study purposes, such as liver function tests that could affect the clinical management of a participant within the study, should be generated under the same quality standard used for clinical tests—i.e., the test should be performed in a CLIA-certified laboratory.

In many circumstances, however, results will not be used for clinical decision making in a study because they are exploratory and their health implications are unknown or unvalidated. For example, the initial results of a study seeking to identify a new biomarker associated with a disease generally should not be used to influence the clinical management of participants until such findings are independently validated. In other circumstances, a result will have known clinical or health implications for a participant but should not be used for clinical decision making without further evaluation and testing. These types of results may be anticipated by investigators or arise in a study as unanticipated results. For example, investigators conducting genome sequencing to identify a new variant associated with a disease may also identify a clinically relevant variant that has a known association with another condition. If such testing is not conducted in a CLIA-certified laboratory, the clinically relevant variant should not be used for clinical decision making but should prompt consultation with a clinician and discussion about confirmatory testing prior to a clinical response. If an investigator offers this type of research result to a participant (or returns it upon participant request), the communication must clearly convey that the result should not be used for clinical decision making without further evaluation by a clinician and confirmatory testing (see Chapter 5 for additional discussion on communicating results to participants). By returning the research result with this qualification, the investigator is not providing information for use in clinical decision making on the basis of the research test alone.

BOX 3-1, CONTINUED

The decision about whether a research result implies that further evaluation is warranted can only be made through consultation between the participant and a health care provider familiar with the participant's clinical circumstances. For example, the participant's genetic risk status may already be known; or the participant may have co-morbidities that make further evaluation inappropriate. Conversely, confirmation of the result in a CLIA-certified laboratory, as ordered by a physician, might contribute to decision making regarding the participant's care. The investigator often is not in a position to make such follow-up recommendations (unless the investigator also serves as the participant's clinician) and should not be placed in the position of doing so. Rather, the investigator should provide what information he or she can about the potential implications, so that the participant and his or her health care provider can have the information needed to decide the appropriate next steps.

CONCLUSION: When individual research results are intended for use in clinical decision making, tests must be performed in laboratories that are CLIA certified.

CONCLUSION: When individual research results are not intended for use in clinical decision making in a study protocol, CLIA certification may not be an appropriate or necessary mechanism to ensure that research test results are of sufficient quality to permit their return. However, no alternative accepted quality standard exists for such research laboratories.

Establishing Quality Management Systems for Biomedical Research Laboratories

Human biospecimens in research

are subject to a number of different collection, processing, and storage factors that can significantly alter their molecular composition and consistency. These biospecimen pre-analytical factors, in turn, influence experimental outcomes and the ability to reproduce scientific results. Currently, the extent and type of information specific to the biospecimen pre-analytical conditions reported in scientific publications and regulatory submissions vary widely. To improve the quality of research utilizing human tissues, it is critical that information

> regarding the handling of biospecimens be reported in a thorough, accurate, and standardized manner. (Moore et al., 2011, p. 57)

These pre-analytical procedures are especially critical when individual research results will be returned to participants, as it documents sample handling, which contributes to confidence that the sample was processed appropriately in a way that preserved the analyte being tested and ensured that the result belongs to a specific individual participant.

In academic biomedical research laboratories, laboratories are not centrally regulated, and the PI sets requirements for quality and monitors compliance with those requirements (Bosch and Casadevall, 2017), although research sponsors or scientific journals may mandate quality standards as part of funding or publication requirements, respectively.[14] The lack of common regulation is not a flaw in the system. Rather, the validation of research results is expected to occur through integrity in the scientific process. In this system, results are verified by peer review and confirmed by other scientists who replicate the results. "In other words, there is no official seal of approval—quality assurance comes from the expert judgment of communities of scientists, who are supposed to be able to filter out the good from the bad on their own" (White, 2015).

However, the widely reported concerns regarding the lack of reproducibility in science may drive changes in the requirements for research laboratories and motivate the development of quality standards or the training of PIs in basic quality management (Begley et al., 2015; Calabrese and Palm, 2008; Collins and Tabak, 2014; Davies et al., 2017; Loew et al., 2015; McNutt, 2014; NIH, 2017b; Titus and Bosch, 2010). The reasons behind the reported reproducibility problems are varied and may include increased scrutiny, the complexity of experiments and statistical methods, pressures on investigators to publish leading to inadequate repetition or even falsified data (Baker, 2016), and a failure to embrace best practices in preclinical study design (Grens, 2017; Vahidy et al., 2016). The lack of reproducibility in biomedical research is concerning because it impedes the translation of research discoveries into clinical practice (Perry and Lawrence, 2017). Some contributing factors can be controlled by implementing quality measures or adopting a QMS.

Although most research laboratories are not formally regulated, some nascent efforts are encouraging the adoption of voluntary quality assurance processes to improve the integrity of the science and to address issues with reproducibility (Calabrese and Palm, 2008; Freedman and Inglese, 2014; Glick and Shamoo, 1993; Herman and Usher, 1994; Scientific Working Group on Quality Practices in Basic Biomedical Research, 2001; Volsen et al., 2004). NIH, for example, has

[14] Testimony of Rebecca Davies of the University of Minnesota at a public webinar of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 7, 2017.

acknowledged that reproducibility is an issue and is taking steps to address quality in pre-clinical research as well as in research on biospecimens (Collins and Tabak, 2014; Engel et al., 2014; NCI, 2011). In fact, a workshop held at the National Cancer Institute (NCI) that discussed biospecimen reporting standards resulted in the development of the Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines. These reporting requirements detail the elements that should be reported in order to improve the evaluation and quality of the data generated from biospecimens. The elements that were identified are tiered and

> prioritized according to the relative importance of their being reported. The first tier, items recommended to report, includes information such as the organ(s) or the anatomical site from which the biospecimens were derived and the manner in which the biospecimens were collected, stabilized, and preserved. . . . Each reporting element included in [the] guidelines is backed by evidence that the factor could have an effect on the integrity and molecular characteristics of the biospecimen or on the ability to perform certain assays on the biospecimen and obtain reliable results. (Moore et al., 2011, p. 59)

Tier 1 BRISQ reporting requirements are shown in Table 3-1. While this list does not include all of the biospecimen quality requirements that should be met for the return of research results, it does provide an example foundation of simple-to-implement procedures that laboratories conducting research on biospecimens can begin executing now in order to improve pre-analytic quality.

Several other organizations, including many outside the United States, are also working in this area. In 2013, for example, the Global Biological Standards Institute published *The Case for Standards*, which emphasizes the benefits of adopting widespread quality standards in order to improve the quality of the biological sciences (Global Biological Standards Institute, 2013). WHO issued a handbook on quality practices in basic biomedical research outlining for

> institutions and researchers the necessary tools for the implementation and monitoring of quality practices in their research, thus promoting the credibility and acceptability of their work. The handbook highlights non-regulatory practices that can be easily instituted with very little extra expense. (Scientific Working Group on Quality Practices in Basic Biomedical Research, 2001, p. 2)

Several ongoing initiatives in Europe are aimed at producing guidance and recommendations to assist investigators in meeting quality management essentials (EQIPD, 2017; PAASP, 2018b). Box 3-2 briefly describes several European initiatives that have been set up to establish standardized quality practices and improve data quality in research.

In the United States there is currently no standardized QMS for biomedical research laboratories that accommodates the wide variation in laboratory procedures, that can be adopted or modified to suit the study context, and that

TABLE 3-1 Quick-Reference Biospecimen Reporting for Improved Study Quality Summary/Checklist: Tier 1 Items to Report If Known and Applicable

DATA ELEMENTS	EXAMPLES
• **Biospecimen type**	Serum, urine
Solid tissue, whole blood, or another product derived from a human being	
• **Anatomical site**	Liver, antecubital area of the arm
Organ of origin or site of blood draw	
• **Disease status of patients**	Diabetic, healthy control
Controls or individuals with the disease of interest	
• **Clinical characteristics of patients**	Premenopausal breast cancer patients
Available medical information known or believed to be pertinent to the condition of the biospecimens	
• **Vital state of patients**	Postmortem

Alive or deceased patient when biospecimens were obtained

- **Clinical diagnosis of patients** — Breast cancer

Patient clinical diagnoses (determined by medical history, physical examination, and analyses of the biospecimen) pertinent to the study

- **Pathology diagnosis** — HER2-negative intraductal carcinoma

Patient pathology diagnoses (determined by macro- and/or microscopic evaluation of the biospecimen at the time of diagnosis and/or prior to research use) pertinent to the study

- **Collection mechanism** — Fine-needle aspiration, preoperative blood draw

How the biospecimens were obtained

- **Type of stabilization** — Heparin, on ice

The initial process by which biospecimens were stabilized during collection

- **Type of long-term preservation** — Formalin fixation, freezing

The process by which the biospecimens were sustained after collection

- **Constitution of preservative** — 10 percent neutral-buffered formalin, 10 U.S. Pharmacopeia heparin units/mL

continued

TABLE 3-1, Continued

The make-up of any formulation used to maintain the biospecimens in a nonreactive state	
• **Storage temperature**	–80°C, 20°C to 25°C
The temperature or range thereof at which the biospecimens were kept until distribution/analysis.	
• **Storage duration**	8 days, 5–7 years
The time or range thereof between biospecimen acquisition and distribution or analysis	
• **Shipping temperature**	–170°C to –190°C
The temperature or range thereof at which biospecimens were kept during shipment or relocation	
• **Composition assessment and selection**	Minimum 80 percent tumor nuclei and maximum 50 percent necrosis
Parameters used to choose biospecimens for the study	

SOURCE: Moore et al., 2011.

BOX 3-2

European Initiatives for Laboratory Quality

- **THE EUROPEAN QUALITY IN PRECLINICAL DATA (EQIPD) PROJECT** – aims to facilitate sustainable solutions for data quality (EQIPD, 2017).
- **PARTNERSHIP FOR ASSESSMENT AND ACCREDITATION OF SCIENTIFIC PRACTICES** – aims to "improve pre-clinical research quality by introducing standards to applied research to enhance robustness and trust in scientific theories" (PAASP, 2018b). A partner in the EQIPD program and funded by the Innovative Medicine Initiative (PAASP, 2018a).
- **THE PREMIER (PREDICTIVENESS AND ROBUSTNESS THROUGH MODULAR IMPROVEMENT OF EXPERIMENTAL RESEARCH) PROJECT** – aims to develop a structured quality assurance system for preclinical academic biomedicine. Compliance with the quality standards therein established would be assessed through new forms of auditing ("peer auditing") (Berlin Institute of Health, 2017, 2018).

documents the data elements that affect result validity. The development of such a system would allow investigators, journal editors, research sponsors, and regulators to better evaluate, compare, and reproduce experimental results, thereby bolstering confidence in the validity of research results that may be returned to participants. The potential benefits to the research enterprise extend beyond the issue of return of results and address a broader need for improved reproducibility and rigor (as discussed in this section above). But while this would improve research, it is important to note that any results that were to be used in clinical decision making in a study protocol would still need to be generated in a CLIA-certified laboratory in order to protect patient safety.

As detailed above, support is growing among investigators, sponsors, and regulators in the United States for the development of a standardized QMS for biomedical research laboratories. However, given the myriad of interested and invested parties, a coordinated effort will be needed with all stakeholders at the table to provide input on the quality system elements and key implementation processes. Many government agencies, private institutions, pharmaceutical companies, and patient organizations are sponsoring and participating in research that

would benefit from the development and use of a QMS for biomedical research laboratories. A joint effort by these stakeholders would increase efficiency and avoid waste, redundancy, and confusion on the part of investigators from different quality standards across sponsors and funding agencies. Investigators funded by both an NIH and a Centers for Disease Control and Prevention (CDC) grant, for example, would not need to implement different quality practices because both agencies would have agreed upon and would require the same QMS.

NIH, as the predominant sponsor of biomedical research in the United States, would be an obvious choice to lead this effort, especially given the groundwork already begun by NCI (Moore et al., 2011; NCI, 2011). The engagement of the relevant federal agencies, including CMS, FDA, and CDC, as well as nongovernmental stakeholders such as the Patient-Centered Outcomes Research Institute, private-sector research sponsors, scientific professional societies, and participant and patient advocacy groups will be critical to ensuring that diverse perspectives are taken into account and thus to ensure that the QMS will be broadly applicable across all types of biomedical research. The involvement of the relevant stakeholders at the earliest steps and throughout the development and into the implementation of the new QMS may help to mitigate the kinds of concerns about lack of flexibility and applicability that arose in 2014 when NIH released new guidelines for preclinical research intended to address rigor in research and scientific publishing (Baker, 2015; Haywood, 2015; NIH, 2017a).

Recognizing that the purposes and methodologies of laboratories engaged in biomedical research are highly variable, the committee does not expect that the required quality practices for laboratories across the translational spectrum should be the same. The committee stresses the importance of a tiered system, akin to that recommended for the BRISQ reporting requirements (discussed above, see Table 3-1). One could envision rubrics for quality being developed that could be adjusted based on the nature of the research and on whether results will involve human biospecimens or be returned to research participants. Attention will need to be given to allowing flexibility in the biomedical research QMS so that it can evolve and be updated over time, as the system is adopted and used by more laboratories and as new technologies are developed. An ongoing advisory committee to review and provide guidance on needed updates, analogous to the Clinical Laboratory Improvement Advisory Committee (CLIAC)[15] (CDC, 2018a), may be considered. It is not just technologies that will evolve, however, but science as well, and as scientific knowledge progresses, interpretations and terminologies will regularly need to be verified and harmonized across disciplines. NCI's Thesaurus

[15] "CLIAC, managed by the Centers for Disease Control and Prevention (CDC), provides scientific and technical advice and guidance to the Department of Health and Human Services (HHS) related to improvement in clinical laboratory quality and laboratory medicine practice, as well as revision of the CLIA standards. The Committee includes diverse membership across laboratory specialties, professional roles (laboratory management, technical, physicians, nurses), and practice settings (academic, clinical, public health), and includes a consumer representative" (CDC, 2018b).

initiative, for example, conducts an ongoing review of the literature to provide reference terminology for research and clinical care that stakeholders can reference and use. Efforts to achieve consensus on definitions, terminology, and standards are also systematically occurring in the genetics field (Caudle et al., 2017; NCI, 2018; Ritter et al., 2016), and to aid in the effective implementation of the QMS across the range of biomedical research, standard terminology for research outside of the field of genetics may need to be developed (as has been done by the Clinical Data Interchange Standards Consortium [CDISC] and its data standards for Alzheimer's disease research) (CDISC, 2011a,b). This will be particularly important if the results generated in laboratories might be used to inform clinical decision making, as clinicians may need to translate research terms to terms more commonly used in clinical practice, making data and terminology standards for interoperability particularly important. However, it should be noted that while standardization will be important, it will not ensure data quality (IOM, 2013b).

A central element of established quality management systems, such as CLIA, is a method for evaluation and external accountability to demonstrate that quality standards are being met by a laboratory. In the absence of a system for independent verification (i.e., inspection by external experts without conflict of interest or intractable bias toward any one investigator or, perhaps even bias toward the institution), determining which laboratories are adhering to quality essentials is challenging. In the development of the NIH-led QMS, stakeholders will need to consider a system of accountability. Several models could be considered, but it will be important to have a body independent of the laboratory that will perform ongoing (e.g., annual or biennial) assessments to verify that the defined standards are being met. The external monitoring function could be housed within the research institution, as is currently the case for institutional biosafety committees; it could be done through an accreditation model similar to that used for clinical laboratories; or the NIH-led stakeholder group could establish a review workgroup to conduct the assessment. Ultimately, the monitoring process will be up to the NIH-led stakeholder group, but external accountability will be critical if research results are to be returned to participants.

With proper representation, an externally accountable QMS that details best practices for laboratories across the biomedical research spectrum has the potential to improve the conduct of research, address current gaps in training and practice, and benefit the whole of the research enterprise. While potentially all research laboratories would benefit from a QMS to improve the reproducibility of their science, the committee was asked to focus on research using human biospecimens. Initiating the development and implementation of a QMS for research that tests human biospecimens would be more limited in scope and more easily tailored than a research-wide QMS. Such a program would also acknowledge the value and potential scarcity of human biospecimens and the participants who contribute to the success of the medical research enterprise.

Recommendation 2: Develop a Quality Management System for Research Laboratories Testing Human Biospecimens.

NIH should lead an interagency effort including nongovernmental stakeholders to develop an externally accountable quality management system for non-CLIA-certified research laboratories testing human biospecimens.

Review of Quality Practices for the Return of Research Results

The committee recognizes that the proposed NIH-led QMS discussed above will not be immediately developed or implemented. In fact, it is likely that once such a standard is developed, the implementation of the system would take several years as investigators, institutions, and other stakeholders become familiar with the requirements and begin to establish the infrastructure, training, and other required support (infrastructure requirements are discussed in more detail below; see section "Addressing Resource and Infrastructure Needs in Research Laboratories to Enable Return of High-Quality Individual Research Results"). Given the extended time-frame necessary for implementation, institutions would benefit from the development of interim processes to assess the quality of research testing conducted by investigators planning to return results from human biospecimens. For example, an institutional review board (IRB) may still approve the disclosure of research results generated in a laboratory without CLIA certification or another recognized QMS when the quality of the laboratory analysis is deemed sufficient and the risks of return are considered low, as long as information is provided regarding the limits of the test's validity (see Recommendation 3c). The limits of test validity will not be a standard definition and will vary based on the test used and the extent of knowledge—i.e., what is currently known about the analyte of interest, the extent to which it has been researched and published on, and what may need to be experimentally completed to provide the test in routine practice.

Implementing this type of review process will likely require training and funding for IRBs and their institutions as IRBs may not have the necessary expertise to review laboratory quality. When expertise in quality essentials is lacking, institutions will need to hire staff with the appropriate expertise, solicit training in quality management practices for their current staff, consult with an external advisor with expertise in quality practices, or work with scientific review committees so that they are able to review laboratory practices. With the proper expertise, this review could be performed through the use of a central IRB, and decisions could be expedited, when appropriate. For research laboratories at academic medical centers, the pathologists and laboratory scientists who oversee the clinical laboratories at the academic hospital may be an excellent resource for the expertise needed to review laboratory quality practices, the quality of the laboratory

tests,[16] and for the implementation and oversight of a QMS in the research setting, whether it is the NIH-led QMS (see Recommendation 2) or another.

In addition to the quality practices of a laboratory, the characteristics of the tests being used will be important for IRBs to consider. Tests in the development phase (intended for either research use or clinical use) may not generate results that are appropriate for return because their validity may still be in question—once validity testing is performed, results could be returned to participants; however, the test would have to be run in the proper laboratory environment following proper protocols. Some specific test performance characteristics as described in CLIA will be important to consider. These include, but are not limited to, precision, analytic measurement range, accuracy (either diagnostic or correlation with other well-characterized assays), analytic reportable range (i.e., sensitivity at the low end or the ability to dilute high-concentration samples above the linear range and what diluents have been validated), interferences, carry-over, and clinical validity. Enabling return from novel, validated tests would require institutional oversight to ensure scientific integrity and proper research and reporting practices.[17]

As part of the NIH-led QMS development process, stakeholders could define a more exact role for the IRB and perhaps develop a checklist to aid in IRB review of study protocols and design. Initially this guidance could be based on the experiences of IRBs or oversight boards already involved in making decisions around the return of research results. For example, some IRBs are already playing a role in the return of research results and provide guidance for the disclosure of research results to participants from non-CLIA-certified laboratories on a case-by-case basis (Office of Ethics and Compliance, 2017). Additionally, informed cohort oversight boards (ICOBs) have been formed in response to the need of IRBs to handle the return of results—specifically, how they will be returned if they are to be returned (see Box 3-3). ICOBs are most often, but not always, associated with a biobank and may provide insight and guidance to IRBs as the return of research results becomes more expected and routine.

Regardless of their approach to the review, however, IRBs will need to assess the critical elements needed for quality assurance. A list developed by NCI of the

[16] The quality of the laboratory tests could be assessed, for example, by knowing the quality systems used in the research laboratory that generated the result as well as by a review of the documentation of the handling and testing of the specific participant's sample, similar to how it is done with CLIA.

[17] There are many research results derived from research with human participants that do not entail removing a biospecimen from the body. The development of an algorithm for insulin delivery, for example, might involve measuring glucose by a glucometer that is worn continuously; efficacy of a medication to treat Parkinson's disease may involve measuring initiation of, or frequency of, movement through a smart phone application; mobile health technologies may be important "research tests" in the future. The development of algorithms generally, and the application of valid, quality artificial intelligence tools, are important research measures for discussion; however, they were out of scope of this committee.

BOX 3-3

Informed Cohort Oversight Boards

An informed cohort oversight board (ICOB) is an advisory body, often affiliated with a biobank or biorepository, that collaborates with an institution's IRB by providing structure and oversight to guide the return of individual genetic research results, where the option for return is allowed by institutional policy (Holm et al., 2014; Kohane et al., 2017; Wolf et al., 2012). Because of the likelihood of discovering secondary findings during the course of genetic research, these bodies were formed to address the need for ongoing, experienced assessment of whether a result should be returned to a participant. The ICOB and similar committee-based models have been used by organizations such as The Gene Partnership at the Boston Children's Hospital (Holm et al., 2014), Coriell Personalized Medicine Collaborative (Stack et al., 2011), Mayo Clinic (Mayo Clinic, 2018), and Electronic Medical Records and Genomics Network (McCarty et al., 2011) to assess the benefits and harms of return and to carry out return where applicable. According to Wolf et al., a potential benefit to a model like the ICOB is the ability to concentrate the review and oversight of the return of results in a single committee "that can learn from experience and build expertise over time. . . . Including in that committee not only expertise on the scientific data in question (genetic and non-genetic), but also clinical expertise such as genetic counselors, ethics expertise, and representation from the biobank contributor population allows robust analysis of the values questions involved" (Wolf et al., 2012, p. 375).

key elements needed for the implementation and auditing of quality assurance and quality control processes is provided in Box 3-4. It would also benefit the NIH-led QMS development process if it capitalized on the existing guidance for best laboratory practices already established for some tests, such as the American College of Medical Genetics practice guidelines for next-generation sequencing (Rehm et al., 2013). In addition, numerous documents exist that may provide guidance to laboratories considering the adoption of quality practices. In addition to CMS, NIH and CDC have issued key resources for proper laboratory procedures for management and quality (CDC, 2017, 2018a; Ned-Sykes et al., 2015; NIH, 2013), as have consensus groups such as the CLSI and international

BOX 3-4

Quality Assurance and Quality Control Essentials

This list in this box is from the National Cancer Institute's Quality Management Best Practices for Biorepositories and Biospecimens (NCI, 2016). While not every one of these elements may be essential in every research setting, these factors are the minimum to be considered in the development of the research quality management system. The following are key issues for quality assurance and quality control implementation and auditing:

STAFF PROFICIENCY

- Staff organization and responsibilities.
- Training and competency programs for personnel, as appropriate; e.g., training in human subjects protections and privacy regulations such as Health Insurance Portability and Accountability Act training, safety training, or bloodborne pathogen training.
- Competency assessment as documentation of training.
- Documentation of staff compliance with policies and procedures.
- Risk mitigation, disaster response, and emergency preparedness.

FACILITY INFRASTRUCTURE

- Equipment validation and change control, calibration, maintenance, repair procedures, and environmental monitoring; e.g., temperature monitoring of freezers.
- Supplier management program, including inspection and validation of reagents and other supplies.

BIOSPECIMEN CONTROL AND DOCUMENTATION

- Control of biospecimen collection, processing, and tracking.
- Documentation of biospecimen collection, processing, and tracking, with detailed annotation of pre-analytical parameters.
- Measurement and analysis of key process indicators to drive quality improvement.
- System security.

continued

BOX 3-4, CONTINUED

RECORDKEEPING AND DOCUMENT CONTROL

- Employment of a data quality management, assessment, and reporting system.
- Clinical data records.
- Accessibility of policies and procedures.
- Documentation records, including audit reports, deviation reports, and corrective action/preventive action reports.
- External document monitoring to ensure that the facility remains up to date with relevant laws, standards, and best practice publications.
- Staff training records, including record of staff adherence to training schedules.
- Data quality management (source documentation and electronic records), assessment of reporting system.
- Supply records.

INTERNAL AUDIT OF PROGRAM AND ITS POLICIES, SCHEDULED AND UNSCHEDULED

- Audit for accuracy of all annotation data; e.g., the biospecimen is where it is purported to be, in the purported volume, with the appropriate labels/identifiers.
- Audit for accuracy of patient data associated with biospecimens; e.g., age, gender, diagnosis, etc.
- Audit of compliance of biospecimen resource with institution policies; e.g., human subjects and privacy and confidentiality protections, prioritization of biospecimen use, etc.
- Audit of SOPs for all activities and processes.
    - Each biospecimen resource ensures that SOPs are written, reviewed, and appropriately approved.
    - Process exists for review and updating at designated time intervals.

SOURCE: NCI, 2016.

organizations such as ISO (CLSI, 2018; ISO, 2018). These existing guidance documents may help inform investigators and institutions interested in improving the quality of research through an interim voluntary quality management system as well as IRBs and other review committees seeking guidelines for use in assessing the quality of laboratory testing.

In addition to IRBs assessing the laboratory quality other issues will need to be considered; these include determining the relative value of return—this value may be from personal and not just clinical benefits—and the relative risk (discussed in more detail in Chapter 4).

If investigators do not adhere to quality practices in the conduct of their research, it would be inadvisable for them to return research results. However, with the appropriate laboratory quality practices in place for the given research and proper institutional oversight, return is appropriate. Recommendation 2 focuses on the development of a research-grade QMS to mirror the clinical QMS that CLIA provides. A research QMS will ensure that the results returned to participants are valid and that any interpretation of the results is backed scientifically by method validation and ongoing control processes. For example, in the case of genomics this would include attention to variant interpretation as well as to laboratory procedures. The committee recommends three pathways for ensuring the appropriate return of high-quality research results; these are detailed in Recommendation 3 and shown schematically in Figure 3-2. The pathways presented in Recommendation 3 are applicable if the research results are originally planned to be returned or if they are later returned upon request of the participant. As noted in Chapters 2 and 4, participants have the right to request their results, and when individual research results are offered, participants have the right to decide whether to receive or to share their results.

CONCLUSION: For investigators conducting research testing on human biospecimens, the adoption of an externally accountable quality management system would improve confidence in result validity and help ensure that the results returned to participants are of high quality.

Recommendation 3: Ensure the High Quality of Individual Research Results That Are Returned to Participants.

To provide confidence in the quality of research test results disclosed to participants, institutions and their IRBs should permit investigators to return individual research results if

- **A. testing is conducted in a CLIA-certified laboratory; or**
- **B. results are not intended for clinical decision making in the study protocol (as defined in Box 3-1) and testing is conducted under the externally accountable quality management system for research laboratories once established (see Recommendation 2); or**

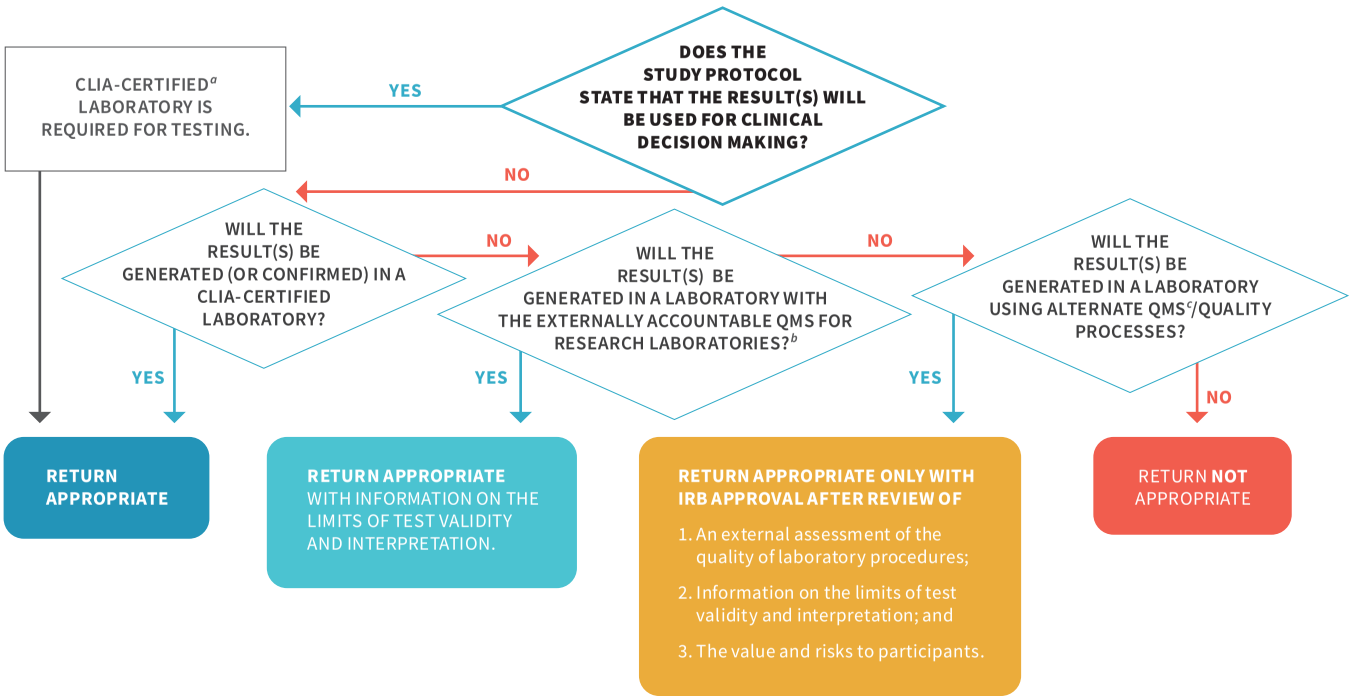
DOES THE STUDY PROTOCOL STATE THAT THE RESULT(S) WILL BE USED FOR CLINICAL DECISION MAKING?
YES
CLIA-CERTIFIED[a] LABORATORY IS REQUIRED FOR TESTING.
NO
WILL THE RESULT(S) BE GENERATED (OR CONFIRMED) IN A CLIA-CERTIFIED LABORATORY?
NO
WILL THE RESULT(S) BE GENERATED IN A LABORATORY WITH THE EXTERNALLY ACCOUNTABLE QMS FOR RESEARCH LABORATORIES?[b]
NO
WILL THE RESULT(S) BE GENERATED IN A LABORATORY USING ALTERNATE QMS[c]/QUALITY PROCESSES?
YES
YES
YES
NO
RETURN APPROPRIATE
RETURN APPROPRIATE WITH INFORMATION ON THE LIMITS OF TEST VALIDITY AND INTERPRETATION.
RETURN APPROPRIATE ONLY WITH IRB APPROVAL AFTER REVIEW OF
1. An external assessment of the quality of laboratory procedures;
2. Information on the limits of test validity and interpretation; and
3. The value and risks to participants.
RETURN NOT APPROPRIATE

FIGURE 3-2 Determining whether laboratory quality is sufficient for investigators to return individual research results.

[a] CLIA-certified includes tests run in a CLIA-certified, -accredited, or -waived laboratory.

[b] See Recommendation 2.

[c] Such as from the International Organization for Standardization (ISO), BRISQ reporting requirements, or other voluntary QMS (see Chapter 3).

NOTES: The above flowchart details two critical aspects in the return of individual research: (1) the use of the result in research protocols and (2) the result validity. If results will be used for clinical decision making in the study protocol, they must be generated in a CLIA-certified laboratory, and return is appropriate. If results will not be used for clinical decision making in the study protocol (see Box 3-1), there are additional pathways for the return of individual research results, as long as the result is accompanied with information on the limits of the test validity and interpretation. For IRBs to have confidence in the quality of a research result and determine that it is appropriate for return, investigators should do one of the following: (1) perform their testing or get confirmation in a CLIA-certified laboratory, (2) use the NIH-led research QMS once it has been developed (see Recommendation 2), or (3) use an alternate QMS or quality processes that a review process independent of the laboratory determines is sufficient. This flowchart is also applicable to a situation in which an investigator has an unanticipated result and is considering whether to return it to a participant. CLIA = Clinical Laboratory Improvement Amendments of 1988; DRS = designated record set; HIPAA = Health Insurance Portability and Accountability Act of 1996; NIH = National Institutes of Health; QMS = quality management system.

C. results are not intended for clinical decision making in the study protocol (as defined in Box 3-1) and the IRB determines that
   1. the probability of value to the participant is sufficiently high and the risks of harm are sufficiently low to warrant return;
   2. the quality of the laboratory analysis is sufficient to provide confidence in the result to be returned, as determined by a review process independent of the laboratory; and
   3. information will be provided to the participant(s) regarding limits on test validity and interpretation (see Recommendation 10).

B and C will require changes to the CLIA regulations, embodied in Recommendation 12, or changes to the interpretation of the CLIA regulations.

In Recommendation 3 above, the committee details situations where the return of individual research results to participants is appropriate; however, the committee acknowledges that given the current interpretation of CLIA by CMS, this will create a potential legal conflict between investigators and CMS. This is because CMS currently interprets CLIA regulations as meaning that any laboratory returning individual research results to participants must be CLIA certified (discussed in more detail in Chapter 6). Therefore, to fully implement Recommendation 3, CMS will need to change the CLIA regulations or else the CMS interpretation of the CLIA regulations to enable investigators to return research results to participants. Allowing research laboratories to return results will not affect the conduct of clinical laboratories or investigators who will generate results for clinical decision making in the study protocol, as the committee emphasizes that it is of the utmost importance that tests used for clinical decision making need to be performed in a CLIA-certified laboratory to protect participant safety.

ADDRESSING RESOURCE AND INFRASTRUCTURE NEEDS IN RESEARCH LABORATORIES TO ENABLE RETURN OF HIGH-QUALITY INDIVIDUAL RESEARCH RESULTS

Given that few research laboratories currently operate under a QMS with external accountability, significant investment in infrastructure will be needed in order to substantially increase the number of laboratories that meet quality standards necessary for the return of individual research results to participants. Investigators will likely need both guidance and assistance from their institutions and research sponsors. The initial training, cost, and time commitment will likely be high, but the value added will be considerable, both for participants and for biomedical research overall.

Challenges and Costs Associated with Implementing a Quality Management System

Despite the need for systems to be fit for purpose and to take into account the nature of the research experiences, there are a number of commonalities in the requirements for implementing a QMS at university laboratories, in departments in academic medical centers, and in research and development laboratories in industry (Hooper et al., 2018; Mathews et al., 2017; Volsen et al., 2004; Zapata-García et al., 2007). Specifically, the development of such systems requires commitment and investment on the part of the investigators, buy-in from staff and faculty across all levels of the organization, extensive training in quality practices, and the commitment and support of general management, the department, or the institution (Vermaercke, 2000).

QMSs can be met with skepticism because they are viewed as rigid, bureaucratic, and impinging on the freedom of research (Vermaercke, 2000). Nevertheless, investigators have responded positively to the implementation of quality measures despite the extra effort entailed because, generally speaking, investigators take great pride in their work and are passionate about delivering high-quality research (Volsen et al., 2004). Obtaining the necessary buy-in from investigators tasked with implementing the standards is easier when they can see how it adds value to their work (Robins et al., 2006) and when the QMS is developed through a bottom-up approach. This enables the investigators, with the support of management, to identify where their critical quality challenges in the laboratory are and to develop quality processes to address these quality gaps (Volsen et al., 2004). The necessary changes in practice and culture will only be sustainably embraced if there are proper incentives and leadership commitment from the outset (see Box 3-5).

While adopting a QMS provides many benefits to a research enterprise, implementing a quality system is not without its challenges. Laboratories and institutions will need to consider the resources necessary to institute a QMS, as the process comes with costs that are not always transparent (Vermaercke, 2000). Figure 3-3 depicts some of the costs, infrastructure, and resources needed to implement a QMS.

Personnel costs are a key expenditure. These costs include training or bringing on additional trained staff, such as quality assurance coordinators, project leaders, and several task leads. However, it is important to note that the cost of staff time drops dramatically after the system has been implemented and becomes more mature (Vermaercke, 2000). Time is another key consideration. A group in Barcelona found that the implementation of the system took a total of 18 months, even having started with part of a previous system in place (Zapata-García et al., 2007). This highlights the point that change will not be immediate. The rollout of a high-quality system will take time and concerted effort on the part of all players in order to be successful. These are just a few of the factors that must be taken

BOX 3-5

Lessons in Quality Management System Implementation from Johns Hopkins Hospital

In 2012 the pathology department at Johns Hopkins Hospital (JHH) implemented a quality management infrastructure that linked departments and supported shared accountability for improvements in patient safety and quality health care. Because of the diversity across university departments in terms of composition, size, resources, and needs, the priorities, training, and support that each required varied widely. The leadership of the initiative recognized that the quality management system needed to be flexible to accommodate innovation and autonomy while still fitting into the enterprise health system. Gaining critical buy-in from faculty and staff required extensive peer support and shared leadership (Mathews et al., 2017). The pathology department developed a quality improvement structure where committees meet monthly to regularly review, update, and receive feedback from the faculty and staff. Salary bonuses were established to incentivize participation in the design of quality improvement projects. In addition, trainees like medical residents can receive awards in quality projects (Hooper et al., 2018). The incentives, involvement, and training of their personnel at every level was identified as key to the success of JHH quality efforts, contributing to the successful implementation of a quality management system and yielding a return on investment from "greater efficiency, and safety and cost savings" (Hooper et al., 2018).

into account when making decisions about adopting a QMS. When approaching the development and implementation of a QMS, the challenges of addressing the key laboratory and institutional gaps must be balanced with the need for quality improvement (see Figure 3-4). Once these challenges are overcome the gains are substantial. Quality management systems have been shown to make work more efficient, facilitate the training of new staff, improve reproducibility, increase patient safety, and enhance data integrity (Davies, 2013; Global Biological Standards Institute, 2013).

The committee acknowledges that the return of research results to participants may not sufficiently motivate research laboratories to adopt a QMS. However, this ought not be the only consideration for laboratories deciding whether to

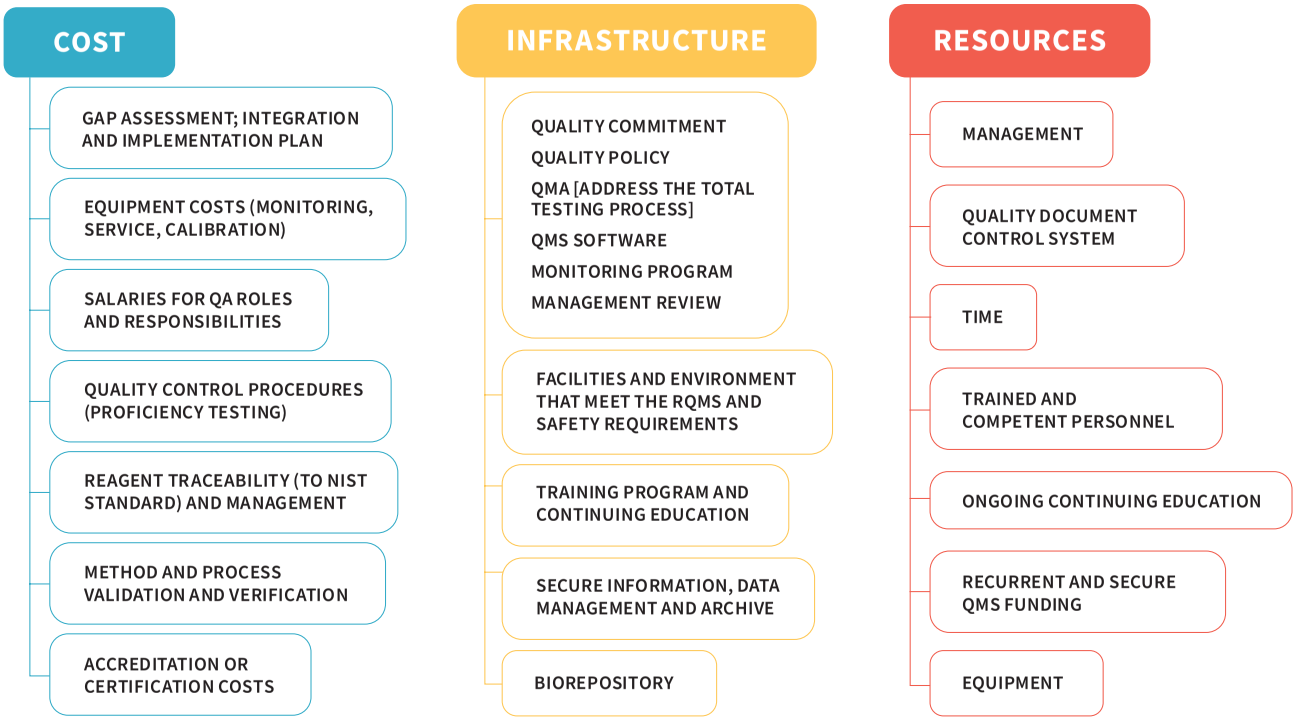

FIGURE 3-3 Costs, infrastructure, and resources needed to implement a quality management system.
NOTE: NIST = National Institute of Standards and Technology; QA = quality assurance; QMA = quality management approach; QMS = quality management system; RQMS = roll quality management system.
SOURCE: Adapted from a presentation by Rebecca Davies, December 7, 2017. -

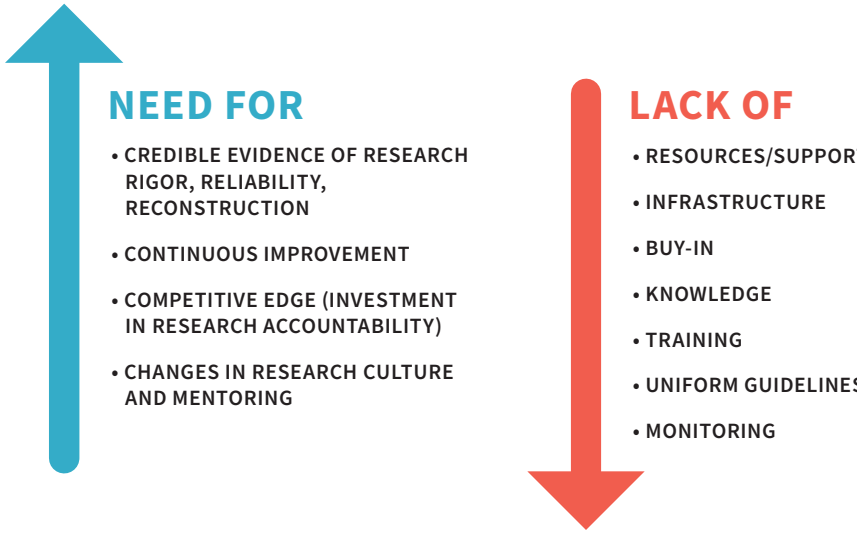

FIGURE 3-4 Opposing forces encountered by investigators when considering implementing a quality management system.
NOTES: This figure highlights the opposing factors that investigators and their institutions will encounter when considering the implementation of a quality management system (QMS). The challenges to implementation may be significant, but the need for quality is also great.
SOURCE: Adapted from a presentation by Rebecca Davies, December 7, 2017.

do so. Rather, investigators should consider how the use of a quality management system could benefit their research overall, including how it can contribute to reproducibility in science and the return on investment from research funding. See Figure 3-5 for how the implementation of standards can benefit all research stakeholders.

Institutional Support for the Generation of High-Quality Research Results

As discussed above, returning results will require assurance concerning result validity and laboratory processes and will create additional demands on investigators for quality practices beyond those required for laboratories that will not return results. As a result, institutions will need to assist investigators in tackling these additional demands. In anticipation of the NIH-led research QMS (see Recommendation 2), it would be prudent for institutions to begin initial groundwork intended to support investigators as they work to adopt the laboratory quality practices necessary for return of individual research results. This may include providing training programs in quality management for investigators, assisting

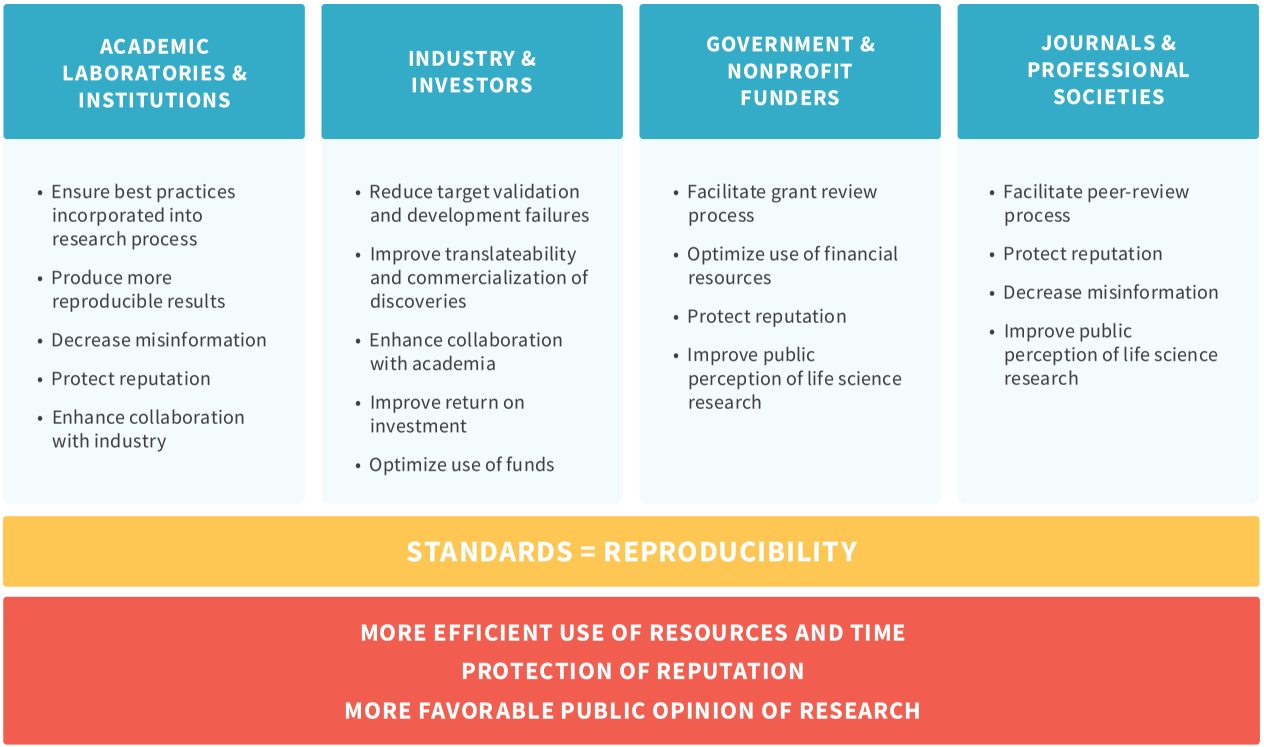

FIGURE 3-5 Systemic benefits of standards.
NOTE: This figure, developed by the Global Biological Standards Institute, highlights the fact that "research standards can be a unifying driver of quality improvement efforts and have the potential to benefit all stakeholders."
SOURCE: Global Biological Standards Institute, 2013, p. 30. -

investigators in an initial gap assessment to identify risks to data quality and integrity, and facilitating the acquisition and adoption of quality management software (for example, electronic laboratory notebooks or quality and data management software). Other institutional responsibilities may include

- educating laboratory leadership and other laboratory staff about QMS expectations;
- establishing platforms, templates, and access to expert consultants to evaluate and assess investigators' current level of quality management practices, advise the IRB, and implement quality standards;
- developing a system for laboratory inspection to support compliance with the external review of quality standards; and
- advising the investigators, IRBs, and institution as to the required compliance with the QMS, which has implications for the potential validity of research results and the ability to return research results to participants.

Numerous guidance documents discussing research laboratory quality practices are available to support institutions in these efforts, including those published by NIH and WHO (Moore et al., 2011; NCI, 2016; NIH, 2017a; Scientific Working Group on Quality Practices in Basic Biomedical Research, 2001).

Many institutions may already have resources in place that could be used to assist investigators with the generation of high-quality research results and facilitate the process of returning results to participants before a QMS is adopted. These include expert review committees that can provide guidance on necessary quality measures and core laboratory facilities that already operate under a quality management system, such as that required by CLIA. The use of core facilities may also help achieve economies of scale and serve as resources for those laboratories without adequate infrastructure to implement a QMS. For institutions without core facilities, one option would be to develop partnerships with institutions that already have established core facilities. This sharing of institutional resources could be further encouraged by NIH, which could call on institutions with federally funded core facilities—Clinical and Translational Science Awards hubs, for example—to make these accessible beyond their parent institution. Additionally, third parties may serve as resources for investigators and laboratories wishing to return results but who do not have the appropriate on-site resources. Identifying and partnering with third-party organizations for research testing performed under a QMS may require institutions to develop a working list of partners for their investigators to consider when research test results on human biospecimens will be returned to participants. Ideally, to help keep costs lower for research budgets, research pricing structures would be available or negotiated by the institution on a contract basis rather than by individual investigators.

Guidance will be needed to assist investigators and laboratories in determining whether they are best suited to pursue CLIA certification, adopt the proposed

NIH-led QMS, or leverage external resources. These decisions should be made based on the type of research that investigators conduct, the types of samples they test, and the intended use of the results as well as the potential value and risks of returning those results to participants. Adopting the NIH-led QMS will not be instantaneous, and some better-resourced institutions will be more able to take on this task. In less well-resourced institutions, there will likely be delayed implementation, but these institutions will benefit from the work of early adopters. The early-adopter institutions can create helpful tools, lessons learned, and best practices that can be shared with other institutions to facilitate their adoption of high-quality practices.

Generating valid results is only one piece of the required infrastructure for the return of individual research results to participants. The other considerations are how to assess the value and risk of returning results and the feasibility of return (discussed in Chapter 4) and how investigators untrained in lay communication and communication of test results can appropriately return results. The process of communication will require additional institutional mechanisms and financial support, as discussed in Chapter 5.

CONCLUSION: Investigators, institutions, and research sponsors will need to anticipate the needed time, costs, and resources required for adopting a quality management system to both enable the return of research results and improve research overall.

Recommendation 4: Ensure Adequate Resources and Infrastructure to Generate High-Quality Research Results.

Research institutions and funding agencies should develop and provide access to the resources and infrastructure needed to ensure that investigators conducting testing on human biospecimens can meet the necessary standards for quality so that research test results can be returned to participants (see Recommendation 3). This may include assisting investigators and their research laboratories in

- **A. training and access to resources to prepare for the future adoption of the externally accountable quality management system for research laboratories (see Recommendation 2);**
- **B. adopting the externally accountable quality management system for research laboratories once established for relevant laboratories (see Recommendation 2); or**
- **C. becoming CLIA certified or facilitating access to core, affiliated, or third-party CLIA-certified laboratories for sample testing, retesting, or a confirmatory testing process when research results are for use in clinical decision making in a study protocol.**

The research enterprise is facing growing expectations—from participants and even research sponsors, as in the case of NIH's Precision Medicine Initiative (*All of Us* Research Program, 2017; Precision Medicine Initiative Working Group, 2015)—concerning the return of research results. The quality of the research results will be a crucial factor to be weighed as investigators and institutions consider whether to return results to participants, but it is only one element in the decision-making process. The next chapter addresses two additional dimensions, value and feasibility, that will help investigators make decisions on what to return, and it describes the need for a plan and process that includes engaging participants and communities in making these determinations.

TABLE 3-2 Common Elements of Quality Systems

✓= REQUIRED	CLIA NON-WAIVED (HIGHLY COMPLEX LABORATORIES)	CLIA ACCREDITATION ORGANIZATIONS	ISO 15189	CLIA EXEMPT STATE STANDARD (NY)	VOLUNTARY STANDARD[a]
External Quality Control					
External inspections required	✓	✓		✓	
External inspections voluntary			✓		
Participation in proficiency testing from an approved tester required for regulated analytes	✓	✓	✓	✓	
Alternative performance assessment required for unregulated analytes	✓	✓	✓	✓	

continued

TABLE 3-2, Continued

✓= REQUIRED	CLIA NON-WAIVED (HIGHLY COMPLEX LABORATORIES)	CLIA ACCREDITATION ORGANIZATIONS	ISO 15189	CLIA EXEMPT STATE STANDARD (NY)	VOLUNTARY STANDARD[a]
Internal Quality Control					
Internal quality control checks required	✓	✓	✓	✓	✓
Documentation describing policies and procedures necessary to assure the quality of test results	✓	✓	✓	✓	✓
Methods, supplies, equipment, and testing are appropriate to provide results within stated performance specifications and type and volume of testing	✓	✓	✓	✓	✓
Requirements for specimen collection	✓	✓	✓	✓	✓
Established and reviewed procedures for specimen transport to and from reference laboratories (timing, record-keeping, environmental conditions, communications)	✓	✓	✓	✓	✓

✓= REQUIRED	CLIA NON-WAIVED (HIGHLY COMPLEX LABORATORIES)	CLIA ACCREDITATION ORGANIZATIONS	ISO 15189	CLIA EXEMPT STATE STANDARD (NY)	VOLUNTARY STANDARD[a]
Guidelines for specimen acceptance and rejection	✓	✓	✓	✓	✓
System for storage and use of supplies	✓	✓	✓	✓	✓
System of equipment checks, calibration, and maintenance (with records)	✓	✓	✓	✓	✓
Defined system for specimen identification, storage, handling, and tracking through all phases of testing	✓	✓	✓	✓	✓
Reportable range is established for all procedures before implementation	✓	✓	✓	✓	
System for reporting results	✓	✓	✓	✓	✓
Information management and record storage systems (tests requested, tests run, results, etc.)	✓	✓	✓	✓	✓

continued

TABLE 3-2, Continued

✓= REQUIRED	CLIA NON-WAIVED (HIGHLY COMPLEX LABORATORIES)	CLIA ACCREDITATION ORGANIZATIONS	ISO 15189	CLIA EXEMPT STATE STANDARD (NY)	VOLUNTARY STANDARD[a]
Established process for documenting and fixing failed conditions	✓ [b]	✓	✓	✓	✓
System for ensuring the privacy of the client (information management protocols) through all phases of testing	✓	✓	✓	✓	✓
Communication system in place to handle internal and external complaints and problems reported to the laboratory	✓	✓	✓	✓	
Verification for unmodified tests	✓	✓	✓	✓	✓
Verification for modified tests	✓	✓	✓	✓	✓
Personnel and Facility					
Hierarchy and personnel responsibilities are clear	✓	✓ [c]	✓	✓	✓

✓= REQUIRED	CLIA NON-WAIVED (HIGHLY COMPLEX LABORATORIES)	CLIA ACCREDITATION ORGANIZATIONS	ISO 15189	CLIA EXEMPT STATE STANDARD (NY)	VOLUNTARY STANDARD[a]
Personnel are trained, qualified, and there is sufficient staff for the work required	✓	✓	✓	✓	✓
Qualified laboratory director (a role with responsibility over the administrative oversight of the laboratory)	✓	✓	✓	✓[d]	✓
Qualified laboratory manager/ supervisor/assistant director		✓[e]	✓	✓	✓
Qualified technical consultant or supervisor (a role with responsibility over the technical oversight of the laboratory)	✓	✓[e]	✓	✓	
Qualified clinical consultant (a role that acts as a liaison between the laboratory and the client and is responsible for matters related to the reporting and interpretation of results)	✓	✓[e]	✓		
Quality Systems Manager			✓	✓	

continued

TABLE 3-2, Continued

✓= REQUIRED	CLIA NON-WAIVED (HIGHLY COMPLEX LABORATORIES)	CLIA ACCREDITATION ORGANIZATIONS	ISO 15189	CLIA EXEMPT STATE STANDARD (NY)	VOLUNTARY STANDARD[a]
Qualified laboratory testing personnel (testing of specimens)	✓	✓	✓	✓	✓
Steps taken to prevent environmental fluctuations (power or humidity fluctuations)	✓	✓	✓	✓	✓
Environment is safety-focused and has adequate space and utilities for all phases of the testing process	✓	✓	✓	✓	✓

NOTE: The table lists common elements of quality systems. A check (☒) indicates that the element is required; if there is no check, the element is not required. This table does not capture nuanced differences (for example, the number of external inspections); rather the aim of the table is to convey the common key elements in quality management systems that laboratories could consider in implementing their own quality management system.

**This table is an example of some elements present in laboratory quality systems.*

[a] The voluntary standards captured in this table are based on recommendations from the WHO and Research Quality Association (RQA) guidelines. A research laboratory voluntarily adopts a research quality management system that applies to research activity throughout the research life cycle.

[b] For CLIA this includes a "Quality assessment system to monitor, assess, and correct problems, review the effectiveness of corrective actions, revise SOPs to prevent reoccurrence, and discuss QA reviews with appropriate staff."

[c] This includes the need for written, clear, and explicit delegation of responsibilities by the laboratory director to individuals qualified to assume those duties.

[d] New York State (NYS) regulations require that there be a qualified laboratory director with responsibility over the administrative and technical oversight of the laboratory. The pertinent NYS regulations are the following:

- Section 19.1(a) of Title 10 of the New York State Codes, Rules and Regulations (10 NYCRR) defines the clinical laboratory director as the individual responsible for administration of the technical and scientific operation of a clinical laboratory or blood bank.
- 10 NYCRR Section 58-1.2(a) states that the director is responsible for direction and technical operation of the laboratory.

[e] One individual may fulfill more than one position (e.g., a laboratory director may also serve as a clinical consultant).

SOURCES: American College of Physicians, 2014; COLA, 2017; College of American Pathologists, 2017; ISO, 2007; New York State Department of Health, 2017; UN Industrial Development Organization, 2009; WHO, 2006.

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4

Processes to Enable Appropriate Decision Making Regarding the Return of Individual Research Results

Chapter 3 discusses the importance of the validity of research results that may be returned to participants, but result validity is not the only consideration for investigators deciding whether to return individual research results. This chapter addresses two other key considerations that need to be weighed by investigators on a study-by-study basis—(1) the value of the result to the participant and (2) the feasibility of returning it—and it also provides a conceptual framework to support decision making.

Given the numerous technical and operational considerations associated with the return of individual research results, investigators conducting research on human biospecimens need to consider early in their study design process whether individual results may be returned to participants. Research sponsors and institutions can ensure that such assessments are performed routinely by requiring return-of-results plans in their funding applications and institutional review board (IRB) review processes, respectively, ensuring that value and feasibility have been appropriately considered and that, when relevant, the costs of returning results are included in budgets. The return-of-research plan should take into account not only whether the investigator will offer some or all research results to participants, but also what he or she will do in the case that a participant requests results or if unanticipated results are generated that warrant disclosure. Research institutions and sponsors can also support investigators by connecting them with institutional resources, networks, and training and by engaging participants, patients, and community groups in the development of policy and guidance.

DIMENSIONS TO CONSIDER IN DECISIONS ON RETURNING INDIVIDUAL RESEARCH RESULTS

If results are to be returned to individual participants, the value, risks, and burdens associated with the return will need to be balanced. Below, the committee discusses several dimensions that influence study-specific decisions regarding whether and which individual research results should be returned to participants. These include the value of the research result to the participant and the feasibility of returning individual research results.

Value of the Result to the Participant

Resources for biomedical research—including research funding and investigators' time—have significant societal value and, accordingly, need to be carefully stewarded. If resources are to be applied to the return of individual research results, the results should have value to the participant, and the benefits of disclosing the results should outweigh the risks. The sections below address different approaches to considering value and discuss steps that can be taken to better understand the value of individual research results from the participant's perspective.

Defining Value in the Context of Returning Individual Research Results

Decision-making approaches regarding the return of individual research results have traditionally focused on several specific criteria for evaluating the expected value or usefulness of the results to participants. The factors that contribute to value include the analytic and clinical validity, clinical utility, and personal utility[1] of the results (Bookman et al., 2006; Ravitsky and Wilfond, 2006).

If analytic validity (AV) and clinical validity (CV)[2] have not been established, the results may be misleading, misinterpreted, or have uncertain meaning. This raises questions about the value to the participant of results that lack AV and CV and the appropriateness of returning them, particularly in cases where disclosure is associated with potential risks (e.g., from taking inappropriate actions or failing to take needed actions due to a false sense of security). However, since CV can change over time (IOM, 2016), uncertain meaning should not automatically rule out disclosure. For example, future research may uncover the clinical significance of a genetic variant that, at the time of a study, may have been categorized as a variant of uncertain significance.

[1] Information has personal utility if it can be reasonably used by participants for personal decision making, actions, or self-understanding (Bunnik et al., 2014).

[2] *Analytic validity* is the ability of a test to measure what it is designed to measure (NASEM, 2017). *Clinical validity* is a test's ability to identify or predict accurately and reliably the clinically defined disorder or final health or medical outcomes of interest in an individual (NASEM, 2017).

As discussed in Chapter 3, it is important to have laboratory quality management systems or peer-review processes in place in order to give stakeholders (investigators, institutions, sponsors, and participants) confidence in the validity of a study's results before they are returned to participants. In many cases, however, even when the AV and CV of a test have been established, its clinical utility may remain unclear (processes for establishing clinical utility are discussed in Box 4-1). The clinical utility of a test is an indication of whether it can provide information that can be used to inform patient–clinician decisions regarding the prevention, management, or treatment of a disease or health condition—and, in particular, information that would be expected to yield measurable improvement in clinical outcomes (Teutsch et al., 2009). The term is often used interchangeably with "clinical actionability," which is "the degree to which a result may be used to guide medical or health decisions" (MRCT Center, 2017, p. 11), though there

BOX 4-1

Establishing Clinical Utility

Determining whether a test, treatment, or other medical intervention has clinical utility (i.e., determining if the intervention makes a difference in a patient's outcome or care) often involves the conduct of randomized controlled trials (RCTs) to generate evidence of its efficacy or effectiveness. In many biomedical research studies, however, research findings may be too early in the translational research pipeline to warrant the costs and resources of an RCT, in which case their clinical utility may need to be assessed in other ways. Initial evidence for the clinical utility of a test also may be obtained by a retrospective analysis of specimens from an RCT relevant to the biomarker or test results; such results may then justify a prospective RCT in which patient outcomes are assessed when the test is actually used for clinical decision making. For some genetic tests, clinical utility is considered to have been demonstrated if the link to disease causation is strong and the disease can be treated. For example, the American College of Medical Genetics and Genomics recommends disclosure of test results related to 59 genetic conditions even in the absence of RCT evidence of clinical utility because those conditions have clear treatment implications and because family members may have the same condition (ClinGen, 2018; Green et al., 2013). The understanding of clinical utility usually evolves over time with further use of the test and additional studies (IOM, 2016).

are subtle differences between the terms since evidence may not yet exist that the clinical action that is taken results in improved outcomes (i.e., clinical utility).

It is important to note that a research result that lacks clear clinical utility may still have personal utility or meaning to a participant. Participants have a variety of motivations for wanting their results, and sometimes the utility and value of the information do not relate to clinical care (SACHRP, 2016). Information has personal utility if it can be reasonably used by participants for personal decision making, actions, or self-understanding (Bunnik et al., 2014). As discussed in Chapter 2, results with personal utility can help in life planning and reproductive decisions or can inform participants on the origins or risk factors for a specific disease or condition, helping patients better understand their disease or risk of disease (Bunnik et al., 2014; PCSBI, 2013). Value can also arise from gaining knowledge about oneself for the sake of knowledge—with no medical or health-related meaning. For a condition like Huntington's disease, genetic test results have no treatment benefit, but for some individuals with known risk, the results may still have personal utility (Bunnik et al., 2014) by, for example, relieving the anxiety associated with not knowing whether one has the disease genes and by informing decisions to have children. Similarly, lineage information from an ancestry study may have significant personal meaning for an individual who was adopted and seeking information on ethnic identity. Personal utility may also arise from the guidance the test results offer for preventative health decisions; such decisions may fall outside of medical decision making with a clinician. For example, expert panels have concluded that exposures to certain endocrine-disrupting compounds should be reduced as a health precaution—which implies that biological measurements of a person's exposure to these compounds may have health value, even though they are not now an established part of clinical care (Bergman et al., 2012; Diamanti-Kandarakis et al., 2009).

There is no clear dividing line between clinical and personal utility, and some results may have both characteristics, particularly if clinical utility is broadly defined. In one real-world example, investigators identified genes associated with hypercoagulability, and the results were returned to a participant on the basis that the individual would be able to take preventive action during lengthy air travel (e.g., standing periodically) to reduce the risk of stroke. Additionally, results that provide an end to rounds of diagnostic testing—the so-called "diagnostic odyssey"—can prevent further unnecessary (and potentially invasive) clinical testing and may also have personal value to participants in the form of a sense of relief from a newfound understanding of a health condition (Sawyer et al., 2016).

Despite this overlap between clinical and personal utility, existing frameworks and decision tools suggest a hierarchy among the characteristics of research results that may be returned to participants, and they tend to prioritize clinical utility over personal utility in assessing the value of research results (Fabsitz et al., 2010; Ravitsky and Wilfond, 2006). As discussed in Chapter 2, strong arguments can be made for investigators having an ethical obligation to offer participants results

that are analytically valid, indicative of a substantial health risk to the participant, and actionable (Fabsitz et al., 2010). Except for this kind of scenario, however, the subordination of personal utility may not be appropriate. In a notable departure from the approaches of past expert groups, the committee has chosen to deemphasize the respective influences of clinical and personal utility in decisions regarding the return of individual research results by focusing more inclusively on results that have "value to participants," with the understanding that the value of a result *from the perspective of the participant* might entail either clinical utility or personal utility or both and may also arise from the result having personal meaning (see Box 4-2 for a summary of previous expert group recommendations). This participant-centric approach recognizes that the value of a result is not necessarily tied to its use. To clarify, defining value in this way is not meant to imply that each participant needs to be queried regarding which results would be meaningful to him or her, but it does require the investigator to consider value from the participant's perspective rather than from the more traditional clinical perspective.

The committee also includes as a key determinant of value the benefits of returning a result relative to the risks to the participant. As discussed in Chapter 3, research testing may not be equivalent to clinical testing in purpose or quality.

BOX 4-2

Previous Expert Groups and the Return of Research Results

Previous expert groups have analyzed and offered guidance on which criteria to apply to investigator decisions when determining whether to return research results to participants. Many of these expert groups have offered clear criteria for when results should be offered to participants, but the issue of when results may or should not be returned is less clear and frequently is delegated to review boards to help decide whether return is appropriate. Below is a list of the common criteria identified by previous expert groups for deciding on return.

Results *should* be returned to participants when participants are consented and results are

- Analytically valid (Bookman et al., 2006; Fabsitz et al., 2010; Jarvik et al., 2014; National Bioethics Advisory Commission, 1999; Wolf et al., 2012, 2015)

continued

BOX 4-2, CONTINUED

- Clinically actionable or able to be used in significant life planning decisions (Bookman et al., 2006; Fabsitz et al., 2010; Jarvik et al., 2014; National Bioethics Advisory Commission, 1999; Wolf et al., 2008, 2012, 2015)
- Indicative of significant health risks or implications (Bookman et al., 2006; Fabsitz et al., 2010; Jarvik et al., 2014; National Bioethics Advisory Commission, 1999; Wolf et al., 2008, 2012, 2015)
- Legal to return (Wolf et al., 2012, 2015)

Results *may* be returned to participants when participants are consented and the results are

- Analytically valid (Fabsitz et al., 2010; Wolf et al., 2012, 2015)
- May or may not be clinically actionable, but the information is of significance to the individual, for example, with regards to reproductive decision making (Wolf et al., 2008, 2012, 2015)
- IRB approved for return with an appropriate disclosure plan, and the benefits outweigh the risks (Fabsitz et al., 2010)
- Legal (Fabsitz et al., 2010; Wolf et al., 2012, 2015)

Results *should not* be returned if results are

- Unlikely to provide a net benefit to the participants (Wolf et al., 2012)
- Of unknown importance or personal utility (Wolf et al., 2008, 2012)

Additional work is ongoing to determine best practices for the return of genetic results with funding from by the National Institutes of Health's National Human Genome Research Institute. It is exploring the ethical, legal, and practical aspects of returning research results, including the incorporation of genetic and genomic data into electronic health records (CSER Consortium, 2018; Mjoseth, 2012; NHGRI, 2017b).

If the limitations of research results are not adequately conveyed and understood, the research results may be misused by participants or their physicians to make unsupported clinical or personal decisions. Similarly, in a non-clinical setting, such decisions can result in inappropriate personal, life partner, child-bearing, and other life planning decisions. It is particularly important that the communication of results and their meaning and degree of uncertainty is done in such a way that it minimizes confusion and misinterpretation (discussed in more detail in Chapter 5). The weighing of benefits and risks is discussed later in this chapter in the context of a decision-making framework and illustrative examples.

It is important to bear in mind that value is not merely a function of the nature of the test result itself. Contextual factors—such as whether an individual has the condition under study or has an increased risk of developing it—will significantly affect participant perceptions regarding the value of a research result (Cadigan et al., 2011). *BRCA1* test results would be expected to have greater value to a participant with an increased risk for hereditary breast cancer than to a participant without such a family history (Bunnik et al., 2014). In the latter case, in fact, the results could provide a false sense of reassurance if they were disclosed without information regarding the incidence of nonhereditary breast cancer in the general population. The study design and the timing for returning individual research results can also influence perceptions of value for some kinds of results. For example, in the case of blinded clinical trials, returning test results may be prohibited until the end of the study in order to maintain the integrity of the research (MRCT Center, 2017). For genetic test results, the informational value to participants may not be diminished if they are returned months or even years later, but some studies may batch test samples at the end of an intervention or observation period, and, for disease states or environmental exposure that may change with time (e.g., cholesterol levels or some volatile environmental contaminants), the timeline for biospecimen collection, testing, and return of results may significantly affect the value of the return.

Ascertaining Participant Needs, Preferences, and Values

Given that the value of a research result to a participant will be influenced by perspective and context, the investigators, institutions, and research sponsors involved in this work need to be cautious about making assumptions regarding the kinds of results that participants may find meaningful. Expert-identified criteria do not always reflect participant preferences and values (Arora and McHorney, 2000; Epstein and Street, 2011; Epstein et al., 2010; Guyatt et al., 2004; Little et al., 2001). For example, recent surveys of participants in three different longitudinal cohort studies found that the participants in one of the cohorts but not the other two expressed a preference for receiving results about gene variants associated with preventability. In fact, for some participants, none of the expert-identified test result characteristics (severity, preventability, disease risk, reproductive implications)

were associated with their preferences for receiving results.[3] Another study which examined preferences for return by using hypothetical scenarios found that participant perceptions varied widely concerning the perceived value of results for untreatable conditions or of a finding of unknown significance, with some participants desiring access to all available results and others suggesting that these data could be a burden to a participant (Murphy et al., 2008). In a study of African American parents, participants viewed the return of aggregate results as less preferable than the return of individual results, as the aggregate results failed to provide any perceived personal-level benefit (Halverson and Ross, 2012). Some participants, understanding the trade-off in terms of slowing scientific discovery, have indicated that they would prefer to receive few or even no research results (Bollinger et al., 2014).[4] These findings emphasize the importance of working to understand what participants would find to be of value and what their preferences are for receiving results after the benefits, risks, and trade-offs have been discussed.

Ascertaining and incorporating participant needs, preferences, and values into decision-making processes regarding the return of individual research results can be done at the study level but also in the development of policy or guidance. Both actions are critical to advancing a more participant-centric research paradigm and may require the engagement of community members or research participants, or both.

In the context of individual studies, engagement is a bidirectional relationship between stakeholders—the individuals or groups affected by the research—and investigators which informs decision making (e.g., about research selection, design, conduct, or use) (Ahmed and Palermo, 2010; CTSA Community Engagement Key Function Committee Task Force on the Principles of Community Engagement, 2011). There is a range of engagement in research, including consultation, collaboration, and partnership (CTSA Community Engagement Key Function Committee Task Force on the Principles of Community Engagement, 2011). Engagement as a partner may not be necessary for the return of research results. The appropriate level and mechanism will depend on the specific characteristics of each study. In general, the imperative to engage community members in decision making about the return of individual research results increases as the degree of interface with participants during the research increases, and it depends on the potential implications of the research findings for participants or a community. For example, in a community-based participatory research (CBPR) study (see Box 4-3) that is assessing the exposure to potentially hazardous materials,

[3] G. L. Splansky, *Preferences for return of genetic results among participants in the Jackson and Framingham Heart Studies*. Document provided to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, October 6, 2017. Available by request through the National Academies' Public Access Records Office.

[4] Testimony of Ellen Wagner of Parent Project Muscular Dystrophy at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

BOX 4-3

Community-Based Participatory Research: Community Members as Research Partners

Biomedical research has historically been conceived, designed, and conducted without input from patients and the broader public. In the last two decades that has changed—in part because of the demands of patients—and engaging patients and community stakeholders has emerged as a key strategy to enhance the quality and safety of health care and to speed the translation of research into practice. The methods of engaging stakeholders in research have evolved, as have the roles and types of activities that patients and community members play in research. A gold standard for engagement has been community-based participatory research (CBPR), a collaborative approach in which partners are equitably engaged and stakeholders are fully integrated across all phases of research (Israel et al., 1998). This approach maximizes the engagement by stakeholders, who serve as principal investigators (PIs) or co-PIs and are leaders involved in every aspect of the study, from conception through dissemination. CBPR has been used for decades to engage stakeholders in research; however, this approach can be challenging to use in some types of biomedical research (O'Fallon and Dearry, 2002; Wallerstein and Duran, 2006) because of the time and resources required and the underlying expectation that results will lead to social action (e.g., efforts to eliminate health inequalities) or policy change. In general, the term "partner" refers to the type of engagement seen in CBPR and other long-term collaborations where there is evidence of power sharing and equitable distribution of funds and resources among researchers and community partners. Until recently there have been few patient and community PIs outside of CBPR; however, there are increasing opportunities for community- and patient-partnered research through funding mechanisms such as the Patient-Centered Outcomes Research Institute.

community members may partner with investigators to jointly decide which results should be returned to participants. Such an approach would not make sense for research using stored human biospecimens, where investigators have little or no contact with the contributors of the specimens. However, it should be noted that IRBs may be unfamiliar with CBPR and may require training to understand the value of results to participants and to accommodate the iterative nature of CBPR to prevent unnecessary delays and barriers to return (Brown et al., 2010; Saxton et al., 2015).

Ideally, the level of engagement in a study would be determined in collaboration with community members or with guidance from engagement experts. Study-specific engagement will not be necessary if individual results cannot be returned to participants—e.g., when biospecimens have been de-identified—and may not be required if investigators can reasonably rely on existing documentation of participant needs, preferences, and values in the literature or from past experiences working with community groups.

Table 4-1 describes the range of stakeholder engagement that can be applied in the return of individual research results. The table has the following key messages: (1) a number of approaches have been successfully used to involve stakeholders in research; (2) the number of stakeholders engaged and the extent of engagement should reflect the goals and aims of the research; (3) stakeholder roles range from providing brief, targeted input to highly involved, leadership roles; and (4) the training and experience required varies based on the stakeholders roles. As shown in the table, there is an inverse relationship between the extent of engagement and the number of stakeholders engaged, which leads some researchers to ask whether it is more important to have more engagement or a larger number of stakeholders. Because the best approach aligns with the aims of the study, neither is always more important. Approaches that are poorly aligned are less likely to elicit the stakeholder input needed and may be burdensome. Furthermore, if feasible, it is often useful for research teams to employ more than one approach—to both get the benefit of hearing from a large number of people in the general population affected by the condition being studied and work in an ongoing manner with a small number of participant or community representatives with deeper knowledge of the study process.

The different methods for engaging patient and community stakeholder groups about the return of individual research results (as presented in Table 4-1) can also be used to help determine an appropriate engagement approach to ascertain participant needs, preferences, and values regarding the return of individual research results to the general population being studied. For example, it may be valuable to solicit input from a large group of stakeholders using methods such as surveys, online polling, crowdsourcing, social media, and listening sessions. When more detailed input is required, investigators can use such methods as focus groups, nominal group techniques, Delphi methods, semi-structured interviews, and community engagement studios (Joosten et al., 2015). In some

TABLE 4-1 The Range of Engagement in the Return of Individual Research Results

STAKEHOLDER ROLE	EXTENT/DEPTH OF ENGAGEMENT	BRIEF DESCRIPTION	EXAMPLES/ METHODS	NUMBER OF STAKEHOLDERS IN ROLE
Principal Investigator (PI) or Co-PI	*Responsible for decision making*	Stakeholders drive the research and serve as leaders or co-leaders of the project. They are responsible for all aspects of the study and are directly involved in all decision making	Partnered research (multiple PIs), community-based participatory research, patient powered research network	1–2
Research Partner or Team Member	*Part of team making decisions*	Stakeholders are members of the research team and have direct involvement in the design, conduct, and dissemination of research; including helping to understand and make decisions on the return of research results	Community-engaged research, engaged team science	2–6
Governance or Advisory Group	*Provides oversight or guidance to make decisions*	Stakeholders consider feedback and findings on participants' needs, priorities, and values and provide guidance to the research team to make decisions on the return of research results	Advisory boards, councils and committees	4–25
Consultants, Interviewees, Panelists, Reviewers, etc.	*Provides detailed input on participant needs, preferences and values*	Stakeholders serve in specific, time-limited roles and provide detailed input on participants' needs, preferences, and values on the return of research results	Focus groups, semi-structured interviews, Delphi techniques, community engagement studios	10–100
Knowledge Users and Experiencers (general population affected by condition being studied)	*Provides input on participant needs, preferences and values*	Stakeholders engage using methods designed to reach a large number of people and provide perspectives on participants' needs, preferences, and values related to return of research results	Surveys, online polling, crowdsourcing, social media, town hall meetings	100+

cases, participant representatives may participate in oversight or advisory roles—for example to guide institutional policy or as members of bodies that make case-by-case decisions regarding the return of individual research results. Joanne Murabito, clinic director for the Framingham Heart Study (FHS), told the committee during its public workshop that an ethics advisory board comprising participants from all of the study cohorts as well as local physicians, key community leaders, a genetic counselor, and a medical ethicist provides guidance to investigators on results that should be returned to FHS participants.[5] Stakeholders in these ongoing roles have effective communication skills and prior leadership experience and may also have research experience. The meaningful engagement of advisory boards and oversight groups requires adequate preparation, clearly defined roles and expectations, bidirectional communication, and numerous opportunities for the stakeholders to provide input (Mott and Crawford, 2008; Newman et al., 2011). Stakeholders may also serve as integral members of the research team, contractually or in a consulting role, or, as in the community-based participatory research model discussed in Box 4-3, as co-principal investigators of the study. Stakeholders across the continuum need appropriate compensation and support to meaningfully engage. Compensation should be commensurate with the stakeholders' roles, responsibilities, and experience (Black et al., 2013a). It may not be necessary to offer compensation for an engagement that is brief and not burdensome.

For certain kinds of studies, particularly those that will involve recruitment and significant interaction between researchers and participants, obtaining stakeholder input on which individual research results should be returned ideally will be initiated in the study design phase in order to help investigators understand participant preferences, weigh the benefits and risks, and plan for disclosure (e.g., concerning consent and the communication of results). At this early stage, input should be sought from representative community members (i.e., individuals who will be able to represent the prospective participants but may not be those enrolling in the specific research study). The timing of this participant preference assessment relative to applying for funding for the research may vary depending on the extent of this assessment. Extensive engagement processes may be proposed as a part of the research to be funded.

If a decision is made to prospectively offer at least some individual research results, it creates an imperative for investigators to later engage the enrolled study participants in discussions (likely during the consent process) regarding the kinds of results that may be returned and how those results could be communicated to ensure that they are meaningful to participants (as discussed in more detail in Chapter 5). In survey and focus group discussions, participants have expressed a

[5] Testimony of Joanne Murabito of the Framingham Heart Study at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

desire to be given choices and an opportunity to indicate preferences regarding which research results will be offered (Murphy et al., 2008). While the personal value of a result will vary greatly depending on the individual, it would probably not be feasible to tailor plans for returning results according to the individual preferences of each participant. One possible way to accommodate varying participant preferences, depending on the study constraints, would be to offer a tiered disclosure approach where participants are offered a range of options for disclosure (Rothstein, 2006). Investigators can also investigate individual preferences for the return of results over the course of the study (see Chapter 5 on consent) or at the end of a study if a participant requests results that were not offered as part of the study plan.

Many investigators have little training or experience in identifying and convening stakeholders and may be unfamiliar with strategies to implement key principles of engagement such as co-learning and cultivating mutual trust and respect. Therefore, to accomplish this researchers will need to leverage the expertise of community engagement cores, engagement specialists, and engagement scientists to develop plans to engage stakeholders if evidence of their needs, preferences, and values has not previously been captured. Due in part to the infrastructure developed by the Clinical and Translational Science Awards (CTSAs)[6] and broader dissemination of engagement methods by the Patient-Centered Outcomes Research Institute (PCORI),[7] many research institutions have engagement experts available to assist researchers. The cost, time, and effort of engagement can be minimized by leveraging existing knowledge resources and engagement infrastructure to assess the preferences and needs of communities. Research funding agencies and sponsors can further support investigators by providing guidance and other resources to ensure that engagement needs are not viewed as a barrier to returning individual research results.

Community and patient advocacy organizations, which are often focused on harnessing the power of groups of patients and strategically deploying their assets to drive better outcomes and increased value from research, also have a role. Community organizations and advocacy groups can facilitate communication between those they represent and an institution's engagement core, a study's investigators, and research sponsors in order to convey the needs and preferences of those in their community concerning the return of results and engagement in those decisions. Over time, as community engagement experts within institutions (e.g., individuals within community engagement cores at CTSA) and investigators

[6] Community engagement has been a key component of the CTSAs since their initial funding in 2006. Each of the approximately 60 CTSAs (Wilkins et al., 2013) has a community engagement program that may provide useful examples of successful local community engagement models (CTSA Community Engagement Key Function Committee Task Force on the Principles of Community Engagement, 2011; Paberzs et al., 2014; Wilkins et al., 2013).

[7] PCORI's Engagement in Health Research Literature Explorer contains a searchable list of publications on engagement in health literature (PCORI, 2018).

gain experience with returning individual research results and publish their accumulated knowledge in the literature, the engagement requirements for ascertaining participant needs, preferences, and values may lessen, reducing the burden for investigators.

CONCLUSION: The study-specific engagement of community members and participant representatives in order to ascertain participant needs, preferences, and values related to the return of individual research results will be important for some, but not all, research involving the testing of human biospecimens. Engagement may be limited or unnecessary when biospecimens have been de-identified or if investigators can reasonably rely on the existing documentation of participant needs, preferences, and values in the literature or from past experiences working with community groups.

CONCLUSION: Many investigators will be new to engagement activities and will need to rely on existing models as they develop study protocols. Engagement models, guidance, and numerous informational resources have been developed to guide and support patient and community engagement. Investigators may need to be made aware of their existence or to receive training to effectively engage participants in decision making about the return of individual research results.

CONCLUSION: As the return of individual research results becomes more routine and a body of evidence is built and becomes more accessible to investigators (see Recommendation 11), the process for understanding and considering participant needs, preferences, and values will become less burdensome.

Recommendation 5: Incorporate Participant Needs, Preferences, and Values in Decision Making About the Return of Individual Research Results.

Research stakeholders should ensure that participant needs, preferences, and values are incorporated into decision making regarding the return of individual research results. To facilitate this,

- **A. Investigators should seek information through various mechanisms, including reviewing published literature, leveraging experiences from similar studies, consulting participant or community advisory boards, and engaging community and participant groups and advocacy organizations in the development of the research protocols;**
- **B. Research institutions and sponsors should enable and facilitate investigator access to the relevant community and participant networks, resources, and training; and**
- **C. Research sponsors should engage community and participant representatives in the development of policy and guidance related to the return of individual research results.**

Feasibility of Returning Individual Results to Participants

The return of individual research results requires not just a consideration of the value of the results to the participants, but also of the feasibility of the return. Broadly speaking, feasibility depends on the burden involved in making the returns and the resources available to carry out the returns. There is a small body of literature (mainly from environmental exposure and genetic studies) that addresses the burdens that investigators face in returning individual research results (Bredenoord et al., 2011; Brody et al., 2014; Christensen et al., 2011; Ohayon et al., 2017). Among the burdens described in this literature are communication challenges, maintaining contact with research participants, and logistical and resource constraints (for example, see Box 4-4 which highlights challenges identified by investigators and IRBs) (Ohayon et al., 2017). Depending on the nature of the research and the laboratory used to test biospecimens, the burden can also include getting Clinical Laboratory Improvement Amendments (CLIA) certification.

The burden associated with the return of results varies widely, depending on the context of the study and the communication approaches used. At one extreme, a study might involve a small number of participants who are also patients of the physician–investigator. In this case, neither contacting the participants nor communicating the results effectively is likely to be a significant challenge. At the other extreme, a study might involve an analysis by a basic scientist of a large number of human biospecimens contributed by individuals who are widely distributed in terms of location and the time of specimen acquisition. In this situation, contacting the participants and organizing an effective communication of results by those with appropriate expertise would be a costly and complex endeavor. However, in some situations methods to enable return to geographically distributed participants—e.g., digital methods of communication—can be employed by investigators to make this more feasible (Boronow et al., 2017). Methods for communication of results are discussed in more detail in Chapter 5.

The resources needed to return research results include money, time, expertise, infrastructure, and personnel. The sections below detail some of the major challenges investigators have encountered when returning research results and some of the issues they should consider when making determinations on a case-by-case basis about returning individual research results.

Communicating Results

Research teams may not have the necessary expertise (e.g., being able to understand the test's meaning in a larger medical context or within the participants' medical context, being able to communicate the results effectively, or simply having had previous experience with these challenges) to appropriately communicate individual research results, and thus the return of results may require additional training or partnerships with professionals who do have this expertise. In the

BOX 4-4

Challenges in Reporting Back Personal Exposure Results

Below are the main challenges reported in a survey of investigators and institutional review boards that returned results from biomonitoring and environmental exposure studies.

ONGOING CONTACT WITH STUDY PARTICIPANTS

- Maintaining connections with participants in the face of the long periods of time between collecting samples and report results
- Post hoc contact with study participants if new health guidelines emerge
- Protocols for the timing of reporting back results for chemicals without health guidelines

DEVELOPING MEANINGFUL REPORTS

- Deciding on clear takeaway messages and summaries, including conveying scientific uncertainty about health outcomes
- Avoiding information overload
- Representing intra-individual temporal variability for rapidly metabolized chemicals

SHARING DATA BEYOND THE STUDY PARTICIPANT

- Deciding whom to share research results with (e.g., physicians, family members, and wider communities) and how to protect privacy

LOGISTICAL AND FINANCIAL CONSTRAINTS

- Limitations in staff time, funding, and other resources

SOURCE: Ohayon et al., 2017, p. 145.

case of genetic research, the availability and cost of genetic counselors is a big concern. At the committee's workshop, Wendy Chung, a professor of pediatrics and medicine at Columbia University, reported that using a genetic counseling service had cost the study approximately $250 per participant, and Jessica B. Langbaum, a principal scientist at Banner Alzheimer's Institute, said that one barrier to returning results in a national study had been that state licensure laws for genetic counselors varied and that the costs could be prohibitive for a counselor to become licensed in multiple states.

Investigators and IRBs will need to consider various literacies of research participants—e.g., general literacy, health literacy, and relevant aspects of scientific literacy—when planning the return of results, which likely will require new or increased interactions with and the involvement of social scientists, communication experts, the community, and patient advocacy groups. Individuals with different levels of literacy will require different levels of support, which may necessitate varying methods of education and follow-up activities (Terry, 2012). Chapter 5 addresses these communication needs in greater detail.

Maintaining Contact with Participants

Maintaining contact with participants is another frequently cited barrier to the return of results. At the committee's public workshop, Carolyn Compton, a professor of life sciences at Arizona State University, said that when she worked at the National Cancer Institute it would not have been possible to re-contact trial participants because they did not maintain contact information in their database. "If there were a way that this information could be centralized and made available so that patients could be contacted, that would be an enormous step forward," she said. Furthermore, contact information may change over time, or research teams may lose contact with participants from transient populations. In the case of one environmental exposure survey (Ohayon, 2017), the researchers involved adopted various strategies to work around these challenges, such as asking for alternative contact information, informing participants when study results would likely be disclosed in the consent process, and "disseminating partial results as they became available to ensure more frequent communication with participants" (Ohayon et al., 2017, p. 145).

Regulatory Requirements

As described in Chapter 3, the Centers for Medicare & Medicaid Services interprets CLIA regulations so as to require that individual results can only be returned if testing is performed in a CLIA-certified laboratory, and getting CLIA certification is a major burden for many investigators who are planning to return

results. At the committee's workshop, all four investigator panelists[8] agreed that CLIA certification would not be practical for many research laboratories, given the nature of the research they conduct (discussed in detail in Chapter 3).[9] While investigators could in theory conduct their follow-up testing in CLIA-certified laboratories on the subset of results they plan to return, the ability to perform this follow-up testing might be constrained if investigators are not part of an institution that is affiliated with a CLIA-certified laboratory that performs the specific test or do not have the budget to perform tests again within their institution or via a third-party facility. Chung said that in her case, getting samples retested in a CLIA-certified laboratory tripled the cost of testing per participant. Furthermore, in many cases retesting requires participants to give new biospecimen samples since it cannot be ensured that research laboratories without certification followed quality management processes when collecting, processing, and storing biospecimens. While in the case of genetic testing, getting additional biospecimen samples from participants may be relatively simple (only requiring a saliva swab), in many other types of research, collecting additional samples (e.g., blood, biopsies) would be much more onerous, invasive, or impossible. Thus, if CLIA certification continues to be a requirement for the return of individual research results, it will not be feasible for many investigators to return results without significant additional resources from their institutions and funding agencies, and even then many laboratories would still be left out. If a new quality management system with a tiered approach was developed that was appropriate for research laboratories (Recommendation 2 in Chapter 3), the costs to implement this system would still be significant for many laboratories not familiar with quality processes, but ultimately it would allow a much broader swath of laboratories to return individual research results.

Another regulatory requirement that investigators planning to return research results should take into consideration is the Food and Drug Administration's (FDA's) investigational device exemption (IDE). The details of the IDE regulatory process and how it applies to the return of individual research results are discussed in detail in Chapter 6. However, it should be noted that if a study falls under this regulation and does not meet the requirements for exemption, then investigators need to prepare an IDE submission to FDA. The rigorousness of the requirements for submission depends on the risk determination of the study, which is determined by the investigators and IRB. According to a meeting

[8] Wendy Chung, the Kennedy Family Professor of Pediatrics and Medicine, Columbia University; Carolyn Compton, a professor of life sciences, Arizona State University; Jessica B. Langbaum, principal scientist, Banner Alzheimer's Institute; Lea C. Harty, a biobank biological materials custodian, Pfizer Inc., representative of the Industry Pharmacogenomics Working Group (I-PWG).

[9] Testimonies of Wendy Chung of Columbia University, Carolyn Compton of Arizona State University, Jessica B. Langbaum of Banner Alzheimer's Institute, and Lea C. Harty of Pfizer Inc. at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

summary from a National Human Genome Research Institute (NHGRI) workshop, "If a study is deemed to be SR [significant risk], investigators should be aware of the time and resources that are necessary to prepare an IDE submission and see it through FDA review, as investigators bear much of the responsibility in the IDE process" (NHGRI, 2017a).

Required Resources

The resources needed to return individual research results include funding, time, expertise, personnel, and infrastructure, and finding such resources is an inevitable challenge for researchers who wish to return results. Given the many factors involved, it is very difficult to estimate ahead of time the costs and time that will be required to return results, but it should be acknowledged up front that the return of results will indeed require both time and money. Some documented costs associated with the return of results include verification of the result, genetic or other counseling beyond the disclosure of results, administrative costs, time and labor required to recontact participants, salaries for trained and qualified staff, protocol preparation, creation and printing of educational materials, and technology to enable the storage and protection of identifiable information to enable return to individual participants (Black et al., 2013b; Budin-Ljøsne et al., 2016; Christensen et al., 2011; Fernandez et al., 2004; Heaney et al., 2010; Resnik, 2011). For example, one study that returned *CDKN2A* research results to melanoma survivors found

> Time demands averaged 161 minutes per completed disclosure. An average of 40 minutes was spent on each of the 39 GEM study participants we attempted to re-contact, plus an additional 78 minutes for each of the 19 participants who agreed to receive results. The financial costs associated with our protocol averaged $1,322 per completed disclosure. (Christensen et al., 2011)

The costs of return will become more apparent as there is now a concerted effort among research sponsors, investigators, and institutions to return results and build an evidence base on best practices and to leverage existing resources to carry out returns more efficiently and effectively. The development of a larger evidence base will aid investigators and sponsors in future cost planning and help lower up front costs as the practices becomes more routine—and more routinely documented—and as the infrastructure and expertise get put in place.

The CTSA program is well positioned to facilitate returns at CTSA-affiliated universities. First, CTSAs provide investigators with access to clinical research cores and research nurse support, which includes providing access to CLIA-certified laboratories to facilitate the testing or retesting of specimens when appropriate. Once established, CTSAs could also provide training to investigators to meet the quality management system (see Recommendation 2) or to

ensure that core laboratories follow those quality management system practices so that they can address the diverse needs of the investigators at the institution. Furthermore, CTSA sites can provide training, expertise, and infrastructure that investigators who are planning to return results could use to effectively engage and communicate with participants (NCATS, 2018). Universities that are not connected with a CTSA may be able to form partnerships with CTSAs housed at other universities, local hospitals, or patient and community advocacy groups to provide similar support to their investigators.

A DECISION-MAKING FRAMEWORK FOR THE RETURN OF INDIVIDUAL RESEARCH RESULTS

Decisions about the return of individual research results will vary on a study-by-study basis, depending on the characteristics of the research, the results, and the participants. Such decisions will require a significant amount of judgment and several groups have provided flowcharts or frameworks to aid in the decision to return research results (Beskow and Burke, 2010; Haines et al., 2011; Holm et al., 2014; MRCT Center, 2017; Ravitsky and Wilfond, 2006)—the committee offers the conceptual framework in Figure 4-1. Under this framework, the justification for returning results becomes stronger as the potential value of the result to participants increases or as the feasibility of the return increases.

In a small number of well-defined cases there are clear and broadly accepted rationales for when a return should be either obligatory or discouraged (see Box 4-5). However, for the most part decisions will not be so clear cut.

Given the numerous technical and operational considerations inherent in the return of research results, the committee chose to provide examples illustrating how these considerations could be applied in practice. The committee found it helpful to organize the discussion into three scenarios: (1) the research team is prospectively planning to offer results to participants; (2) a participant requests his or her results from the research team or laboratory; and (3) the research team has an unanticipated result that was not part of the study protocol and is considering whether the results should be offered to participants.

Decisions on Individual Research Results That Will Be Offered to Participants

In this first scenario, the research team is considering which individual research results, if any, will be offered to participants in the study. In this case incorporating input from patient and community groups is the most helpful strategy for helping investigators understand which results are likely to be of value to participants and which are not. Additional input from scientific and clinical experts may help elucidate the potential risks and benefits and inform the decision-making process (advisory boards and other such bodies are discussed later in this chapter). Because the decisions are being made prospectively

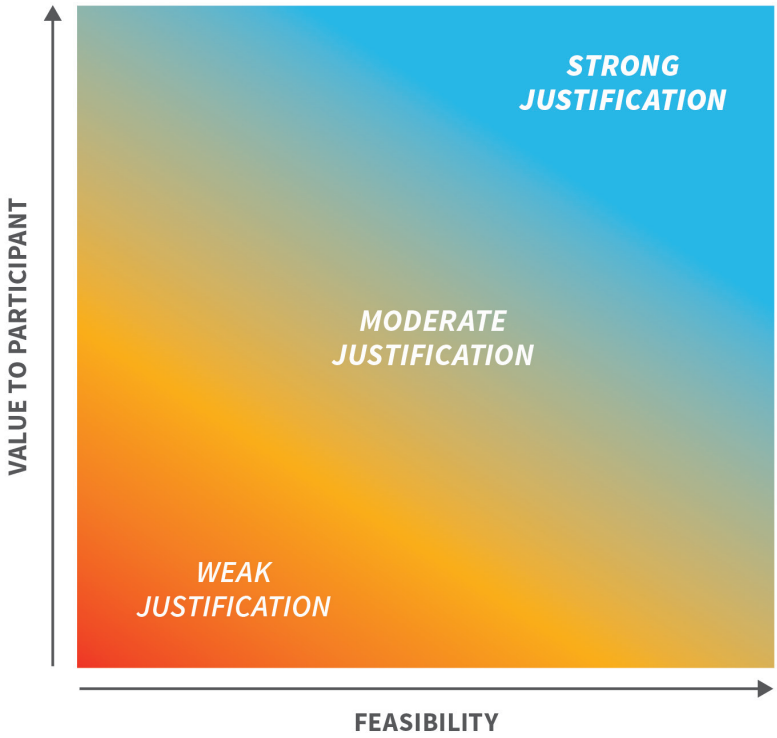

FIGURE 4-1 A conceptual framework for decisions on returning individual research results.
NOTES: This figure demonstrates that as the potential value of the result to participants and the feasibility of return increase, the justification for returning results becomes stronger. **Value** in this context means the value of a result *from the perspective of the participant* and might entail clinical utility or personal utility as well as personal meaning. **Feasibility** is determined by multiple factors, including potential challenges, the costs and burdens of returning results, and whether participants' biospecimens are linked to the participant identity as well as the resources available to communicate the results effectively and appropriately.

and can be planned for, the research team can ensure that sample tracking and testing processes provide the necessary confidence in the validity of the result (as defined in Recommendation 3) and that the team has the necessary resources and expertise to communicate the results effectively. Thus, in this scenario the investigator should decide on the return of results by carefully weighing the value to participants along with the benefits, risks, and costs of return.

BOX 4-5

Individual Research Results That Should and Should Not Be Returned to Participants

RESULTS THAT INVESTIGATORS OR LABORATORIES ARE OBLIGATED TO RETURN

- Urgent, clinically actionable, valid results (ethical obligation under duty to warn/rescue)
- Results that are in the designated record set of a HIPAA-covered entity if they are requested by the participant (legal obligation under HIPAA, the Health Insurance Portability and Accountability Act of 1996)

RESULTS THAT INVESTIGATORS SHOULD BE DISCOURAGED FROM RETURNING

- Results that cannot be interpreted at the individual level without a risk of misinterpretation
- Results that have limited value to participants and would entail significant burden (cost or complexity) to return
- Results without established clinical validity for a life-threatening or sensitive health condition
- Results for which there are serious questions regarding validity or identity (e.g., those generated in a laboratory with no quality management system and for which a peer-review process has determined that quality assurance processes are insufficient to offer confidence in the results' validity or identity)

SOURCES: Bookman, 2006; Fabsitz, 2010; Jarvik et al., 2014; National Bioethics Advisory Committee, 1999; Wolf et al., 2008, 2012.

Investigators conducting research testing on human biospecimens may be faced with decisions on whether to offer individual research results for which the strength of the justification spans the full spectrum depicted in Figure 4-1. The committee identified several kinds of research results it would generally encourage investigators to offer. In surveys and focus groups participants have resoundingly expressed interest in receiving results that indicate the presence of or an increased risk for a preventable or treatable disease or health condition (Middleton et al., 2016; Murphy et al., 2008). For example, most members of a focus group indicated that they would want results from a hypothetical asthma study, and such results should, in most cases, be returned (Murphy et al., 2008). Even certain research results that lack clinical utility may still have significant personal value and would be expected to pose little risk. For example, for individuals with a debilitating disease, a biomarker that predicts disease progression may be of great value to a participant and his or her family or caretakers in life planning.[10] Furthermore, as long as a lack of resources does not make it impossible, offering the results from routine clinical tests generated in the course of a research study is unlikely to pose a significant risk to the participant and should also be encouraged. When it is possible to do so without impairing the integrity of the study, offering such results in real time is likely to maximize their value to participants. It is important to note that the value of clinical test results may depend on the results (e.g., whether or not they are within the normal range) and the characteristics of the participant. For example, clinical test results within the normal range may have greater value to a research participant with a serious health condition than to a healthy volunteer, and this should weigh into decisions regarding disclosure. Investigators should also keep in mind when considering whether to offer results or to return them only upon request that participants may make assumptions when results are not offered that nothing abnormal was discovered.[11]

As discussed earlier in this chapter, the return of personal exposure results (e.g., blood levels of an environmental contaminant) may be expected and may even be part of a contract between the investigators and participants engaged in a community-based participatory research study. Then, depending on what is known about the health effects of the contaminant, the questions for investigators may be focused more on such issues as how the results should be returned (considerations for how results should be returned are discussed further in Chapter 5).

When there may be significant risks associated with returning results, decisions about whether to offer results will require more careful consideration. In such cases, the actionability of a result may influence the strength of the

[10] Testimony of Ellen Wagner of Parent Project Muscular Dystrophy at the public meeting of the Committee on the Return of Individual Specific Research Results Generated in Research Laboratories on September 6, 2017.

[11] Testimony of John Molina of Native Health at the public session of the Committee on the Return of Individual Specific Research Results Generated in Research Laboratories on December 11, 2017.

justification for its return. Participants tend to be more equivocal about receiving results for a disease or condition that is currently not treatable (e.g., Alzheimer's disease) (Murphy et al., 2008). As discussed earlier in this chapter, however, investigators must consider in their decision-making process whether withholding the offer of results in the latter case is paternalistic, particularly given the potential personal benefits to participants who opt to receive such results (e.g., life planning, relief from the anxiety of not knowing), and they should pay attention to participant preferences and values.

As a matter of respect for autonomy, Principle 2 of the committee's guiding principles (see Chapter 2) asserts that participants should have a right to decide whether to receive or share their results with their primary care physician, relatives, an executor, or others. Participants may need to decide whether to share research results with relatives who may be affected by the result while investigators may need to determine the timing of the return and potentially the handoff of the results to a physician if they require further clinical evaluation. While the scientific literature has explored whether an investigator may communicate research results to others, either at the investigator's initiative or upon request by one of these individuals, there is no formal consensus on this topic (Battistuzzi et al., 2013; Beskow and O'Rourke, 2015; Chan et al., 2012; Tassé, 2011; Wolf et al., 2015). These will not be straightforward decisions, and, in particular, they will be highly context dependent. There are many considerations that will need to be taken into account in order to determine when and with whom a participant's research results can be shared, and these will require protocol-specific determinations in conjunction with institutional policy. When there is a result that is thought to be clinically significant, the timing of the return relative to the urgency of the finding should be considered when the return is being planned and reviewed by an IRB. Sharing results with physicians, children, or community members may also be a key challenge for investigators and IRBs, particularly if participants do not want their results shared; if the result has meaning for the community, investigators struggled with how to share the data in a way that is valuable for the community while protecting participant privacy (Ohayon et al., 2017). In general, the communication of results to a participants' family member or proxy should be done with the permission of the participant.

In some research scenarios, there may be challenges to the research team's ability to solicit, consider, and respect the participant's preferences for receiving or sharing results because the participant is underage, has reduced decision-making capacity, or is deceased. Offering results to the participants, their caretakers, or their family members in these situations, therefore, involves complex ethical decisions and may require additional oversight mechanisms.

Return of Results for Children, Adults Who Lack Decision-Making Capacity, and Deceased Individuals

The return of research results raises a number of considerations and complexities when the participants are young children, adults or older children who lack decision-making capacity, or individuals who die during the conduct of the study. Each of these scenarios requires special decision-making processes to ensure that sufficient protections are in place. The formulation of such guidance is beyond the scope and ability of this committee, but below we raise key issues that are part of active consideration by the scientific, medical, ethics, and legal communities.

As discussed in Chapter 2, the ethics for the return of results to individuals who lack decision-making capacity differ from the considerations relevant to those who make an informed decision to join a study. The return of results to children or to individuals who lack capacity or are deceased hinges less on considerations such as transparency, reciprocity, or perceived value by the participant and more on considerations of potential benefits to the participant and his or her family members or significant others.

Children In situations where children are participating in research, the return of research results should be addressed during the assent process with the older child and the informed consent process with parents (Anastasova et al., 2013; Avard et al., 2009). All documents and methods of communications used should be adapted to suit the child's language, age, and sociocultural context (Avard et al., 2009). Older children's preferences regarding whether and what type of results they would be interested in having returned, including a preference to have no knowledge of their research results (Anastasova et al., 2013), should be taken into account and considered alongside the child's age and development (Holm et al., 2014). However, the parent or guardian of the child-participant retains the right to know health information that is relevant to the management of the child's health (Anastasova et al., 2013), although this does not imply a right to all of the child's research results. In developing their protocols, investigators should anticipate whether the child's results will have relevance to the health of the child or the health or welfare of other family members. For example, a genetic variant identified in a child is likely to have been inherited from a parent, with potential health implications for that parent, and the variant may be shared by siblings and other "blood" relatives. Similarly, the results of testing for environmental toxins in a child might have importance for that child and family members or others who may share the same exposure. As in other circumstances, the justification for the disclosure of results is strongest when the results have the greatest value to participants or family members and when disclosure is most feasible for investigators. In these situations, results may be offered, or made available upon request, to the parents or legal guardian of the child. Often in such circumstances, the

parents should assist or take primary responsibility for communicating appropriate information to other family members.

Adults Who Lack Decision-Making Capacity Decision-making capacity may never be present in some individuals, or it may be temporarily or permanently lost due to illness or injury. Decision-making capacity is often not simply present or absent but rather should be considered as existing along a spectrum. Furthermore, it can be task specific—that is, an individual may have capacity for some simple decisions but lack capacity for more complicated tasks (SACHRP, 2009). Adults who lack sufficient decision-making capacity for research informed consent can be participants in research with the consent of a legally authorized representative (LAR). The federal regulations governing human research do not specifically address adults without capacity other than to require consent from the participant or a LAR.[12] Who qualifies as a LAR is a matter of state law, with some variability across the 50 states and territories. IRBs will be familiar with LAR requirements in the jurisdictions where the research is being conducted. Federal regulations do not require an assent process for adults with limited decision-making capacity, although such measures have been recommended and should be considered by investigators and the IRB (SACHRP, 2009).

Consistent with Recommendation 6, the plan regarding the return of results should be addressed in the consent materials reviewed and signed by the LAR (Wolf et al., 2015), and consideration should be given as to whether the return-of-results plan should be included in assent materials. During the design of the research, all components of the participants' vulnerabilities should be considered (Lange et al., 2013), and additional support should be made available during the informed consent process, such as supplementary educational activities, the presence of specially trained personnel, and genetic counseling. Researchers, IRBs, and participants' representatives are responsible for ensuring that this informed consent process sufficiently protects the participant's autonomy (Groisman et al., 2012). The participant should be an active participant in the informed consent process whenever possible, even if there is a surrogate present, and should be given the information necessary to give or decline assent to participate (Lange et al., 2013).

For adults who are at risk of losing decision-making capacity during the study, Wolf and colleagues recommend that the prospect of sharing the results with family or others be addressed in the consent process and that the participant's decisions be honored after the participant has lost capacity (Wolf et al., 2015).

Deceased Persons Currently there is no standard practice regarding whether and how to return research results to the relatives of deceased research participants (Wolf et al., 2015). A study by Beskow and O'Rourke found that IRB chairs

[12] 45 C.F.R. § 46.116.

did not endorse the return of research results to family members in scenarios where the decedent had stated that he or she did not want the research results shared (Beskow and O'Rourke, 2015). Deceased persons are not considered research subjects under the Common Rule; however, under the Health Insurance Portability and Accountability Act (HIPAA) deceased persons retain certain rights to their medical data. Researchers should be aware of the possibility that family members may want to receive the research results of the decedent (Chan et al., 2012) and should address access to research results by family members following the death of the participant during the informed consent process. If the participant's preference has not been determined in the consent process in advance of the study, HIPAA may prohibit the return of results to persons who are not the participant's executor; this is an issue because it has been found that participants may want an individual who is not the executor to be the recipient of any results (Goodman et al., 2017). The privacy of the deceased individual also remains a consideration with respect to the return of results, particularly when the individual did not have an opportunity to decide about disclosing the results to others.

In cases where the result has clinical relevance to family members or to significant others, Chan et al. (2012) recommend that the researcher make an effort to contact the executor of the decedent's estate or next of kin to assess whether there is interest in receiving the decedent's results. In contrast, Wolf and colleagues recommend that investigators follow a passive disclosure policy, meaning that results, rather than being offered, would be disclosed to relatives or others only upon their request (Wolf et al., 2015). These authors suggest that a more active disclosure policy may be warranted in rare cases when the results may be critical to avert imminent harm (Wolf et al., 2015).

Decisions on Individual Research Results That Will Be Returned to Participants Upon Request

When a participant requests a result from the research team or laboratory, the calculation of whether or not to return the result is different from the above scenario. By virtue of the request, it can be assumed that the result has value to the participant. There are few data to suggest how common such requests might be (particularly if participants are informed of the option during the consent process; see Recommendation 9), but as long as the burdens or risks to the participant are not prohibitory, the committee believes that investigators should be amenable to returning, upon request, results that they had not previously offered to return. This may include results that investigators might themselves think to be of limited value to participants, such as

- drug or volatile biomarker levels from samples collected during a clinical trial but batch tested months or even years later;

- potential diagnostic biomarkers from an individual who is already aware of his or her condition (e.g., the presence of a protein biomarker in a stroke survivor that may have value in future diagnostic tests to differentiate the kinds of stroke); and
- genetic variants of uncertain significance.

In the case of genetic variants of uncertain significance, it is important to bear in mind that the significance of a result may change over time as scientific knowledge advances. Given that investigators cannot generally be expected to return results after the study funding is gone (Fabsitz et al., 2010), investigators should consider returning such results upon request whenever feasible so that participants have the option of following the state of scientific knowledge and referring back to their individual results as new discoveries are made regarding the significance of variants and other kinds of biomarkers previously not well understood. This would apply to all fields of biomedical research, not just genetics and genomics. The committee agrees with the National Heart, Lung, and Blood Institute working group that investigators do not have the obligation to return results for an indeterminate period; this includes their obligation to reanalyze participant data and follow up, as this would not be feasible. "In practical terms, investigators cannot maintain an open-ended commitment to return results and thus should plan to have the results provided before the end of the operating grant period" (Fabsitz et al., 2010, p. 6). Institutional advisory bodies may be of help to investigators as they consider the return of results with unclear significance, but, as discussed earlier in this chapter, such bodies should include representation of the participant perspective. Perhaps an extreme case of this scenario relates to an individual's whole-genome sequence. While the committee focus in this report is on the return of results that have meaning to the participant, it recognizes that in this era of next-generation sequencing and precision medicine, the question of whether to return a whole-genome sequence is one that many investigators working in the field of genomics are facing. The return of a whole-genome sequence can be justified in much the same way as returning variants of unclear significance can be, and, in fact, returning whole-genome sequences may be less burdensome for investigators as it requires less analysis. In some cases, investigators may even feel more comfortable providing raw sequencing data upon request, as it puts the onus for seeking interpretation on the participant.[13]

Although, as noted in Box 4-5, the committee generally encourages the return of individual research results upon request when the resources are available to do so, it discourages the return of results where there is little confidence in the validity of the result (see Recommendation 3). However, if the laboratory that produced the result is a HIPAA-covered entity and the results are part of the

[13] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

designated record set as defined by the Office of Civil Rights (see Recommendation 12), then the laboratory has a legal obligation to return the requested result.

Decisions on the Offer of Unanticipated Individual Research Results

This scenario is similar to the first one (the prospective offer of results) except that the research team does not have the advantage of planning for disclosure because they did not anticipate the result in question. In the case of findings that can be anticipated, the committee is not commenting on whether there is a duty to hunt for them, as that was outside the scope of this report. Rather, this scenario refers only to those unanticipated results that are organically generated over the course of the study but the investigator was unable to foresee. In considering what can be anticipated, however, investigators have a responsibility to look beyond the primary goal of a test and consider what other results may arise in the conduct of testing.[14] In some cases such results may be urgent and should be offered to participants consistent with the ethical obligation related to duty to warn/rescue. This might include, for example, a genetic marker associated with a preventable or treatable life-threatening disease or health condition discovered during a DNA sequencing study for a different medical condition. In other cases, the result may have no clear clinical utility, and the justification for returning it will be weaker. An example could be a sex chromosome anomaly that does not require medical management that was discovered during a study on a sex-linked genetic disease. Given that the research team did not anticipate the result and therefore did not seek input on participant preferences and values during the study design phase, investigators may need to rely on published or otherwise available documentation on potential personal utility and meaning as they carefully weigh the value to the participant and the risks of disclosure.

PLANNING FOR THE RETURN OF INDIVIDUAL RESEARCH RESULTS

The responsible return of individual research results requires careful forethought and preparation (MRCT Center, 2017). Most individual research results that will be generated in the course of a study and that may be expected to have value to participants can be anticipated. Doing so can ameliorate any risks that may arise from hasty decision making and ad hoc processes for disclosure. Incorporating the return-of-results plan into the research protocol fosters transparency and enables appropriate budgeting and allocation of resources, while IRB review

[14] Thoughtful investigators and IRBs can anticipate results outside of the primary study objective. This aligns with the 2013 report of the Presidential Commission for the Study of Bioethical Issues where the commission concluded that there is "a duty on the part of a research investigator to consider what incidental and secondary results might occur from genomic testing, to create a plan for the possible return of results to participants, and to inform research participants of that plan before the tests are conducted" (Weiner, 2014, p. 562).

ensures that the risks and benefits to participants are carefully considered in a peer-review process. Anticipating the consent needs of participants may improve the ability of investigators to communicate their intentions to participants and set appropriate expectations (Ravitsky and Wilfond, 2006). Advance planning also provides investigators with an opportunity to consider community needs and how results can best be returned so as not to perpetuate or deepen existing health disparities and inequities (e.g., by ensuring that factors such as race and ethnicity, language barriers, insurance status, and literacy do not affect whether a participant benefits from the disclosure of individual research results). Thus, developing a plan during the design phase of the study that addresses whether, when, and how results will be offered to participants or provided in response to a participant request can help maximize the benefits and prevent or mitigate the potential harms of returning individual research results.

During the planning process investigators should consider the types of results that might be shared, including results generated in the course of research from routine clinical tests (e.g., cholesterol levels), urgent or unanticipated findings, and primary or secondary endpoints, as well as when during the study life cycle results might be offered and shared without impairing the goals of the research. For some study designs, the sharing of in-study results—for example, those generated in real time during intervention or observation periods—may require more attention to the risks of unblinding or the introduction of bias than the baseline (e.g., used for inclusion/exclusion) and end-of-study test results (SACHRP, 2016). Importantly, the development of the plan should not be viewed as a one-time process. The plan should be dynamic, with feedback potentially informing refinements at multiple points in the study timeline. Such feedback may arise during the IRB review, during the funding application review, and from public and participant engagement (when relevant) prior to the study's initiation and during the consent process.

In recommending that investigators conducting testing on human biospecimens be required to plan for the return of research results, the committee does not mean to imply that individual research results should be returned in all studies. In some situations it may be reasonable for the plan to state that investigators will not offer individual results to research participants. However, in such cases the plan will need to clearly convey the rationale for the investigator's decision and how that rationale will be explained to participants during the consent process. Moreover, the investigators will still need to address whether the results will be provided upon request—for HIPAA-covered entities, this may be legally required when the results are included in the DRS—and how investigators will handle unanticipated but urgent findings.

CONCLUSION: Sponsors, institutions, IRBs, and investigators will need to balance the needs of each stakeholder and make informed decisions at each phase of the research so as to respect the participants while not hindering the conduct of science.

Recommendation 6: Include Plans for the Return of Individual Research Results in Research Protocols.

For all studies using human biospecimens, investigators should routinely address their plans regarding the return of individual research results in their funding application or research protocol. The investigator's plan should describe

- **A. whether individual research results will be offered to participants and, if so, when and how. The plan should also provide the rationale for these decisions, including how participant needs, preferences, and values were considered;**
- **B. how the consent process will reflect transparency and effective communication with participants regarding whether and, if so, how individual results will be offered;**
- **C. how investigators and their institutions will respond if participants request their results, including how information in the designated record set will be released to participants when they have a right to access their individual research results under HIPAA; and**
- **D. the budget and resources for the return of individual research results, when appropriate.**

The Role of Research Sponsors in Supporting Appropriate Planning for the Return of Individual Research Results

The National Bioethics Advisory Commission (NBAC) recommended in 1999 that investigators conducting research on human biospecimens be required to include in their study proposals documentation of whether and how individual research results will be returned to participants (National Bioethics Advisory Commission, 1999). Although there are few data to estimate how common such plans are across all relevant disciplines, one study found that only 30 percent of survey respondents had a formal plan for returning results. More than one-third of the investigators who had no formal plan indicated that they had not considered the need for one (Rigby and Fernandez, 2005). These data, along with the reported variability in investigator and IRB experience with planning for the return of individual research results (Dressler et al., 2012; Williams et al., 2012), suggest that the NBAC recommendation has not been widely adopted. In fact, some researchers have suggested that questions regarding the need to return individual research results and incidental findings should be handled on a case-by-case basis as issues arise, rather than developing policies and plans in advance (Williams et al., 2012). Consequently, it is likely that incentives will be needed to push the field to conduct routine advance planning for the return of individual research results.

Research sponsors and funding agencies (e.g., the National Institutes of Health, PCORI, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences) have considerable leverage to set

requirements and provide guidance related to planning for the return of individual research results in the studies they fund (Ohayon et al., 2017). Of note, recommendations for funding requirements related to planning for the return of individual research results have been made previously in the context of human biomonitoring studies. In 2006 the National Research Council recommended that research sponsors of human biomonitoring studies and programs require explicit planning for the communication of results in any application for funding (NRC, 2006).

Instituting funding requirements has been an effective mechanism for advancing practices that sponsors believe will benefit research and improve the consistency of practice across institutions and studies. For example, recognizing that effective stakeholder engagement requires careful advance planning, PCORI requires that all funding applications include an engagement plan, which is evaluated in the application review process (PCORI, 2015). Beyond promoting advance planning, the funding application review process provides an important opportunity to ensure that key considerations for the responsible return of individual research results (e.g., laboratory quality systems and approaches to assessing participant needs, preferences, and values) have been attended to and, in the case that investigators plan to return results to participants, that there is an appropriate budget to cover the expected costs. By allowing investigators to budget for the return of individual research results in funding applications, research sponsors can send a powerful message in support of a new research paradigm in which results are more routinely returned to participants.

CONCLUSION: By requiring, reviewing, and supporting return-of-results plans, research sponsors can foster a culture in which the return of individual research results is more routinely considered and conducted.

Recommendation 7: Ensure Planning for the Return of Individual Research Results in Applications for Funding.

Research sponsors and funding agencies should ensure that investigators are considering whether and how individual research results will be returned to participants, by

- **A. requiring that applications for research funding consistently address the return of individual research results, indicating whether, and if so, when and how individual research results will be offered to research participants, as well as the rationale for these decisions;**
- **B. including in the scientific review process for funding applications an assessment of plans for the return of individual research results; and**
- **C. building funding into grants and contracts or providing administrative supplements for the return of individual research results.**

The Role of IRBs in Reviewing Plans for the Return of Individual Research Results

IRBs play a critical role in human biomedical research. Given their core responsibility within research institutions for protecting the rights and welfare of participants, IRBs are well positioned to help investigators consider the return of individual research results in the development of research protocols (Dressler et al., 2012). In surveys and interviews, IRB professionals have generally held the view that investigators should anticipate the return of results prior to a study's implementation and that the issue of returning individual research results should be covered in the IRB application and informed consent document for IRB review and approval (Beskow and O'Rourke, 2015; Dressler et al., 2012; Ohayon et al., 2017; Williams et al., 2012). The IRB could then "ensure that an appropriate, ethical process is followed for making decisions and communicating with participants" (Beskow and O'Rourke, 2015, p. 7).

IRBs are more hesitant about being tasked with determining whether specific research results meet the criteria for return to participants and feel that their more appropriate role is to oversee the process for decision making (Beskow and O'Rourke, 2015; Dressler et al., 2012). Many IRB professionals expressed concerns about a lack of scientific (e.g., genomic) and medical knowledge that would be needed to make sound decisions and provide well-informed guidance to investigators based on the expected reliability and value of the result and the potential risks to the participants from returning it (Dressler et al., 2012). The necessary scientific expertise, however, need not always reside within the IRB membership. IRBs may have to rely on additional outside expertise—for example, by developing more involved partnerships with investigators, clinicians, participants, or community or patient advocacy groups or through using scientific review or community advisory boards (see Box 4-6)—to bolster their scientific knowledge base and understanding of participant perspectives so as not to be paternalistic in their decisions. Such institutional advisory bodies can also serve as resources investigators, providing direct guidance concerning the return of individual research results. The IRB will also have to take the context of the study into consideration when making decisions about investigators' plans for return. This is particularly the case in situations where the investigator is also the physician or caregiver for the participant, including in situations where the investigator is only transiently responsible for care in the context of the research, as this might influence the laboratory environments in which the research tests are conducted.

While recognizing the importance of having policies and procedures in place, few IRBs describe having actual experiences with the return of individual research results (Dressler et al., 2012; Williams et al., 2012), making it challenging to develop institutional policies and procedures. This gap in IRB experience will necessitate additional support for IRBs, including education and training as well as guidance (Beskow and O'Rourke, 2015; Dressler et al., 2012; Fabsitz

BOX 4-6

Memorial Sloan Kettering Cancer Center's Genomic Advisory Panel

In 2015, the Memorial Sloan Kettering Cancer Center established a genomic advisory panel (GAP) as a subcommittee to its IRB, which had a diverse membership, including physicians, scientists, psychologists, patient representatives, and clinical research administrators. The panel was charged with reviewing genetic results that were brought to its attention and advising investigators as to whether the results should be returned to participants or family designees. When a laboratory identifies a finding that may warrant return, it is sent to the GAP, which then reviews the finding, the patient's chart, and the consent documentation. If the finding is clinically actionable and the patient has consented to be re-contacted, the treating physician will then be notified about the research finding and can refer the patient for confirmatory testing. The development of these standard operating procedures by the panel ensures a standardized institutional approach to the handling of incidental genetic findings.

SOURCE: Memorial Sloan Kettering Cancer Center. Comment provided to the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, Washington, DC, October 20, 2017. Available by request through the National Academies' Public Access Records Office.

et al., 2010). Such guidance should include providing a guiding framework or "ground rules" while preserving the flexibility of IRBs to make decisions based on study and community context (Dressler et al., 2012; Fabsitz et al., 2010). Training exercises could be developed to allow IRBs and researchers to practice making contextual decisions based on case scenarios, and they would also help IRBs, institutions, and investigators better understand and plan for the logistics, infrastructure, and resources needed to support the return of individual research results (Dressler et al., 2012).

In the near term, this lack of experience with the return of individual research results may result in some reservations and a conservative approach (Ohayon et al., 2017). As with similar surveys of investigators, the positions of IRB professionals on returning individual research results have varied (Dressler et al., 2012;

Ohayon et al., 2017). On balance, however, these professionals expressed general support for returning validated individual research results, particularly when such results have clinical significance, are medically actionable, or have personal utility to participants (Dressler et al., 2012). In one survey, IRB chairs noted the "potential to overstate the risks of possible . . . disclosure, and talked of the difficulty of documenting the potential for harm" (Simon et al., 2011, p. 8). As researchers and IRBs gain more experience with returning individual research results, and as a stronger empirical evidence base on the benefits and risks is developed, IRBs may feel more comfortable with providing guidance and may become stronger proponents for expanding the practice of returning research results. In the meantime, interfacing with researchers who have experience returning individual research results may help IRBs develop and consider experience-based perspectives (Ohayon et al., 2017).

CONCLUSION: Some IRBs currently lack sufficient scientific and participant engagement expertise to assess research design and the likely validity, actionability, or utility of research results. IRBs will need additional expertise from an IRB–researcher partnership or outside input from scientific review committees and participant, community, or patient advocacy groups to help inform responsible and feasible institutional approaches to offering and returning research results. IRBs may also require input from engagement specialists and community advisors in order to acquire the expertise necessary to evaluate whether participant preferences have been appropriately considered in planning for the return of individual research results.

Recommendation 8: Develop Policies and Procedures to Support the Review of Plans Regarding the Return of Individual Research Results.

Research institutions and their IRBs should develop policies and procedures that support the assessment of plans for the return of individual research results. Policies and procedures should ensure that

- **A. the IRB has, or has access to, the necessary expertise to review the return of individual research results plans;**
- **B. appropriate consideration has been given to participant needs, preferences, and values (see Recommendation 5);**
- **C. the research teams have access to the appropriate expertise (e.g., a scientific review committee) to consider the factors relevant to decisions on returning individual research results, including analytic validity, clinical validity, and the value of the results to participants;**
- **D. the consent process is aligned with the return of individual research results plan (see Recommendation 9); and**
- **E. the investigators have access to the necessary resources (e.g., core resources) and expertise to enable the communication of individual research results in an effective manner (see Recommendation 10).**

CONCLUSION

The return of individual research results will create new demands on the research enterprise. The committee recognizes that many institutions and researchers currently lack the experience and resources to return individual research results appropriately and that balancing the validity of the results (discussed in Chapter 3) with participant preferences, needs, and values will not be an easy task. However, the committee emphasizes the need to consider participant preferences while ensuring the validity of the results so that only high-quality results are returned to participants with the appropriate information. The committee does not expect that the routine and widespread return of individual research results will begin overnight, but it does foresee an evolving set of responsibilities. The recommendations in this report are intended to help stakeholders discuss and prepare for these responsibilities in order to develop the necessary expertise, infrastructure, and resources over time. As that capacity is being developed, a tiered approach to implementation may be prudent for the operational reasons discussed in Chapters 3, 4, and 5 as well as for the legal reasons discussed in Chapter 6. As discussed earlier in this chapter, some institutions (e.g., those with CTSAs) have existing infrastructure and resources that enable them to serve as early adopters. While a tiered approach may support important learning processes, it will be important to ensure that mechanisms are put in place to assist those currently lacking the needed infrastructure and expertise so that this new set of responsibilities is not perceived as an unfunded mandate.

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5

Advancing Practices for Returning Individual Research Results

In the previous chapters, the committee addresses why returning results provides value to participants and scientific stakeholders, what research results could be returned, and the timing of returning individual research results. This chapter focuses on the "how." As discussed earlier in this report, the return of individual research results is a natural progression in the push for increasing transparency in the research enterprise, and the committee envisions a future where participants have greater access to their individual research results. The committee acknowledges, however, that expanding the return of research results places new demands on the research enterprise, including the development of needed expertise on study teams and assembling the resources needed to offer and return individual research results appropriately. Inconsistency in practices will need to be addressed in order to minimize the risk of harm from the return of results, an evidence base will be needed for the development of best practices for returning results, best practices will need to be developed and disseminated, and these best practices will need to be broadly implemented in order to prevent inequities. Recognizing that it will take time to fully implement best practices for the return of results—and that in the immediate term this will be an aspirational target—the committee sees opportunity for incremental progress. In the beginning, a number of relatively simple measures ("low-hanging fruit") could be implemented in ongoing and near-term studies without prohibitive investments of time or resources. These early steps have the potential to help the research enterprise begin to develop an evidence base for the return of results and will be important when working toward the committee's vision of a broad return of research results, as discussed in the previous chapters.

In this chapter the committee provides some concrete strategies for advancing practices for offering and returning results, including setting appropriate expectations for participants (for example, in the consent process) and incorporating established principles for effective communication into the return-of-results process. The chapter also discusses how the appropriate return of individual research results requires investment and careful forethought regarding the necessary contextualizing information, takeaway messages, and disclaimers. To return research results effectively will require research stakeholders to consider how to communicate in ways that are appropriate for participants with different needs, resources, and backgrounds. Returning research results can be done (and it can be done well), up-front investments can be scalable, and the development of best practices over time will improve the consistency and quality of the process of returning individual research results.

OPPORTUNITIES TO IMPROVE THE RETURN OF RESEARCH RESULTS: LEARNING FROM CURRENT PRACTICES

Given the complexity and uncertainty often inherent in research results, research teams would benefit from guidance on how to accomplish the challenging task of accurately communicating research results to individual participants. Investigators will need to understand how to effectively enable understanding and simultaneously communicate how to use individual research results when appropriate and how to caution against overuse. Importantly, previous experiences with returning results in health care and research settings can inform future best practice and guidance development by helping pinpoint what is effective and what is not with different groups of participants. In addition, principles for the disclosure of risks and benefits in the informed consent process will need to be adapted for use in best practices for the return of results.

Learning from the Return of Clinical Test Results: Opportunities and Limitations

The health care enterprise has considerable experience with the generation, interpretation, and return of clinical test results. In most clinical contexts, the flow of information passes through a clinician before reaching the patient. The clinician's role, therefore, has been one part gatekeeper and one part interpreter. It is important to note, however, that information technology is increasingly changing this pattern. In many health care systems, patients can access laboratory test results directly through patient portals to electronic record systems, thereby reviewing these data without a clinician present to explain the results and their significance (AHA, 2016). Furthermore, health systems vary in the degree that clinicians are required to review or annotate results before they are released to patients. Direct-to-consumer testing represents another model for the direct

return of results to an individual, one in which a clinician may not even know that a test has been conducted until the patient presents the result report to their physician (O'Connor, 2016).

While the health care delivery experience may offer lessons for the return of research results, this is not to say that best practices for communication are always (or even usually) applied in clinical practice. Research indicates that the current level of information provided with clinical test results may be insufficient to enable patients to understand their meaning (O'Kane et al., 2015). Clinical biomarker results, for example, are generally returned in numerical or tabular form with a standard reference range. However, recent evidence suggests that many patients struggle to determine whether a result is inside or outside of the standard reference range, which is the most basic form of understanding needed for meaningful use (Zikmund-Fisher et al., 2014). Sometimes (but not always) results are also accompanied by an interpretive statement from the ordering clinician, but the language used in such statements may vary across clinicians and situations. Despite this, there are situations in which clinical results are returned with additional contextual information where the purpose of the test and the information generated during the test are addressed. For example, in clinical genetics patients are often given substantial contextual information (e.g., counseling, the meaning of a negative result, clear statements of known impact of particular mutations) to help them understand their results (Haga et al., 2014). The same practices may be appropriate for research-based genetic testing, although research results may be associated with greater uncertainty, which may require further clarification.

Challenges communicating clinical test results and other medical information effectively may stem, in part, from gaps in health literacy[1] and other forms of literacy, such as graph literacy and health numeracy.[2] In 2006 the National Center for Education Statistics released a National Assessment of Adult Literacy and found that "the majority of adults (53 percent) had intermediate health literacy while about 22 percent had basic and 14 percent had below basic health literacy" (National Center for Education Statistics, 2006, p. v). Extensive research shows that low health literacy, poor numeracy, poor graphical literacy (Joint Commission, 2007), and language barriers all impede an individual's ability to interpret and use information such as test result communications (Rodríguez et al., 2013; Zikmund-Fisher et al., 2014, 2017). This underscores the importance of understanding the limitations that poor literacy may impose on understanding and emphasizes the importance of clear communication in the provision of health information (Joint Commission, 2007), including clinical and research test results. To address literacy

[1] Health literacy is "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (IOM, 2004, p. 20).

[2] Health numeracy is "the degree to which individuals have the capacity to access, process, interpret, communicate, and act on numerical, quantitative, graphical, biostatistical, and probabilistic health information needed to make effective health decisions" (Golbeck et al., 2005, p. 375).

and numeracy barriers, such information needs to be provided in a format and with content that is accessible to the target audience (Parker et al., 2016). This may entail

- creating materials in users' primary languages and considering language-based sources of misunderstanding to address language barriers,
- creating materials that reflect participants' preferences regarding terminology,
- using plain language to overcome low literacy (CDC, 2016; IOM, 2014), and
- using evidence-based formats that facilitate understanding of quantitative information by those with low numeracy and graphical literacy (IOM, 2014).

In addition, the National Academies of Sciences, Engineering, and Medicine's Roundtable on Health Literacy published a perspective on health literacy and precision medicine, which concluded that "participant input into the crafting of clear, navigable, and useful messages and processes" is a hard-learned lesson from the field of health literacy (Parker et al., 2016, p. 3). While those in the field of health care have acknowledged these gaps in practice which inhibit patient understanding and have made strides to correct this, there are still areas where improvements can be made to the processes of clinical test return and messaging. Research has the opportunity to learn from both the good and the bad in clinical test return. Doing so will allow the research enterprise to shape the return of research results into a practice that simultaneously benefits the participant most fully and is done in a way that does not burden the investigator. However, research sponsors and funding agencies will need to support an assessment of best practices and how to apply these to a research context first.

CONCLUSION: Many existing practices in the return of clinical results are potentially applicable to the return of individual research results, but they will need to be critically evaluated before they are adopted in the return-of-research-results context.

Learning from Current Practices in Return of Individual Research Results

Research results differ substantially from clinical test results in a number of ways, which limits the degree to which clinical experience can offer guidance on the return of research results. Most notably, research results are often associated with a greater degree of uncertainty as a result of incomplete scientific knowledge, and the uncertainties present at the level of individual results are even larger than the uncertainties present in aggregate results. However, as research continues, quality management systems are adopted by research laboratories, and evidence accumulates, the uncertainty in research test results can be reduced.

When patients' results are returned by the treating clinicians or clinical laboratories, the results are often accompanied by well-established population distributions or reference ranges[3] that enable interpretation by the patient and clinician (Medscape, 2014). Expected reference ranges for clinical tests (e.g., blood counts) are known because the results are generated by standardized procedures used across broad populations of patients which allow for the establishment of normal result ranges for different patient characteristics, such as age or gender. In contrast, because of the significant variability in practices used in research settings, a result may need to be accompanied by documentation on what was actually done or not done in order to evaluate its meaning (and potential value or actionability). Moreover, reference information (e.g., standard ranges) for research results is often unavailable, non-representative, or unreliable for understanding whether a result is normal or abnormal and for guiding decision making. As discussed in more detail later in this chapter, research teams will need to think carefully about what reference information is available and potentially valuable for use in communicating with participants about the meaning of their individual results.

Uncertainty is difficult to communicate, particularly when it relates to something that is already probabilistic in nature, such as genetic-related risk; therefore, uncertainty is often ignored (Han et al., 2011). A critical part of the return of research results, uncertainty needs to be conveyed effectively, or else investigators risk the participant putting too much or too little trust in the results. As discussed in more detail later in this chapter, attention needs to be paid to providing reference information that enables participants (and, in some cases, their treating physicians) to be able to interpret and understand the potential (or lack thereof) for using the research results.

Although the return of individual results is not currently widespread among research studies, certain investigators are already returning research results to individual participants. This is particularly true in the fields of genetics and environmental health (discussed in the sections "Returning Individual Genetic Research Results" and "Environmental Health and the Return of Individual Research Results"). These fields' experiences with the return of research results may be valuable in the development of best practices and guidance for other types of research results.

Returning Individual Genetic Research Results

In the field of genetics, some research investigators and direct-to-consumer (DTC) companies have been using and exploring methods for returning individual

[3] "A reference range is a set of values that includes upper and lower limits of a lab test based on a group of otherwise healthy people. The values in between those limits may depend on such factors as age, sex, and specimen type (blood, urine, spinal fluid, etc.) and can also be influenced by circumstantial situations such as fasting and exercise. These intervals are thought of as normal ranges or limits" (American Association for Clinical Chemistry, 2017).

results for years. Numerous surveys have been done to assess customer comprehension and interpretation and the psychological effects on customers of receiving their genetic results. While usability research has helped to mitigate concerns, the possibility that customers may not fully comprehend or will misunderstand results is always a worry. For example, the Food and Drug Administration (FDA) decision summaries for 23andMe carrier screening and genetic health risk tests include special controls that describe not only the criteria for user comprehension studies and the required performance on comprehension assessments, but the specific language that must be included when reporting results to the lay user to convey the likelihood that a particular positive test was in fact positive (FDA, 2015, 2017a,b). These studies find that consumers may overrate their ability to interpret test results, which may help explain why consumers are not likely to consult health professionals for assistance with test interpretation, even when such services are made available (e.g., genetic counseling offered via telephone) (Roberts and Ostergren, 2013). One important conclusion from studies evaluating consumer comprehension of DTC genome testing is that

> there may not be a one-size-fits-all approach to communicating genetic test information. Greater tailoring of the presentation of personal genetic testing information based on individual characteristics and type of test result may be needed—especially when results are not delivered in a clinical setting or via a trained health care professional. (Ostergren et al., 2015, p. 9)

In the 1990s, when the link between BRCA and breast and ovarian cancer was being established (prior to the development of a clinical test), a group at the University of Michigan developed a process for returning results to family members involved in a linkage study.[4] The process involved pre-counseling education and assessment, during which the risks and benefits of receiving results were explained and informed consent was obtained, and also a post-testing disclosure of results with clinical counseling by a multidisciplinary team (Biesecker et al., 1993).

Similarly, a survey of investigators who planned to return genetic research results found that the investigators frequently used more than one method for return, with the results most commonly returned using a genetic counselor or other trained professional (Heaney et al., 2010). The genetic counseling community is a rich source of expertise and experience in explaining laboratory test results to individuals. These professionals have skills and an understanding of genetic disorders combined with an education in laboratory methods that allows them to communicate effectively about test results, accuracy, interpretation, and

[4] "Genetic linkage study: A genetic linkage study is a family-based method used to map a trait to a genomic location by demonstrating co-segregation of the disease with genetic markers of known chromosomal location; locations identified are more likely to contain a causal genetic variant. This technique is particularly useful for the identification of genes that are inherited in a Mendelian fashion" (Nature.com, 2018).

limitations (what the test results do and do not mean) (Doyle et al., 2016; Miller et al., 2014; Patch and Middleton, 2018). In addition, these professionals focus on tailoring the return of complex information so as to respect the cultural, religious, and ethnic beliefs of the participants (Warren, 2011; Weil, 2001). It may be useful to engage genetic counselors once discussions progress to the design and implementation of return-of-results communication plans. Other methods used by investigators for the return of results by telephone, via mail, in person, via referral to a physician, or by e-mail. While some investigators were more inclined to return results if they had a medical degree and were able to provide detailed information to the participant in the context of the participant's personal health care, other investigators found that it was not always necessary to use a care provider to return results and interact with the participant.

A number of studies have emphasized the importance of the relationship between researchers and clinicians. For example, in the Framingham Heart Study results are given to the treating physician, who interprets results for the participant.[5] Geisinger Health System places genetic results in the electronic health records (EHRs) and notifies the primary care physician, who then discusses the results with their patient.[6] Additionally, a study returning results for genome sequences associated with pancreatic cancer emphasized that the ideal scenario for return would be one in which a close relationship existed between researchers and clinicians in order to enable full communication among investigators, clinical teams, and the participant (Johns et al., 2014).

However, this level of face-to-face communication with the input of a physician is not always possible, nor always necessary. Wendy Chung, the Kennedy Family Professor of Pediatrics and Medicine at the Columbia University College of Physicians and Surgeons, has discussed the variety of methods used by her team to return research results in their studies of the genetic basis of human diseases (Wynn et al., 2017).[7] The communication methods employed included giving participants the option of receiving results with a genetic counselor present to enable in-depth interpretation and contextualization of the genetic results or providing participants their nucleotide sequence data in a BAM file,[8] leaving interpretation up to the participant (perhaps through the use of outside interpretive services the participant could pay for) (Wynn et al., 2017). In providing a BAM file to the

[5] Testimony of Joanne Murabito of the Framingham Heart Study at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[6] Testimony of Adam Buchanan of Geisinger Health System at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[7] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[8] The BAM format is a binary format for storing sequence data (University of Michigan Center for Statistical Genetics, 2013).

participants, Chung said, she was not concerned that they would not understand the results, but rather she was concerned about perpetuating health disparities—by providing only the sequence data to participants, it could put those who could not afford outside services for analysis at a disadvantage.[9] However, Chung did caution against providing participants a VCF[10] file containing a list of their genetic variants because the genetics community is not in consensus about what many variants mean, so providing these files could lead to misunderstanding on the part of the participants.[11] Similarly, Jessica Langbaum of the Banner Alzheimer's Institute described options for returning genetic results, including in-person counseling, telemedicine, and Web modules. She said that the field is still struggling to determine what delivery modalities are available, scalable, and most appropriate and that further work needs to be done.[12]

The various practices discussed above ultimately demonstrate that the return of results involves varying types of data, can be done using a wide range of methods, and can be tailored to the nature of the research being conducted. This heterogeneity represents a significant challenge to the design of return-of-results processes, particularly when potentially incorporating participants' varying preferences. There is both value in adjusting the format or language of communication according to participant preferences and evidence that what participants say they want is not always what will maximize their comprehension. Because the trade-offs may be different in different situations, the committee suggests that investigators should consider incorporating participant preferences, but it has not specified exactly how that should be done.

Environmental Health and the Return of Individual Research Results

The return of research results from environmental health biomonitoring[13] studies is well established both in the literature and by guidelines proposed by expert groups (Brody et al., 2014; Dunagan et al., 2013; Exley et al., 2015; Haines et al., 2011; Judge et al., 2016; Morello-Frosch et al., 2009; Quigley, 2012). The return of results in this field is done because the research participants generally have a significant interest in learning their individual research results for their

[9] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[10] The variant call format (VCF) is a generic format for storing DNA polymorphism data such as single nucleotide polymorphisms, insertions, deletions, and structural variants, together with rich annotations (Danecek et al., 2011, p. 2156).

[11] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[12] Testimony of Jessica B. Langbaum of the Banner Alzheimer's Institute at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[13] Biomonitoring is "the assessment of human exposure to chemicals by measuring the chemicals or their metabolites in human specimens such as blood or urine" (CDC, 2005, p. 1).

own use and safety (Brody et al., 2014). A key consideration in determining how best to report results in an environmental monitoring study is whether a known clinical range or action level has been established for the analyte being assessed (a point we reinforce later in this chapter). Where a clinical or preclinical effect is known, this knowledge allows better guidance to be provided to participants, particularly in terms of follow-up. As is the case with exposure to lead or arsenic, acceptable blood levels and public health procedures are defined with the goal of mitigating future exposure (CDC, 2018; WHO, 2017), although it is not uncommon for such guidance to change over time. For example, The Maternal–Infant Research of Environmental Chemicals study used predetermined guidelines to define its return and communication strategy, specifically, whether a result exceeded normal levels and might be associated with a health risk (Haines et al., 2011). However, it is not uncommon for a chemical, pesticide, or other environmental contaminant to lack reference-range information, (i.e., an analyte that is not well characterized in a population) or to have differing reference ranges or other bias in datasets that can cause challenges in interpretation (NRC, 2006). Therefore, determining the meaning and clinical interpretation of such test results can be a challenge, and "reference ranges do not provide conclusions on safety or risk. Presenting that fact and other limitations is an essential aspect of communicating reference-range information to individuals, the general public, and organizational decision-makers" (NRC, 2006, p. 151).

The return of research results with unknown clinical significance is also practiced in environmental health research. In 1999 the Household Exposure Study, which focused on identifying 89 endocrine-disrupting compounds, grappled with questions of whether the results (both from biomonitoring and environmental samples) should be returned to participants, including those results with unknown clinical meaning. Ultimately, after consideration of ethical guidelines and in consultation with community members, investigators allowed participants to access their individual and household results (Brody et al., 2007, 2014; Dunagan et al., 2013). Similarly, in 2004 the University of Michigan Dioxin Exposure Study, which conducted tests for the presence of 29 dioxins, furans, and polychlorinated biphenyls in participants' blood, household dust, and residential property soil, also gave participants the option to choose whether they would receive the results from each of their samples (Garabrant et al., 2009). This option was provided for two key reasons. First, regulations were not available for the dioxin content of household dust, nor were medical guidelines available for the interpretation of serum dioxin levels at the time. Second, the researchers were aware that the disclosure of soil levels to property owners could cause those participants financial harm by affecting their property values.

In general, this literature concludes that the unknown should not dissuade investigators from returning results with uncertain meaning because "what little evidence we have suggests that a globally uncertainty-averse public is a myth; responses [to receiving uncertain information] vary widely across the population"

(NRC, 2006, p. 207). This variability does, however, emphasize the need to return information with the input from the community or study population as results can often have community-wide implications or health risks.

As the committee heard in discussions with environmental health researchers, those participating in environmental exposure studies frequently want to know their results because they are the ones carrying the products of these exposures in their bodies.[14] For this reason, investigators in this field may feel a greater need to return such results. Such studies also frequently take place in communities where several households are affected and, therefore, the results of the study will likely be translatable to many in the community. To this end, investigators may use community partnerships in the design of communication plans. In a study by Erin Haynes of the University of Cincinnati, community engagement was used to develop the methods of communication used in the return of results (Haynes et al., 2016). Working together, the study team and community members developed easy-to-read graphics and written materials tailored to the reading level of the recipients as well as a comparison to help in the interpretation of their results (i.e., comparing a recipient's results with those from other studies or for other children). The research team found that including community input in the development of its dissemination plans helped them translate biological data into a format that was usable by the target audience. Haynes et al. concluded that "scientists should include community partners from the target population in the development of research and data disclosure strategies in order to enhance the quality of research, to support the rights of the study participants to know their individual results, and to increase environmental health literacy" (Haynes et al., 2016, p. A26). See Box 5-1 for select engagement and communication practices for the return of research results in environmental health.

CONCLUSION: Current research projects that return research results to individual participants use a variety of practices that have been tailored to reflect differences in study goals, populations, types of results, and other factors.

Applying Principles for Effective Communication to the Return of Research Results

Applying existing principles for clear communication represents a concrete strategy for improving the quality of return-of-results practices. While the body of evidence is still small, these issues have begun to be examined in health communication and environmental health studies. California law, for example, requires that biomonitoring results be made available to participants, and the state has

[14] Testimony of Nicholas Newman of the University of Cincinnati at the public session of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on October 24, 2017.

BOX 5-1

Select Engagement and Communication Practices for the Return of Research Results in Environmental Health

CANADIAN HEALTH MEASURES SURVEY (CHMS)

This environmental exposure study used peer-test focus groups to determine that the return of results was a primary motivation for participation. CHMS personnel met with local public health officials prior to data collection with information about the study and its possible results. Local doctors were asked to reach out to these public officials for advice or support if their patients came to them with research results. The return-of-results communication plan was developed in collaboration with the CHMS Laboratory Advisory Committee, Physician Advisory Committee, and the reference laboratory. Individuals could choose whether they wanted to receive results, but if something of concern was discovered during testing, the participant would receive a written notice asking whether he or she wished to learn about a result of interest or concern. Results that were above the population reference range were flagged for return. When requesting results, participants received a disclaimer noting that, given the current state of scientific knowledge, it was not possible to provide an interpretation of individual risk. Information about health risks, dose–response relationships, and intervention strategies was uncertain or not available for most variables measured (Haines et al., 2011).

LA FAMILIA STUDY

This community-based participatory research study sought to address likely challenges, such as explaining the uncertain health significance of data where action levels have not yet been set by the Centers for Disease Control and Prevention (CDC). Researchers reviewed existing risk communication strategies, networked with more experienced investigators, sought the community's input, and assessed local health literacy and numeracy. The return-of-results communication plan was approved by the university's institutional review board (IRB) and used

continued

BOX 5-1, CONTINUED

face-to-face meetings between study staff and the participant for the delivery of results. Participants were given their results in comparison to results from other households and given information about the health impacts of pesticide exposure and information about environmental abatement and exposure prevention (Quandt et al., 2004).

GROWING UP FEMALE

During the consent process, the child participants were informed that elevated blood sugar, insulin, blood pressure, and cholesterol would be reported back to their parents and that "the investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study" (Hernick et al., 2011, p. 2). Participants and their guardians were not told which biomarkers would be analyzed. During the data collection phase, the CDC alerted the investigators that there were elevated perfluorooctanoic acid (PFOA) levels among a specific cohort of participants. Researchers searched the literature to better understand the potential risk of elevated PFOA and what follow-up should be conducted. The investigators also sought advice from environmental health research organizations and researchers with experience reporting biomarker results to participants. The IRB was notified that new results were going to be returned, given a description of the communication plan, and provided with copies of all materials to be distributed to families. The communication plan included presentations, an informational packet, a visual depiction of results, a summary of study findings, a glossary, FAQs, contact information for a phone line for questions, and a press release. Families were invited (both in written form and over the phone) to family meetings. The primary investigator and a physician known by the families presented a study update and the cohort's biomarker results, including a comparison of the cohort's PFOA results with national data and data from other cohorts in other parts of the country. Families then received the individual serum and urine biomarker reports for their children. The primary investigator and other researchers facilitated one-on-one or small group discussions of the results (Hernick et al., 2011).

conducted usability testing for content, allowing others to benefit from this work (Biomonitoring California, 2018; Brown-Williams and Morello-Frosch, 2011). More empirical testing is needed to guide stakeholders, but there is work already occurring in this arena (as discussed above). IRBs would benefit from using best practices and reviewing the literature outside of their field; e.g., biomedical scientists can benefit from the existing guidance in environmental monitoring in developing their return-of-results communication plans. IRBs do not need to rely on gut opinions when evidence-based guidance exists and can inform participant and community input in plans. The key principles in communication that have been identified include (1) taking audience characteristics and needs into consideration and (2) having a clearly defined communication objective (i.e., what cognitive, emotional, motivational, or behavioral outcomes should ideally result from the communication) (Haga et al., 2014; Nelson et al., 2009; Schiavo, 2014).

Consideration of audience characteristics and needs includes taking into account how much background knowledge a research participant has (i.e., what he or she knows about a particular disease or condition, about research, etc.) and what kinds of experiences the participant has had in the past. Research studies need to approach all participants and every community with respect and cultural humility. Doing so supports the development of trust between researchers and participants, and such trust is especially important given the known history of exploitation in racial and ethnic minorities and intellectually disabled individuals (Carlson, 2013; Corbie-Smith et al., 2002; Yancey et al., 2006). Because different stakeholders will have varied perspectives and preferences, those differences need to be considered and weighed. It may be necessary to design separate return-of-results communication plans for different stakeholder groups, since something designed for one audience is likely to be non-optimal for other audiences. As a result, a one-size-fits-all approach will rarely be effective in results communication.

Research studies are designed to produce generalizable information that is applicable to the broad population and results have meaning to multiple users, from the participants who contributed to the study to the investigators who ran the study. Results can sometimes be interpreted as a characteristic of an individual participant rather than an aggregate result reflective of a broad population, making it relevant or meaningful to family members, a physical community, or a demographic group, which may have implications for the communication approach. For example, the discovery of a genetic variant in a participant provides information about that individual participant's future disease risk but, if the variant is heritable, the discovery may also offer information about family members' risks and lead to generalizations about a group's risk. Similarly, an environmental exposure result may be relevant not only to the participant, but potentially to others who share that environment (e.g., family members, neighbors, coworkers).

Using layered presentations of information is a key communication approach for meeting different needs. For example, many communications should start with a clear and concise summary of the primary points that is designed to be

maximally understandable to all users. However, providing access to more detailed information (which may be more difficult to understand) is often beneficial for users with greater personal interest, literacy, or numeracy skills. When participants have different informational baselines and literacy levels, research teams will need to consider how much background information to provide to each audience. For some people, "less is more," while for others, "more is more" (Arcia et al., 2016).

When returning results to participants investigators need a clearly defined communication objective and should consider what specific change in knowledge, beliefs, motivation, or behavior is intended. The objectives of the communication will need to take into account the individuals' needs more than the investigators' needs, and they should be focused, with just one or a few objectives. A general truth is that the more one attempts to convey in a communication, the less effective that communication is likely to be (Heath and Heath, 2007).

Good design practices can significantly improve people's ability to overcome communication barriers. For example, the CDC's Clear Communication Index identifies key characteristics that enhance and aid people's understanding of information. These include the use of materials translated into the recipient's primary language, use of plain language with minimal jargon, use of good visual design principles, and use of evidence-based visual displays of data (CDC, 2016; Kosslyn, 2006; Plain Language Action and Information Network, 2018; Tufte, 2001). These practices represent minimum standards that all results communications (including clinical results) should achieve. As such, they should be included as part of training initiatives for investigators and clinicians as the research enterprise works to build the necessary expertise for effective return of results.

SETTING PARTICIPANT EXPECTATIONS IN THE CONSENT PROCESS AND BEYOND

In returning research results to participants, investigators should set participants' expectations up front (Tarrant et al., 2015). This will require investigators to plan for when and how results will be returned early in the study process both so that participant preferences can be incorporated in the study design and participant expectations for the return of results can be addressed during the initial consent process. Addressing expectations during the initial consent process not only helps build trust between the researcher and participants, but it also provides information to participants to make a decision about whether to participate in the study.

Consent is more than just telling a participant what he or she should expect and ensuring participant comprehension. Consent design also prepares investigators for the role of administering consent; this requires investigators to establish a strategy for how consent will be administered (including the use of educational materials) (Nusbaum et al., 2017). Consent may be a one-time event or an ongoing process, particularly if results will be returned at intermittent times over the course of the study. In particular, the traditional consent occurring only

at the time of enrollment may not always be sufficient (Appelbaum et al., 2014). There are several key issues related to the return of research results that investigators need to convey clearly to participants, regardless of the model of consent used. These include (1) what will be returned to research participants and how it will be returned, (2) the appropriate reference information and communication formats to enable understanding, and (3) the benefits and harms that may occur.

First, during the consent process, investigators will need clarity regarding what individual results will be offered to participants or what individual research results participants can access upon request;[15] when participants can expect results; the conditions under which researchers will alert participants of the availability of results; and how and when results will be communicated to participants (Fernandez et al., 2012; Simon et al., 2011). The Multi-Regional Clinical Trials collaborative has developed a toolkit that provides guidance for informed consent documents and processes for the return of general as well as genomic research results (MRCT Center, 2017b). In planning the consent process, investigators also will need to consider whether participants have a right to request and receive their results under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) access right (i.e., when research laboratories operate as part of a HIPAA-covered entity, discussed more in Chapter 6). It is not clear how many participants (or patients) are aware of their HIPAA access rights, but researchers and institutions have an obligation to disclose participants' right to access research results under HIPAA, when applicable. Regardless, information about access rights should not be buried in the consent form. Rather, this particular pathway for accessing results, when applicable, should be made clear during the consent process. The consent should also explain how results will be returned in response to a request under HIPAA. The HIPAA access right may grant access to raw data, but it does not require that participants receive a tailored message as might be expected in a clinical care setting. Still, while HIPAA does not require the investigator to provide interpretation, in any case where results are to be returned, the goal should be to provide them in a way that is useful.

Second, due to the variability in research results and the frequent lack of clear reference information, participants may need help in determining whether they want the results and, if so, what the results might look like. To further shape participant expectations and guide decision making during the consent process regarding which results, if any, they would like to receive, it may be helpful to provide participants with examples of what results may look like (NHGRI, 2018) and

[15] As discussed in Chapter 3, what research results will be offered will depend on the analytical and clinical validity, the value to the participant, and how feasible it is for the investigators to return the results. These considerations will be weighed in determining what to return and the timing for return. Timing will be especially relevant in longitudinal studies or trials where information may need to be withheld to support study design objectives. Additionally, if blinding is required in a clinical trial, results may not be able to be returned as they are generated because it may jeopardize the scientific integrity of the study (MRCT Center, 2017a).

how they may experience possible outcomes of their choice (Hibbard and Peters, 2003). Concrete examples can help people consider how they would feel or what they would do based on specific findings (versus whether they want to know "their results" in general) (Kim et al., 2017), which may be particularly helpful when addressing the risks and benefits of receiving results. While descriptions of possible outcomes are important, case studies or hypothetical narratives may also be useful to enable participants to anticipate not just what the possible results might be but also their potential implications (medical, emotional, or otherwise) (Shaffer et al., 2013). The examples that investigators provide of the types of results that might be returned would not be based on the participants' data, but rather would be derived from previous research that used similar assays; this will give participants a sense of what the information will look like upon return. Having participants engage in a brief values clarification exercise may help them determine what they care about and hence whether the receipt of different types of test results might confer benefits or risks to them (Fagerlin et al., 2013; Holly et al., 2016).

Third, receiving either clinical or research test results can result in both benefits and harms, and it is critical to address these during the consent process. The benefits of receiving results may include the identification of treatable disorders, enhanced life planning, or increased knowledge about oneself. Certain types of results may have immediate practical benefits, and participants should be informed of the conditions under which researchers will alert them of the availability of urgent results. However, framing the possible value of information in a purely positive manner (overly focusing on benefits in relation to risks) is ethically inappropriate. The risks associated with the return of results can take the form of participant anxieties and fears or the misuse of research results in a medical context, leading to inappropriate medical or personal actions. In addition, results that are not actionable may cause emotional or other sorts of distress (Zikmund-Fisher, 2017). Investigators will need to consider both the benefits and the risks prospectively, but under certain circumstances they may not even know that tests will be done; therefore, they may not always be able to offer participants a great deal of specificity when describing the potential benefits and risks (Appelbaum et al., 2014). To adequately address the potential harms from return of research results, investigators will need to acknowledge the uncertainty in research and the possibility that non-useful information will be generated. Furthermore, in addition to sometimes lacking usefulness, research results may also sometimes be incorrect. For example, a research test may generate a false-positive[16] or false-negative[17] result, either of which can cause emotional, physical, or financial harm. Alternately, the understanding of the science behind the result may change, thereby affecting

[16] False positive is when an individual is incorrectly identified as having a disease or condition (Baratloo et al., 2015).

[17] False negative is when an individual is incorrectly identified as healthy and not having the disease or condition (Baratloo et al., 2015).

the meaning of the result for the participant. The emotional or psychological harms that may be associated with return should be discussed with participants during the consent process and again later in the study process, when investigators are actively returning results.

The design of the consent process should consider that participants' desires and willingness to take on risk may change over time and that the meaning of the results may change over time. As a result, participants ought to be given the opportunity to determine whether they want to receive their research results when they are eventually made available to the participants. Even if a participant consented to receiving results at the start of a study, he or she should have the opportunity to refuse (or accept) results once available. To accomplish this, when planning their studies investigators may need to consider models of flexible consent that will include return of research results. One option outside of a one-time consent is a staged model for consent (Bunnik et al., 2013). Staged consent means that investigators "obtain consent in stages, with brief mention of [incidental findings] at the time of initial consent, but with more detailed consent obtained if and when reportable results are found" (Appelbaum et al., 2014, p. 6). The flexibility of staged consent models must, however, be weighed against the fact that participants who are re-contacted for further consent may infer (accurately or inaccurately) the type of result that has been found (i.e., positive or negative, good or bad) simply because of the new contact.

Models of Consent

Current consent processes are not standardized and are frequently inadequate to ensure understanding on the part of all participants. In fact, some research suggests that clinicians rarely meet even the minimum standards for disclosure necessary for the purposes of obtaining true consent (Hall et al., 2012). Unfortunately, many investigators do not have appropriate training in consent practices. Furthermore, they can (much like participants) be susceptible to therapeutic misconception and may, as a result, convey biased messages to participants (Larson et al., 2009).

In selecting a consent model and administering consent, investigators may want to consider how technology can facilitate the consent process. For example, technology can be a particularly helpful way to incorporate the principles of health literacy (as discussed previously). Health literacy has a strong impact on what individuals understand and how they use information related to health care and decision making. As such, investigators would benefit from capitalizing on best practices in health-literate informed consent (see Box 5-2). "The challenge is finding practical, non-onerous ways to respect persons' choices that have minimal negative effects on the science. Information technology may provide new opportunities to implement informed consent with minimal intrusion" (Grady et al., 2017, p. 857). For example, technology-assisted consent, such as the Apple

BOX 5-2

Best Practices for Health-Literate Informed Consent Related to the Return of Individual Research Results

ORGANIZATIONAL LEVEL

- Create a culture that places a high value on the transparency of the return of individual research results during the informed consent process. Creating a culture that values truly informed consent leads to better patient-centered practices and communication.

TRAINING AND STAFFING

- Train staff on the informed consent process for the return of individual research results, including how to address possible challenges that may occur, how to encourage participant questions, and how to prioritize information shared with the participant.

MATERIALS FOR CONSENT

- Write with little to no technical jargon.
- Format documents using large type and white space.
- Translate all documents into the primary language used by participants.
- Measure the reading level of documents to ensure a less than eighth-grade reading level.
- Match level of risk associated with the return of research results with the amount of information provided.
- Augment materials as needed for people with low health literacy or limited English proficiency.
- Use supplemental decision aids and other visuals as needed, which can be in a video, on a computer, or in an infographic format.
- Weigh the benefits of using multimedia and new technology against population characteristics such as age, education, health literacy, cultural values as well as digital literacy.

BOX 5-2, CONTINUED

CONSENT PROCESS

- Assess comprehension before beginning informed consent procedures to determine what the participant already knows about the return of research results to tailor information that can efficiently address needs and gaps in understanding.
- Prioritize the most important pieces of information at the start and end of the process.
- Rely on verbal exchange for supporting and reminding participants about the most important aspects of returning research results, including risks and benefits as well as confidentiality.
- Use the "common language" used by participants as well as plain language.
- Encourage participants to ask questions.
- Repeat information in different ways until participants understand.
- To ensure comprehension of the return-of-research-results options, apply strategies such as asking open-ended questions, teach-back, and teach to goal.

SOURCES: Adapted from Aldoory et al., 2014; IOM, 2015.

Research Kit for mobile devices, which includes a layered approach to consent in which the formal consent document is augmented by a visual, animated sequence, helps the user better understand the consent contents (ResearchKit, 2017).

Additionally, video-aided consent, like that used in the ADAPTABLE trial, can contribute to participant understanding (ADAPTABLE Asprin Study, 2018; Grady et al., 2017). Tele-consent is another method that enables researchers to remotely video-conference with prospective research participants. With tele-consent, investigators create a display that interactively guides participants in real time through a consent form, which they then electronically sign (Welch et al., 2016). However, while the use of electronic methods for consent may offer advantages for the return of research results in terms of convenience as well as providing varied approaches (e.g., use of multimedia interactive formats) for increasing understanding of the information and making possible structured assessments of that understanding, there are also a number of challenges that need to be considered

(Welch et al., 2016). These challenges include the fact that many people do not read terms of agreements on computers and mobile devices, there is a dearth of evidence regarding the advantages and disadvantages of electronic methods in terms of understanding of information, and since there are no face-to-face visits, verifying the identity of the individual giving consent may be difficult (Grady et al., 2017; NPR, 2014).

In addition to ensuring that investigators are meeting the communication needs of participants with health-literate consent, investigators and IRBs will need to consider the trade-offs among consent models and formats, no matter which model of consent is used, whether traditional paper or electronic format. See Table 5-1 for an example of how the advantages and disadvantages of consent models were assessed for the return of secondary findings. Table 5-1 discusses these secondary findings (also referred to as "incidental findings") and consent. The committee considers secondary findings to be results that can be anticipated on the part of the investigator and that considerations similar to those presented in this table can be made for any anticipated result, whether or not it is the primary aim of the study or test. Fully assessing the models of consent and closing gaps in communication during consent, particularly with the added considerations that accompany returning results, will require training for investigators and clinicians. Such training will take concerted effort, but it has the potential to enhance benefits, minimize harm, and build trust in the research enterprise.

CONCLUSION: Details regarding the return of individual research results to participants are currently only addressed during the consent processes on an ad hoc basis, creating inconsistency across studies and institutions and inadequately setting participant expectations.

CONCLUSION: How the return of individual research results is, or is not, addressed in the consent process affects participant expectations.

CONCLUSION: The heterogeneity of research study designs and populations means that different consent processes will be appropriate in different situations, but regardless of the type of consent process, clear communication appropriate to varying levels of health literacy is essential.

Recommendation 9: Ensure Transparency Regarding Return of Individual Research Results in the Consent Process.

In the consent process, investigators should communicate in clear language to research participants

A. which individual research results participants can access, if requested, including any results participants have a legal right to access under HIPAA, and how to request these results; and

TABLE 5-1 Potential Advantages and Disadvantages of Models of Consent to Return of Secondary Findings

MODEL NAME	POTENTIAL ADVANTAGES	POTENTIAL DISADVANTAGES
1. Traditional Consent	• Resembles traditional process, familiar to the research community • Participant receives all secondary findings information prior to deciding whether to participate • Participant maintains choice about types of secondary findings to receive, or about opting out	• Adds time and information to lengthy and complex process • Participant preferences may change after initial consent
2. Staged Consent	• Reduces time spent discussing secondary findings during initial consent; more detailed information provided later if secondary findings occur • Participant makes decisions on secondary findings closer to the time of receipt, can consider current circumstances • More detailed and specific information for participant • Participant maintains choice about types of secondary findings to receive, or about opting out altogether	• Following-up and recontacting participants for consent could be costly and burdensome • Participant's decision to enroll in study made without full information about potential return of secondary findings • Depending on procedure, recontacting participant may reveal unwanted information about a secondary finding, with negative impact on participant

continued

TABLE 5-1, Continued

3. Mandatory Return	• Simplifies consent at enrollment: participant receives information only on selected secondary findings, does not have to choose which findings to receive • Researchers' obligations to return secondary findings clearly defined and limited to a pre-determined list • Degree of choice maintained about whether to participate in the study	• Participant choice restricted—cannot choose which findings to receive, and cannot refuse to accept designated findings • Lack of participant choice may be disincentive to enroll in genomic research • Efforts to follow up and re-contact participants could be costly and burdensome for researchers
4. Outsourcing	• Researchers do not have to spend time explaining implications of secondary findings—would be outsourced to entities that specialize in interpretation/ communication of, for example, genomic information • Costs associated with return of results avoided, including recontacting participants, hiring additional staff to communicate results, etc. • Participant spared immediate task of deciding which secondary findings to receive; can pursue this question later with entity of their choice • Researchers' obligations simplified to the return of each participants raw data	• Though participant receives all data, may not become aware of medically significant data • Services for genomic interpretation and counseling not widely available at present—could be mitigated if demand increases • May exacerbate health disparities, since further interpretive services may be costly and hence limited to wealthy participants

SOURCE: Adapted from Appelbaum et al., 2014.

B. which individual research results, if any, will be offered to participants and why, and the participant's option to decline to receive their research results.

C. If results are going to be offered, the following elements should also be communicated during the consent process:

1. **the risks and benefits associated with receiving individual research results;**
2. **conditions under which researchers will alert participants of urgent results;**
3. **at what time and through what process results will be communicated to participants;**
4. **whether the results will be placed in the participant's medical record and whether the results will be communicated to the participant's clinician; and**
5. **when relevant to the research protocol, the participant's option to have results shared with family members in the event the participant becomes incapacitated or deceased.**

EFFECTIVELY COMMUNICATING INDIVIDUAL RESEARCH RESULTS TO PARTICIPANTS

Once test results have been generated and the decision has been made to return these to research participants, investigators and institutions need to ensure that the results are delivered in an appropriate manner that achieves the communication goals and meets participants' needs. Optimal communication methods need to be determined on a study-by-study basis both because the goals for each study are different and because the research team will need to take into account context-dependent considerations, such as the type of the research results (and their associated uncertainty) and the characteristics of the participants. As discussed above, participants with low health literacy, low numeracy, low graph literacy, or limited English proficiency are likely to have more difficulty with interpreting the results and understanding what kinds of actions may be appropriate in response to the result (Perzynski et al., 2013). Consequently, the processes for returning individual research results must either (1) use a "universal precautions" approach (Brega et al., 2015), which assumes that all research participants may have difficulty comprehending the information and promotes communication in ways that anyone can understand, or (2) include tailored approaches to meet the information needs of the research participants who wish to have more detailed information. (Box 5-3 highlights FDA experience with communication.)

BOX 5-3

Presenting Laboratory Results to Consumers—Experiences of the Food and Drug Administration

The Food and Drug Administration (FDA) may provide useful examples for how to ensure reader comprehension. FDA has been reviewing and approving over-the-counter (OTC) tests (either to be performed at home or to be collected at home and sent to a laboratory for testing) since the passage of the 1976 device amendments to the Food, Drug and Cosmetic Act (FDA, 2018c). With their years of experience on how to effectively label laboratory tests for the consumer, FDA has established guidance that includes methods to ensure that results are reported (and risks are addressed) in a way that lay users can understand (FDA, 1989, 1995, 2001, 2009, 2018b). Reader comprehension studies are part of the requirements for OTC products to ensure that labels are understood appropriately by the users (FDA, 2018a). A good example of the type of reader comprehension studies and their importance in the review process can be found in the summary of safety and effectiveness posted by FDA about the approval of the first HIV home test kit (FDA, 2012). In many research settings, the exhaustive list of caveats that FDA requires on consumer tests may not be necessary, but it may serve as helpful guidance for investigators when considering the types of information to include.

Facilitating Understanding of the Meaning and Limitations of Results Through Reference Information

Having access to information is not the same as being able to understand and use that information. In particular, studies in both the consumer product marketing and medical decision-making fields have shown that people find it difficult to interpret unfamiliar data in the absence of relevant reference standards (Hsee, 1996; Zikmund-Fisher et al., 2004). As a result, hard-to-evaluate information is often ignored or not used in decision making. Many recipients of clinical test results are unable to interpret them because of a lack of familiarity with test characteristics or the possible range of test outcomes. Furthermore, even when recipients know what the result is, they may not understand its practical meaning (in terms of whether concern or action is appropriate) (O'Kane et al., 2015).

In sharing individual research results with participants (especially when results are offered as part of a return-of-results plan), research teams need to communicate not just what research or test was done, but why it was done and how. To improve the meaningfulness of research test results, especially those that are difficult to understand or that are generated from tests that are not commonly used, research teams need to provide clear cues regarding (1) how much participants should trust the result and (2) what the result means or what is not known about the meaning of the result. This is because the types of laboratory tests used in research studies may generate results that are more likely to produce hard-to-evaluate data because these tests are novel, their analytic validity is unknown or being established, or their clinical validity is unknown (see Chapter 3 for more details). To help make it easier for participants to understand results, investigators need to pay attention to what reference information (e.g., standard reference ranges, comparative risks, or categorization information) is needed or appropriate for each type of result communication. The information provided with the result may dictate recipients' understanding and actions even more than the result itself. In some cases, results may need to be accompanied by multiple types of reference information (when available) to enable participant understanding.

To be clear, providing reference information for a result is not the same as providing personalized interpretation, such as clinical guidance. Clinical guidance requires integrating a research test result into the participant's individual circumstances (e.g., known medical conditions, family history). While such integration is sometimes expected in certain study contexts, investigators may not be clinicians or may not be familiar with the specific health of the participant, in which case providing clinical guidance would not be appropriate. Additionally, clinical guidance may be labor intensive, requiring investigators to tailor the research results and reference information to each individual participant's circumstances. Reference information, however, is a function of the test and the circumstances of the study but not of the individual. Consequently, providing reference information is scalable: investigators can more easily return results to a large number of participants because, in general, the reference information is applicable to all of them or to all similar participants receiving the same test. Emphasizing the identification and communication of appropriate reference standards is hence a cost-effective way of improving return-of-results communications.

Relevant reference information may be well established and standardized or may be unknown. For example, environmental contaminants such as radon and arsenic have established action thresholds or other benchmarks set by the Environmental Protection Agency. Similarly, standard clinical tests have established reference ranges (often interpreted as the range of normal values) and sometimes even pre-defined critical values (i.e., values high or low enough that a laboratory is obligated to immediately notify treating clinicians about the result to minimize associated risks; an example would be an elevated glucose level). In a genetics context, the impact of having a known *BRCA1* mutation on lifetime breast cancer and

ovarian cancer risk is relatively well established when family history is also known (Paul and Paul, 2014). Other times, however, reference knowledge is known but no standard guidance is available; i.e., the reference information that is available cannot be generalized to a population. Alternately, reference information may not be well understood or may be completely unknown in research contexts. For example, safe or dangerous levels for a particular toxin or novel biomarker may not have been established. Dose–response relationships may be unknown or difficult to estimate for particular populations. Even relative standards, such as percentiles compared to reference distributions, may be unavailable or incorrectly used if no previous studies exist or if previous studies involved different populations, such as different racial or ethnic groups (Holland and Palaniappan, 2012). Genetic variants often have no clear significance or correlations with health outcomes, and many times the prevalence of the variants in different populations is unknown (Caswell-Jin et al., 2017; Saulsberry and Terry, 2013).

The more that is unknown about reference standards for a particular result, the more that the participant and either the investigator or the individual performing the communication should have a two-way communication to clarify "what this result means for me." Clarification of meaning via dialogue is important not merely to improve participant understanding, but also to prevent an inaccurate interpretation or over-interpretation of results. When reference standards for a result are not known, investigators should weigh the benefits and risks of return and consider whether a return of aggregate results only would be more appropriate than a return of individual results. Regardless of whether aggregate or individual results are returned, the fact that reference information does not exist should be explicitly communicated to participants.

When developing a return-of-results plan, one explicit step should be the identification of appropriate reference information to be provided to participants. The reference information varies by the nature and type of results generated and by how informative the result is to the participant. Box 5-4 summarizes the kinds of reference information that may be appropriate to provide to participants, given the types of results that laboratories generate. Laboratory results are of two distinct types—continuous (e.g., biomarker levels that may vary across a continuous range of possible values) or binary (e.g., presence/absence of genetic variant or marker). In the clinical laboratory, these types of results are referred to as quantitative and qualitative results.

Continuous or Quantitative Results

When communicating continuous results, providing relative standards to which an individual result can be compared (e.g., a second data point for comparison or an observed distribution) can provide a certain degree of meaning (i.e., that the current result is higher or lower). However, relative standards may not sufficiently convey whether action should be taken, say, whether a participant

BOX 5-4

Types of Reference Information

Presented in the lists below (ordered from most to least informative) is a summary of the types of reference information discussed in the chapter text that, if provided with continuous or binary test results, can help recipients understand their limitations and meaning.

FOR CONTINUOUS/QUANTITATIVE RESULTS

1. Action references (e.g., critical values, action thresholds, or similar benchmarks)
2. Harm/risk references (e.g., a high risk threshold or borderline risk range)
3. Normal/standard references (e.g., range of values found in individuals without the disease)
4. Relationship to external reference distributions (e.g., other studies)
5. Relationship to prior results for a given participant (if available and relevant)
6. Relationship to the distribution of values observed for the current study

FOR BINARY/QUALITATIVE RESULTS

1. Classification of the result into action categories (e.g., should be retested, should consider a particular therapy, etc.)
2. Classification of the result into evaluative (risk or meaning focused) categories (i.e., risk stratification)
3. Associations of result with levels/rates of harm (e.g., absolute risk increase/reduction). Note that providing relative risk increase/reduction is not recommended (Trevena et al., 2013)
4. Prevalence in external reference populations. Note that prevalence is of high value in determining the likelihood that a test result represents the true value
5. Prevalence observed for the study

should consult a physician. If, for example, a study has measured blood levels of a specific pesticide, then returning the individual result and the range of values obtained for the other study participants will not indicate whether an individual is at risk of harm from exposure to that pesticide. Nor does it indicate whether the investigators know if the pesticide poses a health risk and, if so, at what dose. For instance, if an entire community has been exposed, having average exposure levels compared to other community members may nonetheless represent a significant risk.

Because relative standards provide only limited and potentially misleading meaning, it is generally preferable to provide absolute reference information (just as absolute risk communication is generally preferred over relative risk communications), though the committee acknowledges that this will not always be possible (Dunagan et al., 2013; Trevena et al., 2013). The absolute reference standard commonly provided with clinical test results is a standard or normal range, which in principle allows recipients to determine whether their results are normal when compared to the general population.[18] In practice, however, many people with lower literacy and numeracy skills have significant difficulty determining whether the result is inside or outside of a standard range (Zikmund-Fisher et al., 2014). Furthermore, in many research contexts the substance being measured either should not normally be present or else normal ranges are unknown. The absolute meaning of continuous results can be communicated by binning results into easy-to-evaluate categories (e.g., high, moderate, low risk), noting whether a result falls within or outside of a target range; by mapping a result onto a dose–response curve; or by reporting whether the result falls above or below a harm, alert, or action threshold (Peters et al., 2009). For the latter method, marking the individual result and the harm threshold on a visual display of the range can be an intuitive way to convey this information (Zikmund-Fisher et al., 2018). Care should be taken, however, to ensure that important variations in meaning are not obscured by a categorization process and that people do not interpret below threshold results or those categorized as "low risk" to mean zero risk of harm.

Another critical challenge that arises when communicating continuous results involves conveying the degree of imprecision in an estimate and the corresponding uncertainties related to interpretation. Test results that are presented as point estimates without measures of variability and reliability fail to convey the uncertainty of the results (Pocock and Hughes, 1990). Therefore, people tend to assume that the value they receive from a test is both precise and accurate,[19]

[18] "Typically, *reference values* or *reference intervals* are established for each laboratory test to delineate the range of values that would usually be encountered in a 'healthy' population" (Boyd, 2010, p. 84).

[19] "A test method is said to be accurate when it measures what it is supposed to measure. This means it is able to measure the true amount or concentration of a substance in a sample. . . . A test method is said to be precise when repeated determinations (analyses) on the same sample give similar results. When a test method is precise, the amount of random variation is small. The test method can be trusted because results are reliably reproduced time after time. . . . A test method can be precise (reli-

when in fact the true level may be higher or lower. The degree of uncertainty directly relates to the likelihood of misinterpretation of the meaning of the result. For example, if the value of a result is close to some reference value, people may overinterpret what is actually an unreliable difference because of the inherent error in the estimated value.

The limits of accuracy for point estimates can be communicated through confidence intervals, error bars, or standard errors. Even when such measures are provided, however, people often do not understand their meaning (Dieckmann et al., 2012). People tend to interpret uncertainty in such a way as to be favorable to their preferences or worldviews—the so-called "motivated evaluation" (Dieckmann et al., 2017). The use of plain language can help research participants better understand the limitations related to the validity of the test result and the implications in terms of whether the data should be relied on for decision making. For example, while many people may not be familiar with the term "95 percent confidence intervals," the extent of uncertainty can be conveyed by discussing minimum and maximum levels or best and worst case scenarios (i.e., "the value might be as high as X or as low as Y"). However, including a description of capture probability (e.g., a 90 percent confidence interval) increases the likelihood that people interpret the distribution of values within that range as more normally distributed rather than uniformly distributed (Dieckmann et al., 2015). Further research is clearly needed to determine optimal language for expressing value uncertainty in different situations.

Binary or Qualitative Results

Despite the seemingly simple nature of binary results (i.e., the characteristic is either present or not, and the test result is accurate or not), meaningful communication of this type of test results remains challenging. The prevalence of the characteristic or finding, either in a study population or an external reference population, can be reported with the result. Prevalence rates and pretest probability information are of high value in determining the likelihood that the test result represents a true-positive rather than a false-positive result, or a true-negative rather than a false-negative result. In many research circumstances, the prevalence of the target characteristic may be uncertain, as may be the sensitivity and specificity of the test, all of which are relevant to an estimate of positive and negative predictive values (as discussed previously in Chapter 3). Prior knowledge, or lack of knowledge, of prevalence and test sensitivity and specificity will be relevant to a decision about whether results should be returned and to what degree confirmatory testing is recommended.

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ably reproducible in what it measures) without being accurate (actually measuring what it is supposed to measure), or vice versa" (Lab Tests Online–AU, 2018).

In other cases, the question is not as much whether a result is accurate, but whether it is meaningful. An example would be a test that identifies a genetic variant. In such cases, prevalence rates have limited value in guiding recipient perceptions or actions (Zikmund-Fisher, 2013), especially once repeat testing provides confirmation of a finding. For example, how common or uncommon a particular genetic variant is in the population generally should not affect what the individual might want to do about a valid and true result. Prevalence rates should not be used by recipients as a proxy for how serious a finding is or whether action is needed, since common characteristics may sometimes have limited risk impact and rare conditions can sometimes have enormous impact on an individual's risk. For binary results that are indicators of a disease (or other condition), penetrance information (i.e., information about the extent to which a particular gene is expressed in those carrying it) and relative risk statistics (i.e., information about the risk of the disease in people with the characteristic relative to the risk in those without the characteristic) are more useful than prevalence rates for helping recipients understand the meaning of their results. Furthermore, guidance documents for risk communication recommend communicating absolute risk reduction or risk increase whenever possible (Trevena et al., 2013; Zikmund-Fisher, 2013).

The meaning of binary results is most clear when they are classified into a specific action category (e.g., someone with a particular biomarker should consider a specific intervention) or at least a risk category (e.g., labeling as normal), although care must be taken to avoid misinterpretation of such labels (Marteau et al., 2001). However, classifying binary results into a specific action category is not always possible, particularly in the research context, both because disease is often multifactorial and because the scientific understanding of how binary risk factors (e.g., genetic markers) are associated with outcomes is often highly incomplete (Coulehan, 1979). For example, it may be difficult to communicate to research participants how much or how little effect a particular genetic marker may have on the incidence or severity of a condition—and, accordingly, whether an intervention or other action is appropriate. In such cases, as discussed below, the areas of uncertainty should be explicitly communicated to the recipient.

With binary results, the primary concern when trying to communicate issues of reliability is false certainty—that is, people often fail to consider the chance that the finding is wrong. The idea that a test may result in false-positive or false-negative results can be hard to understand. Consequently, recipients are likely to act on the assumption that the result they have received is accurate (Garcia-Retamero and Hoffrage, 2013; Kelman et al., 2016). Explicit statements that emphasize the potential for inaccuracies of all types (e.g., sample swaps, false positives, or false negatives) can help to offset this tendency, though their effectiveness is likely to be imperfect. Note that once a result is known, it is appropriate to communicate in plain language only the false-negative or the false-positive rate, whichever is relevant, since the other rate does not affect that particular participant and speaking about it is likely to add to confusion. However, a concrete visual

presentations of risk (e.g., icon array[20] displays) may be needed to support a participant's understanding of how likely it is that the returned binary result is in fact the opposite result (Garcia-Retamero and Hoffrage, 2013; Trevena et al., 2013).

CONCLUSION: The meaning of a test result is determined by what the result is compared against. The ability of individual participants to understand and make use of research results depends on the provision of relevant reference information that clarifies what is known or unknown about the meaning of the specific result. For some individuals, a reference range alone would do nothing because of their limited health literacy and numeracy.

CONCLUSION: The state of scientific knowledge about a particular test guides the types of reference information that are available and can be provided to research participants when returning individual research results. When the context for a test result is well established and standardized, then a strong presumption is that this reference information will be provided. When the context is unknown or uncertain, however, being clear how little is known is essential to participant understanding.

Communicating Key Takeaways, Including the Actionability of Individual Research Results

When returning results to participants, a single, clear takeaway message is important. Being given information and not knowing whether or how it should be acted upon can be disconcerting and potentially emotionally harmful to participants (Shani et al., 2008). Consistent with the ethical principles of beneficence and non-maleficence, research teams have some obligation to minimize and mitigate such potential harms. When results are being offered to participants, the most straightforward way of offering a single, clear takeaway message is to provide a concise statement of why the results are being returned and a clear summary of the meaning of the results based on the research team's current knowledge of the test performed at that point in time. Given that scientific knowledge is constantly evolving, especially in terms of understanding research results, investigators should clarify both the date when the message is being generated by the study team and how likely or unlikely it is that the interpretation of the result might change in the future. In addition, given the evidence discussed above of substantial language and literacy barriers to comprehension, the importance of providing action steps (if appropriate) clearly and in plain language cannot be overstated.

The takeaway message can vary depending on the state of knowledge regarding the test result and its implications. When the meaning is uncertain (i.e., the investigators do not know how to interpret the result), this uncertainty and the fact

[20] "Icon arrays are graphical representations consisting of a number of stick figures, faces, circles, or other icons symbolizing individuals who are affected by some risk" (Galesic et al., 2009).

that no action can be recommended is the takeaway message. Such a clear message of no recommended action needs to be stated explicitly to prevent people from making inaccurate assumptions. In some cases, the meaning of the result may be known, but it has no implied action. An example of such a result would be the return of "normal" results from clinical testing that was conducted in the course of a research study. However, determining the appropriate takeaway message is not always so straightforward, such as when a genetic variant of unknown significance is identified in genetic testing. A communication with no recommended action can be particularly difficult because people may not believe that researchers would return a result but not want the participant to take any further action; there is also the issue of the potential "emotional burden, concern, or worry of knowing that there is nothing [the participant] could do about it" (Hyams et al., 2016, p. 5). Providing such information can have both positive effects (e.g., by drawing a participant's attention to a particular disease risk) and negative effects (e.g., inducing anxiety or motivation to pursue unnecessary screening tests). In other cases, the result may indicate the need for possible or even highly encouraged action.

In the consent document, key information is optimally included at the beginning of the consent document and will contain a "concise and focused" description of the research and summarize the project information that is most important to potential participants in making their decision whether to enroll in the study (*Federal Register*, 2017). Similar methods (i.e., requiring concise and focused descriptions of the findings and its implications) should be applied in the return-of-results communications.

When participants will need to carefully consider a potential action (e.g., because of trade-offs), the more that a communication can identify both why participants should consider actions and why they might not want to do so, the more useful the communication will be. In addition, if a result implies an action that is highly encouraged, acknowledging the potential barriers or challenges to undertaking these actions is beneficial by helping to frame realistic expectations and prepare participants to overcome those barriers, when appropriate.

Guiding principles for the design of return-of-results procedures parallel the best practices for consent procedures and support the importance of providing key takeaway messages. Best practices need not be developed at the level of the individual investigator alone. Changes in community, federal, or industrial practices may be needed to develop better guidance for how the research committee needs to approach these situations. To deal with the fact that research participants often struggle to make sense of consent documents, the 2018 proposed revisions to the Common Rule mandate that consent documents provide a "key information" section at the beginning of the consent document that contains a "concise and focused" description of the research and summarizes the project information most important to potential subjects in making their decision whether to participate (*Federal Register*, 2017). Similar remedies (i.e., requiring concise and focused

descriptions of the findings and its implications) should be applied in the context of returning research results.

CONCLUSION: Individual research results need to be communicated with a clear takeaway message that includes a statement of actionability (or lack thereof).

Communicating Caveats and Uncertainties

Previous chapters discussed multiple reasons why research results often have substantial variance or potential for error which limits interpretation and usability for an individual participant. Even after accounting for the quality of laboratory procedures, research results may vary in their level of certainty and potential to guide personal action. For example, a cholesterol level obtained in a research study is likely to provide a research participant with readily interpreted information about cardiac risk (assuming that appropriate laboratory quality measures were in place), while other research results may reflect evolving knowledge that has substantial uncertainty. For example, a study might discover an association between a biomarker and a particular health risk, with an unknown effect size and no information to guide actions to reduce risk.

Most research participants, however, are unlikely to think about these threats to validity and interpretability. Hence, research results are prone to misinterpretation (e.g., confusing a research result with an established clinical test result) or misuse. As a result, it may be necessary to include a formal caveat or warning statement in return-of-results communications. Depending on the context, such statements may address

- uncertain standards,
- uncertain interpretation,
- an elevated potential for error in the result, and
- the fact that the result may not be the participant's result (e.g., in the case of a sample swap or mislabeling).

For example, appropriate disclosure to the participant might include the caveats that the level of risk is still unknown and that no actions to reduce risk are known. Researchers might also include information about plans for future research to study these questions.

Investigators are not used to identifying the full list of threats to validity, uncertainties, and caveats that are applicable to their study. In fact, incentives in both the funding application process and the research publication process minimize attention to such threats. Consequently, investigators need both guidance (e.g., a list of key questions that should be asked) and incentives (e.g., explicit consideration in IRB review) to do this task. The Multi-Regional Clinical Trials Center toolkit

includes a checklist to guide IRBs and other ethics committees in reviewing plans for the return of research results (MRCT Center, 2017b).

Because people tend to assume that any test results they receive are both precise and accurate, providing information that conveys the uncertainty of the result is critical, particularly since the potential for error increases in research contexts. Furthermore, given that understanding and adjusting for uncertainty is psychologically difficult, it is reasonable to believe that, on average, the potential for over-interpretation of results and under-consideration of uncertainties is likely to be greater in practice than the reverse. The committee is already advocating for the return of results in novel circumstances, including (under certain conditions) when reliability is lower than it is for clinical results. As a result, the committee believes it is prudent to err on the side of promoting recipient attention to caveats and uncertainties. An outcome in which participants feel a need to confirm important results before acting on them would be appropriate in many situations. When a significant risk of therapeutic misconception is possible,[21] a disclaimer distinguishing a research result from a clinical result is particularly critical.

Since clarity and concreteness are critical, caveats, cautions, or warnings that accompany the return of results need to be written in plain language. For example, many users will not understand or react to a statement that a test has "low validity." Instead, statements should describe specific potential risks in simple terms, e.g., by making statements such as "Your result might be wrong," "Your true results may be higher or lower than what is shown," and "It is even possible that this result may not be yours." Similarly, uncertainties about the meaning of the result could be stated as plainly as "We do not know what your results mean" and "We cannot recommend any actions for you to take."

As caveats and warning statements are developed and used for the first time, they will need to be reviewed by the appropriate individuals (or groups) and tested for understanding and efficacy. Engagement with target populations is essential both for identifying which caveats are most critical to communicate and for determining the optimal methods for communication. Research has demonstrated that warnings can be used successfully to communicate benefits and risks, but only when they are specifically designed for the target audience (Andrews, 2011). Work in the environmental exposure field can offer some useful models and templates to share. The Association of Public Health Laboratories and Biomonitoring California offer models for communicating environmental exposure information to participants (Association of Public Health Laboratories, 2012; Biomonitoring California, 2018) and Biomonitoring California prototypes have undergone usability testing

[21] "Therapeutic misconception (TM) was first described in the 1980s, when it was noticed that some research subjects 'fail[ed] to appreciate the distinction between the imperatives of clinical research and of ordinary treatment.' People who manifest TM often express incorrect beliefs about the degree to which their treatment will be individualized to meet their specific needs; the likelihood of benefit from participation in the study; and the goals of the researchers in conducting the project" (Appelbaum et al., 2012, p. 2).

by Health Research for Action researchers (Health Research for Action, 2011). Additionally, FDA has explored the issue of whether and how results should be provided directly to consumers many times through the use of advisory panels or workshops that have asked experts and lay users on preferences, to explore risks of return, and develop mitigations to those risks (FDA, 2010, 2016).

Once effective warning statements are developed by investigators in a variety of fields of research, the research community would benefit from the sharing of templates and examples to avoid repeating unnecessary effort, while still allowing adaptation for a given need or context-specific communication.

CONCLUSION: Research participants may fail to understand the degree to which research results may have substantially greater uncertainties than clinical results. Little evidence exists to guide best practices for communicating warnings and qualifiers that address potential inaccuracies or potential variance in interpretation.

Identifying the Appropriate Communication Modality

Different types of communication may be appropriate in different contexts. The communication methods commonly used for returning results include

- in-person discussion,
- phone- or video-conference–based discussion,
- electronic delivery (e.g., through secure portals, including those tethered to EHRs), and
- mailing of printed materials.

Other reports have described a number of different factors that go into the selection of an appropriate communication method for returning individual research results (Fitzpatrick-Lewis et al., 2010; MRCT Center, 2017a), and the committee recommends that study teams use available guidance. For example, the Multi-Regional Clinical Trials collaborative has developed toolkits that support the return of individual as well as aggregate results and provide guidance for investigators, sponsors, and ethics review committees throughout the study life cycle from planning through study completion (MRCT Center, 2017b). As discussed above, ideally participants should be queried on their preferred communication method early in studies in which results are to be returned, and investigators should take participants' preferences into account. However, given that the potential cost, required infrastructure, and expertise will vary from study to study, the choice of how results will be communicated reflects a cost–benefit trade-off that needs to be evaluated for each study.

Delivering results in person maximizes the ability of the investigator to provide clarification, answer participant questions, and assess and address potential confusion or emotions from the participants. In some cases resources are needed

to support the inclusion of specialized expertise in return, for example when genetic counselors assist an investigator in returning results to participants. As a result, this return strategy is the most time and resource intensive. Wendy Chung estimated that returning results for a large study using a team of genetic counselors cost approximately $250 per participant.[22] Because of the time and resources required to plan for in-person return, this strategy is not well suited to scenarios where the results to be returned are time sensitive. Additionally, the return of results via a genetic counselor may lead to participants declining to participate due to the time commitment of counseling sessions, as was encountered by Chung and colleagues (Wynn, 2016).

The return of results via phone has many of the advantages of in-person return, including opportunities for clarification, participant questions, and addressing emotions, but it is less personal. This method can be carried out quickly if the return is time sensitive and the participant must be reached promptly. The costs associated with return by phone, like in-person delivery, remain high due to the time and expertise required.

Many patients are familiar with using electronic portals, which are commonly used for delivering clinical laboratory or other medical results (Giardina et al., 2015). These portals can be used to provide documents detailing results to participants as well as to provide links to additional educational resources. In some instances, the research results could be tethered to an existing patient portal or EHR, such as in cases where a research participant may also be a patient receiving clinical care within the institution. Although such portals typically feature a secure two-way e-mail communication option, there are a number of potential disadvantages, including a lack of opportunity for the synchronous communication of a phone or in-person return and the fact that the portal is less likely to be used by racial and ethnic minority and rural populations and those with limited health literacy or technology proficiency (Sarkar et al., 2010, 2011; Sharit et al., 2014). Furthermore, including research results in a patient's EHR may affect what is included in that patient's designed record set. Investigators in environmental health have tested other digital methods to return personalized results and engage participants in the research (Boronow et al., 2017). Establishing and using a portal has some initial and maintenance cost, but it is more easily scalable than in-person delivery, with only a marginal cost for the addition of many participants.

The return of results by mail is most useful in scenarios where researchers are returning non-urgent, reference communications and may be particularly effective for accessing individuals in remote locations, like some tribal areas where telecommunications access is limited, unreliable, or unavailable.[23] While mail is an

[22] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

[23] Testimony of John Molina of Native Health at the public session of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on December 11, 2017.

inexpensive method for return, communication by mail has a number of shortcomings, especially a lack of opportunity for dialogue and limitations in what can be communicated in a paper-based, visual format. Certified mail can be used to help prevent sensitive participant information from being received by someone other than the participant.

Data visualization is an effective tool for helping people understand their health data (see an example in Box 5-5), and many tools have been created to assist with the development of appropriate data visualizations. For example, the Data Viz Project by Ferdio is a website that organizes visualizations by functions (e.g., comparison, part-to-whole, correlation) to make it easier to select the right visualization for a particular communication goal (Data Viz Project, 2018). Resources also are available to help in choosing the most effective type of chart (e.g., the Extreme Presentation Method; see Abela, 2018). Developed by the Risk Science Center and Center for Bioethics and Social Sciences in Medicine at the University of Michigan, Icon Array provides open-source icon arrays for communicating risk (University of Michigan Risk Science Center, 2018). Electronic Infographics for Community Engagement, Education, and Empowerment (EnTICE^3) is open-source software that allows a user to create tailored messages and visualization outputs that are responsive to overlapping participant characteristics such as language, age, and level of health literacy (Arcia et al., 2015; Unertl et al., 2016). This software has been used during participatory design sessions to create a communication style guide tailored to inform and engage the target community. Such communications also can be used to stimulate health-motivating behaviors, for example, by offering comparisons to national rates of depression (Bevans et al., 2014) or providing dietary standards, associated risks, or recommendations for preventative action (NASEM, 2017). Under the Precision in Symptom Self-Management Center at Columbia University, EnTICE^3 is being expanded beyond its original use to support biomarker result reporting including cytokines, ancestry informative markers, and genetic mutations.[24]

As with any tool, visualization for returning research results must be well matched to the communication goal and data type (Arcia et al., 2013, 2018). No single visualization is ideal for all situations (Torsvik et al., 2013). Visual simplicity is also valuable, as visual embellishments (e.g., three-dimensional charts) tend to inhibit user comprehension (Tufte, 2001). A variety of authors have argued against three-dimensional graphs on both conceptual grounds (e.g., three-dimensional bars are more difficult to visually align with an axis to determine the level shown) and empirical grounds. In particular, while three-dimensional graphics may attract attention, they tend to perform worse in accuracy, which is perhaps the most critical dimension in the application to return of research test results (Fausset et al., 2008). Nor are more technologically advanced displays necessarily better: in at least some situations, interactive or animated data visualizations can be

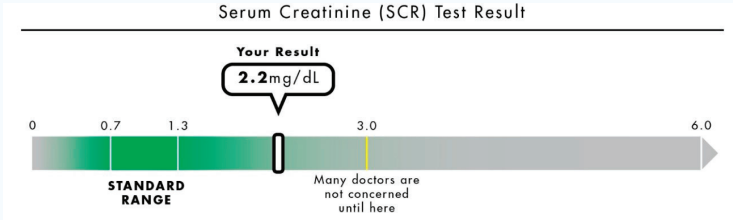
[24] Personal communication with Suzanne Bakken of Columbia University.

BOX 5-5

Examples of Visualizations Relevant to Results Reporting

EXAMPLE 1

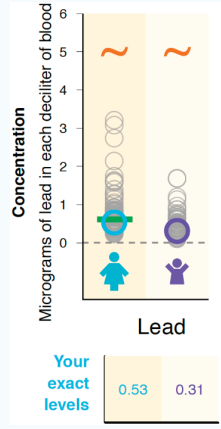
A number-line display of a clinical test result of a type demonstrated to increase people's sensitivity to variations in clinical laboratory results when compared to displaying results in tables (Zikmund-Fisher et al., 2017). The below example of a number-line display includes both color gradients and an additional harm anchor to help users identify the values at which a particular test result becomes clinically concerning (Zikmund-Fisher et al., 2018).



SOURCE: Zikmund-Fisher et al., 2018.

EXAMPLE 2

Strip plot visualization of serum lead levels in both mothers and babies used to communicate test results in the Chemicals in Your Bodies project. The blue and purple circles represent levels observed in a participant mother and baby, respectively, the grey circles are other observations in that study, the green bar shows the national median level, and the orange tildes represent "levels of concern" (i.e., an action threshold) (Dunagan et al., 2013, p. 108).

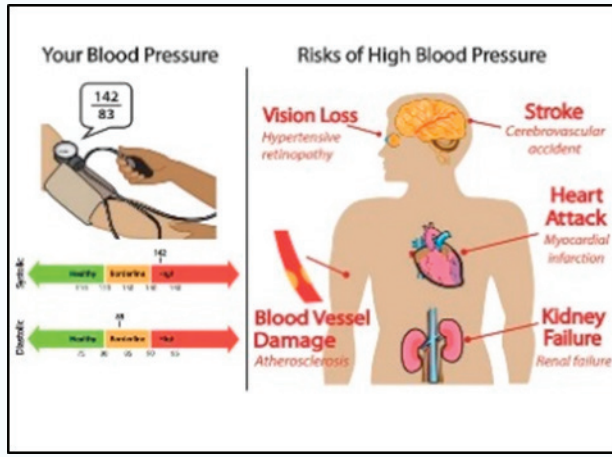


SOURCE: Dunagan et al., 2013, p. 108.

BOX 5-5, CONTINUED

EXAMPLE 3

As one visualization used to return research results from a large community survey, the infographic was designed through participatory methods with English- and Spanish-speaking research participants of varying levels of health literacy (Arcia et al., 2016, p. 180). The design displays results in multiple ways (e.g., number line, color) and also includes a brief visual summary of the key take-home messages to display the risks associated with the test results. The design was based on best practices for visual displays as well as the research participants' preferences for communication that provided important context about the result including reference range and associated risks.



SOURCE: Arcia et al., 2016, p. 180.

counterproductive, actually hurting an individual's ability to process the underlying data (Torsvik et al., 2013; Trevena et al., 2013; Zikmund-Fisher et al., 2012). Additionally, the Health Level Seven standard for infobuttons supports context-aware retrieval (Health Level Seven, 2018), which is increasingly being used in clinical research and can be added to a variety of electronic communication methods (portal, designated website, e-mail, etc.) to link to additional context-specific explanatory content and resources, including those that are visual or are

related to the participant's specific research result (Cook et al., 2016; Torsvik et al., 2013; Trevena et al., 2013).

In many situations, a multimodal approach to returning individual results will be beneficial (e.g., delivering results via mail or electronic portal and then following up with a phone discussion or in-person meeting to offer participants a chance to ask questions and seek clarification). Consequently, health care standards that support the integration of additional sources of information into EHRs and tethered patient portals provide a foundation for multimodal approaches. Beyond infobuttons, a National Academy of Medicine Genomics and Precision Health Roundtable Action Collaborative, DIGITizE: Displaying and Integrating Genetic Information Through the EHR, has specified a set of standards including Fast Healthcare Interoperability Resources (FHIR), Substitutable Medical Applications and Reusable Technologies (SMART) on FHIR, SMART on FHIR Genomics, and Clinical Decision Support (CDS) Hooks (see Box 5-6).

CONCLUSION: Research results can be returned through a variety of communication methods that are matched to participants' needs and the context of the research results.

CONCLUSION: The appropriate use of visualizations can help achieve the communication goal for the return of research results.

CONCLUSION: Existing and emerging technical standards for the exchange of health data are available and relevant to support the return of research results at scale through electronic systems such as EHRs and secure portals.

Recommendation 10: Enable Understanding of Individual Research Results by Research Participants.

Whenever individual research results are communicated to participants, investigators and institutions should facilitate understanding of both the meaning and the limitations of the results by

- **A. ensuring that there is a clear takeaway message and necessary reference information to convey what is known and not known about both the meaning of the result and potential clinical implications;**
- **B. communicating effectively the level of uncertainty in the result validity;**
- **C. providing mechanisms for participants to obtain additional information and answers to questions when appropriate and feasible;**
- **D. providing guidance for follow-up actions/consultations when appropriate;**
- **E. aligning the communication approaches to the particular needs and preferences of the participants and the context of the study;**

BOX 5-6

Standards That Support Integration of External Resources with Electronic Health Records and Patient Portals and Are of Relevance to Return of Research Results

FAST HEALTHCARE INTEROPERABILITY RESOURCES (FHIR, pronounced "Fire") is a Health Level Seven standard that supports the exchange of well-defined content (defined as resources that can be processed by a computer and also have human-readable components) among various electronic clinical information systems. For the return of results through EHR or a patient portal, this would include core content such as participant name, name of laboratory test, and laboratory test result (Fast Healthcare Interoperability Resources, 2017).

INFOBUTTONS, a Health Level Seven standard, supports context-aware (e.g., participant characteristics, test result) knowledge retrieval from an institutional or external knowledge resource. For the return of results, a genomics result in a patient portal could include an infobutton that links to an information sheet created by the research team, to an information prescription of sources for additional knowledge, or to a federally supported and updated knowledge source such as the Genetics Home Reference (National Library of Medicine, 2018).

The **SUBSTITUTABLE MEDICAL APPLICATIONS AND REUSABLE TECHNOLOGIES** (SMART) platform is a framework that enables EHR systems to behave as "iPhone-like platforms" through an application programming interface and a set of core services that support easy addition and deletion of third-party apps, i.e., the core system is stable and the apps are substitutable. For the return of results, an app could focus specifically on visual displays of laboratory results in a manner suitable for individuals with low health literacy and numeracy (Bosl et al., 2013; Mandl et al., 2012).

continued

BOX 5-6, CONTINUED

SMART-ON-FHIR genomics specifies genomic variant data resource definitions (e.g., Sequence Resource represents the raw genetic information of a patient and contains information about the specific read given by a sequencer for amino acid, RNA, or DNA sequences) to support the development of clinico-genomic apps that display genomic and clinical data through a specified user interface such as an EHR or patient portal (Bosl et al., 2013).

CDS HOOKS is designed to invoke external (rather than native to the EHR) clinical decision support (CDS) services from within the EHR workflow based on a triggering event (e.g., medication-prescribe on authoring a new prescription). This avoids the need for changes to the EHR system, which simply needs to "call the CDS service" via CDS Hooks. For the return of results, the receipt of a research laboratory result in an EHR or portal tethered to an EHR could trigger a set of automated actions such as notify researcher or research participant, provide tailored information about results, or initiate consultation (HL7 and Boston Children's Hospital, 2018).

F. providing a written summary of the results and other information communicated to participants for future reference by participants and investigators; and

G. leveraging existing and emerging health information technologies to enable tailored, layered, and large-scale communications when appropriate.

DEVELOPING A LEARNING PROCESS TO IMPROVE THE RETURN OF RESEARCH RESULTS

The return of individual research results is a relatively new process for the research enterprise. To communicate effectively, the research community will need to develop a learning system in which processes for returning research results are continuously evaluated for benefits and harms in order to support the development of best practices over time. The committee notes that research to study the impact of returning individual research results is already under way, but more work will be required to generate best practices (Genomes 2 People, 2018; Miller

et al., 2008; MRCT Center, 2017a; Wynn et al., 2017). As best practices are identified, systems for translating that knowledge into practice will be needed. Given that most investigators are not currently trained in communication and may not be able to contextualize the meaning of a result, training will be critical if the return of results is expected for research on human biospecimens. Communication is a skill that needs to be developed over time, and what matters is the communicator's ability to contextualize information and respond to questions by participants. In fact, the individual tasked with addressing participant expectations of return and communicating the results may not be the person with the most advanced expertise in the test itself (i.e., the principal investigator or someone on the research team) but rather may be a trained community member, a communication expert at an institution, or another individual adept in communication.

In developing training for current and future investigators, stakeholders will need to consider different methods of communication. Specifically, guidance is needed regarding what training should be expected for face-to-face interactions, phone interactions, or communication through patient portals, e-mail, or mail. Communicating the meaning of data in plain language will likely require different approaches, depending on the method used to communicate. Investigators will need assistance in determining which methods are most appropriate for their study.

These new communication tasks will, of course, have financial implications. The more context and interpretation that is required to be provided for a specific result (perhaps due to the potential harms associated with returning it), the higher the likely cost. To this end, future research into communicating results will need to address whether additional expertise should be included and factored into grant applications, under what circumstances face-to-face communication is needed and by whom, and which possible methods for return are appropriate for different types of research and groups of participants. As discussed in Chapter 3, institutions may be able to assist research teams by developing the required infrastructure for the return of results, and this could include infrastructure that enables investigators access to core communication expertise. As the return of individual research results becomes more widely practiced, including research communication cores into institutional development grants may be considered and would provide investigators access to experts and a standardized mechanism for communication and avoid potential costs associated with study-by-study assessments.

CONCLUSION: Ensuring effective return of research results requires developing skills and expertise among research teams as well as access to the resources, training, and relevant expertise needed to achieve good quality communication outcomes.

Recommendation 11: Expand the Empirical Evidence Base Relevant to the Return of Individual Research Results.

To expand the empirical evidence base relevant to the return of individual research results, sponsors and funding agencies should support additional research to better understand the benefits and harms of the return of results as well as participant needs, preferences, and values and to enable the development of best practices and guidance.

When it comes to funding empirical research for the return of individual research results, the National Institutes of Health (NIH) is the obvious, and likely primary, sponsor to fund such an endeavor. However, this should not be an NIH task alone. The return of research results will soon become part of the research enterprise, it is a global endeavor, and all sponsors of research using human biospecimens should put resources into addressing the needs of investigators and participants through the funding of empirical research in the practice. Having more unified guidance to the practice of return will help prevent dramatic variability in practice between institutions and aid IRBs in making informed decisions. Funding agencies have a responsibility to ensure that the processes for return are both feasible and implemented appropriately.

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6

Reshaping the Legal and Regulatory Landscape to Support Return of Individual Research Results

In the preceding chapters, the committee has provided strategies that it envisions will, over time, result in improved access to individual results for those who have participated in research. At present, however, a number of legal and regulatory barriers impede the return of individual research results to participants and contribute to unevenness in access across states and research institutions. This chapter examines whether the regulatory environment is appropriately calibrated to the risks and benefits of participant access to research results and describes changes in the legal and regulatory landscape that are needed if the committee's recommendations are to be implemented and its vision for the return of results to participants as a more commonplace practice in research is to be achieved.

LEGAL AND REGULATORY PROTECTIONS IN RELATION TO THE BENEFITS AND RISKS OF RETURNING INDIVIDUAL RESEARCH RESULTS[1]

The legal and regulatory landscape pertaining to the return of individual research results is governed by a complex assortment of federal and state laws (including statutes and regulations, see Box 6-1). Currently in the United States, no federal law confers a fundamental right to access research results generated

[1] This section draws on a paper commissioned by the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, "Analysis of Legal and Regulatory Landscape Relevant to Return of Individual Results Generated from Biospecimens in Research" by Christi J. Guerrini (see Appendix C).

BOX 6-1

Overview of Federal Laws and Regulations Relevant to the Return of Individual Research Results

Federal laws and regulations pertaining to the return of individual research results include those focused on oversight of laboratories that conduct testing for clinical care, the oversight of investigational devices, the protection of human participants in research, privacy protections, and anti-discrimination protections. Key federal laws and regulations include the following:

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 (CLIA): The Centers for Medicare & Medicaid Services is the authority responsible for administering CLIA, the regulatory requirements governing laboratories. CLIA requirements focus on certifying good laboratory practices through biennial surveys (CMS, 2006).

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 (HIPAA) PRIVACY RULE: The Office for Civil Rights (OCR) is the authority responsible for implementing and enforcing the HIPAA Privacy Rule. The Privacy Rule standards are directed toward protecting individuals' health information "while allowing the flow of health information needed to provide and promote high quality health care and to protect the public's health and well-being" (OCR, 2013a).

FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS (the "**COMMON RULE**"): Fifteen federal departments and agencies have adopted regulations codifying the Common Rule, and three additional agencies and departments comply with the Common Rule (OHRP, 2016b), a policy that addresses the protection of human participants in research and that includes requirements for informed consent and institutional review board review of research protocols.[a] The Office for Human Research Protections (OHRP) leads the Department of Health and Human Services' (HHS's) efforts to protect human participants in biomedical and behavioral research and to provide leadership for all federal agencies that conduct or support human participant research under the Common Rule (OHRP, 2016c). In January 2017, HHS announced its adoption of revisions to the Common Rule,[b] which for the first time

BOX 6-1, CONTINUED

require that investigators disclose their plans on whether and under what circumstances "clinically relevant research results, including individual research results," will be returned to participants.[c] The changes are expected to go into effect on July 19, 2018.[d]

FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS: FDA is responsible for protecting and promoting public health by ensuring the safety and effectiveness of medical drugs and devices.[e] Devices regulated by FDA are defined broadly to include many laboratory tests, including in vitro diagnostic tests. FDA regulations describe procedures that apply to clinical investigations to determine the safety or effectiveness of investigational devices.

GENETIC INFORMATION NONDISCRIMINATION ACT OF 2008 (GINA): Passed in 2008, GINA limits access to and the use of an individual's genetic information in health insurance and employment contexts. The legislative purpose of GINA is to promote genetic testing for personal health and research purposes by mitigating concerns over the potential misuse of information learned from genetic tests.[f]

[a] 45 C.F.R. § 46.

[b] Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149 (Jan. 19, 2017).

[c] *Id*. at 7266 (revised § 116(c)(8)).

[d] See Federal Policy for the Protection of Human Subjects: Delay of the Revisions to the Federal Policy for the Protection of Human Subjects, 83 Fed. Reg. 2885 (Jan. 22, 2018).

[e] 21 U.S.C. Chapter 9, Part A Drugs and Devices.

[f] Genetic Information Nondiscrimination Act of 2008, Public Law 110-233, 110th Cong. (May 21, 2008).

from biospecimens collected during the course of research,[2] despite the perception among some individuals that they continue to own their biospecimens and any personal data generated from them (Obama, 2016; Rothstein, 2015). At least one scholar has argued that patients' and consumers' right of access to health-related data is a federal civil right provided by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule (Evans, 2018a), but there is no legal consensus or formal precedent about the breadth of this right.[3] A few states (e.g., Colorado,[4] Alaska[5]) have enacted statutes that recognize individuals' property rights to certain biological samples or the results of analyses on those specimens, or both, but in general state courts have held that biospecimens donated during research and the results of tests performed on those specimens are not the legal property of research participants (Francis, 2014).

Despite this lack of legal consensus, a number of ethical and practical reasons for disclosing individual results (as discussed in Chapter 2) collectively form a strong argument for creating pathways to enable research participants access to their information. Indeed, the past few years have seen a significant shift in the regulatory environment toward allowing individuals greater access to their laboratory results. For example, since 2000 the Health Insurance Portability and Accountability Act (HIPAA) regulations have recognized the right of individuals to inspect and obtain a copy of their protected health information (PHI)[6] contained within a designated record set (DRS).[7] This right of access is binding on all HIPAA-covered entities,[8] except that before 2014 this right did not apply to

[2] Changes in the European Union under the new General Data Protection Regulation, which went into effect May 25, 2018, confer a right to access personal data that is being processed, including research data, except in cases where providing access would impair the research (Regulation [EU] 2016/679, article 15).

[3] This sentence was changed from the prepublication report.

[4] Alaska Stat. § 18.13.010(a)(2).

[5] Colo. Rev. Stat. Ann. § 10-3-1104.7(1)(a).

[6] PHI is defined as individually identifiable health information, which is any information (including genetic information) that (a) is created or received by a covered entity or employer; (b) "relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual"; and (c) identifies or could be used to identify the individual (45 C.F.R. § 160.103).

[7] A designated record set is defined as a group of records maintained by or for a covered entity that comprises the (1) medical records and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) other records that are used, in whole or in part, by or for the covered entity to make decisions about individuals (45 C.F.R. § 164.501). This includes records used to make decisions about any individuals, whether or not the records have been used to make a decision about the particular individual requesting access.

[8] HIPAA-covered entities include health plans, health care clearinghouses, and health care providers that transmit health information in electronic form in connection with a covered financial or administrative transactions (e.g., billing transactions). Research laboratories are HIPAA-covered entities if they electronically conduct a covered transaction or if they function as part of a larger covered entity

HIPAA-covered laboratories. Similarly, the original access rule for the Clinical Laboratory Improvement Amendments of 1988 (CLIA) did not allow the release of laboratory test results to the individual undergoing testing except in states that provided for direct access. Individuals not residing in these states were dependent on their ordering health care provider to share test results. But in 2014, in a final rule to CLIA and HIPAA,[9] the Department of Health and Human Services (HHS) announced the elimination of the laboratory exclusion from the HIPAA access rule as well as the CLIA prohibition on the return of test results to individuals (Barnes et al., 2015; *Federal Register*, 2014). Although the change was primarily aimed at ensuring patient access to clinical laboratory information, the revised HIPAA access rule, which preempts any state laws that restrict an individual's direct access to test results, has opened doors for participants to access their individual research results. As currently written and implemented, however, the laws and regulations governing access to laboratory results are not harmonized; they afford inconsistent and inequitable access for participants to permitted results, and the regulatory conflicts create dilemmas for laboratories, forcing them to choose which regulation to intentionally violate in order to comply with the other. These issues and some approaches to their resolution are discussed below.

CLIA and Its Restrictions on Returning Individual Results

Laboratories in the United States that perform tests on human specimens for the purpose of providing information for the diagnosis, prevention, or treatment of a disease or for the assessment of the health of an individual are regulated by CLIA[10] and are required by the Centers for Medicare & Medicaid Services (CMS) to be CLIA certified through a process that ensures that certain quality control assurances and requirements are in place (see Chapter 3). CLIA and its associated regulations were put in place to protect patients from harm resulting from inaccurate laboratory testing. Laboratories licensed in states that have enacted laws with requirements equal to or more stringent than those required under CLIA and where CMS has approved the licensure program qualify as CLIA exempt.[11,12] CLIA also allows for an exception from certification requirements in the case of laboratories that conduct tests on human specimens for research purposes and

(e.g., hospitals, medical centers). HIPAA also extends to business associates of covered entities (45 C.F.R. § 160.103).

[9] The final rule to the CLIA Program and HIPAA Privacy Rule amended 42 C.F.R. § 493; 45 C.F.R. § 164.

[10] 42 C.F.R. § 493.2.

[11] 42 C.F.R. § 493.2.

[12] New York and Washington both have implemented laboratory licensure programs with requirements at least as stringent as those required by CLIA and laboratories in these states are recognized as CLIA exempt. Both states have rules prohibiting the return of research results from non-certified laboratories (CMS, 2017).

that do not report patient-specific results for the diagnosis, prevention, or treatment of a disease or for the assessment of the health of an individual (CMS, 2014). If laboratories report individual results that could be used for clinical decision making, even if this is not the intended purpose of returning results, CMS has interpreted the regulations to mean that those laboratories must be CLIA certified. These laboratory categories are summarized in Table 6-1.

Many laboratories that generate research results with the potential for use in health care are CLIA certified. For example, CLIA-certified clinical laboratories may be (but are not always)[13] used to conduct testing on biospecimens collected for clinical trials (Barnes et al., 2015). In such cases, CLIA does not pose any impediment to the return of research results (or to the return of clinical test results generated in the course of a research study). However, a number of potential scenarios in which results are clinically actionable or otherwise valuable to participants could be generated in laboratories that are not CLIA certified (e.g., academic or industry laboratories conducting more basic research, such as biomarker identification, using innovative methodologies that have not yet been validated for clinical use, or laboratories engaged in assay development). Research testing performed in laboratories that are not CLIA certified may create a dilemma for investigators and institutions that feel an obligation to return such results, particularly when they are urgent and might not otherwise be discovered. Under CMS's interpretation of CLIA, investigators would be prohibited from disclosing the results without first becoming CLIA certified. It has been argued that investigators may have a First Amendment right under the U.S. Constitution to share the results of genetic research tests with interested participants as a form of protected free speech (Evans, 2014). However, the validity of this argument has not yet been tested in court (Jarvik et al., 2014), and the potential consequences for CLIA violations may deter investigators from returning results generated in a non-CLIA-certified laboratory. CMS is authorized to impose a civil monetary penalty ($50–$10,000 per day of noncompliance per violation) and can file a civil lawsuit to obtain a court order that prohibits a laboratory from continuing an activity that CMS believes to represent a "significant hazard to the public health."[14] Although the committee is not aware of any cases where such enforcement actions have been taken against non-CLIA-certified laboratories for the return of research results, CMS recently intervened in the activities of a direct-to-consumer genetic testing firm, directing the company to obtain CLIA certification before providing genetic testing results to consumers (Lee, 2017).

The committee recognizes the importance of ensuring the quality and integrity of laboratory test results. If investigators and their research laboratories

[13] When laboratory testing for clinical trials is not conducted in a CLIA-certified laboratory, other standards, such as good clinical laboratory practices, can be adopted to help to support the quality of those results (Ezzelle et al., 2008).

[14] 42 U.S.C. § 263a(h)–(j); 42 C.F.R. § 493.1806(c)(3)–(d), 493.1834(a)–(d), 493.1846.

TABLE 6-1 CLIA Categories of Laboratories

LABORATORY TYPE	CLIA DEFINITION[a]	CLIA CERTIFICATION REQUIRED?
Regulated by CLIA	"[F]acilit[ies] for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."	Yes
"CLIA-exempt"	Laboratories licensed by states that have "enacted laws relating to laboratory requirements that are equal to or more stringent than CLIA requirements" and CMS has approved the licensure program.	No, but subject to CMS-approved, state regulations
Research	Facilities "that test humans but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients."	No

[a] 42 C.F.R. § 493.2.

plan to offer individual research results to participants, the testing of human biospecimens under an acceptable quality management system is essential (see Recommendation 3). However, as discussed in Chapter 3, expecting all research laboratories to meet CLIA requirements in order to return research results may not be reasonable. The current absolute prohibition on the return of research results from non-CLIA-certified laboratories also fails to account for several factors, including the high quality maintained by some research laboratories, the value that many participants place on results despite uncertain validity, and the access rights afforded by HIPAA to individual results regardless of quality standards. Additionally, there is a paucity of evidence of harm from the return of research results, though as discussed in Chapter 2, the overall body of evidence is limited and "the current state of knowledge reflects lack of evidence, not evidence of a lack of effect." Thus, as stated in Recommendation 11, it is important for investigators to expand the body of evidence on the benefits and harms associated with the practice as it evolves and becomes more widespread.

CONCLUSION: As many research laboratories are not CLIA certified, CLIA represents a formidable obstacle to the return of individual results to research participants even though the results may meet other quality standards and a right of access to laboratory results has been gaining credibility in other regulatory policies.

Concerns Regarding an Access Right to Research Results Under HIPAA

Since 2000, HIPAA has included a rule that individuals have a right of access to inspect and obtain a copy of their PHI maintained in a designated record set. According to guidance issued in 2002, "any research records or results that are actually maintained by the covered entity as part of a designated record set would be accessible to research participants unless one of the Privacy Rule's permitted exceptions applies" (OCR, 2013b). Prior to 2014, there was an explicit exception from the access right for all HIPAA-covered laboratories "subject to" CLIA and laboratories "exempt from" CLIA.[15] As discussed earlier in this chapter, the 2014 amendment removed both of these exceptions.[16] As a result of this amendment, all laboratories that are part of a covered entity, regardless of their status under

[15] 45 C.F.R. § 164.524(a)(1)(iii) (effective to April 7, 2014).

[16] Although CLIA defines the term "CLIA-exempt" in reference to those laboratories operating in states that have established a CMS-approved licensure program with requirements that are at least as stringent as those under CLIA, for the purposes of the privacy rule's access right, HHS's Office for Civil Rights (OCR) has interpreted the term "CLIA-exempt" to also include research laboratories operating under the CLIA exception (i.e., those that do not require CLIA certification because they conduct tests on human biospecimens for research purposes and do not report patient-specific results for the diagnosis, prevention, or treatment of a disease or the assessment of the health of an individual). This issue is illustrative of the confusion generated by ambiguity in terminology used in regulations and guidance and the need for harmonization of terminology (discussed later in this chapter).

CLIA, must now comply with the access right under the HIPAA Privacy Rule.[17] This means that all of an individual's protected health information in the designated record set, regardless of whether it is generated in a clinical laboratory or during the course of research, must be provided to that individual upon request.

This recent regulatory change has been met with mixed reactions and has been a focus of significant controversy. The change has been welcomed by some as a critical step forward in the movement to acknowledge participants' critical contributions to research and to respect their desires to receive information about themselves, even research information. At the same time, however, the increased access has generated concern among some researchers, clinical care providers, and regulators by providing an access right to research results and even uninterpreted data (e.g., genomic sequence data), which may not meet the high standards for quality that are required of clinical test results (Barnes et al., 2015; Evans, 2018a). Laboratories may now be compelled to share research results with unclear meaning (e.g., genomic variants of unknown significance) or questionable validity, raising fears that, without proper context or a clear understanding of the limitations, the receipt of such results could cause undue anxiety or prompt unnecessary intervention. Institutions have also expressed concerns regarding the potential financial impacts of the disclosure requirements on laboratories, because the HIPAA access right is an unfunded federal mandate (Evans, 2018b).

In addition to these concerns, the expanded right of individuals to access their laboratory results under HIPAA creates the potential for conflict with other federal regulations related to the protection of patients and research participants, as discussed below.

HIPAA and CLIA

For those non-CLIA-certified research laboratories that are HIPAA-covered entities, a legal dilemma can arise if a participant requests individual research results that constitute PHI contained within a DRS (the respective obligations of laboratories regarding individual access to laboratory results under CLIA and HIPAA are summarized in Table 6-2). Returning research results that are part of the DRS in order to comply with the expanded HIPAA access rule would force non-CLIA-certified laboratories to either violate CLIA (as currently interpreted by CMS) or forfeit the exception for research laboratories and obtain CLIA certification, which has significant cost and resource implications (Barnes et al., 2015).

[17] In 2016, OCR published guidance on the types of information that may be contained within the DRS (HHS, 2016), indicating, for example, that this may include results of genetic testing maintained by or for a clinical laboratory, including gene variant information. However, this guidance did not refer specifically to test results generated by research laboratories. Older guidance that does address obligations of research laboratories pre-dates the 2014 regulatory changes. This earlier guidance states that research participants shall have access to "any research records or results that are actually maintained by the covered entity as part of a designated record set" (OCR, 2013b).

TABLE 6-2 Legal Obligations Related to Individual Access to Laboratory Test Results

	HIPAA-COVERED LABORATORY	NON-HIPAA COVERED LABORATORY
CLIA-certified laboratory	Mandatory disclosure under HIPAA *Example: Clinical laboratory*	Permissive disclosure under CLIA *Example: Direct-to-consumer genetic testing laboratory that does not seek third-party reimbursement*
Non-CLIA-certified laboratory	Mandatory disclosure under HIPAA (but act of disclosure then requires laboratory to become CLIA certified) *Example: Academic research laboratory*	Mandatory, permissive, or prohibited disclosure under state law *Example: Independent research laboratory*

One researcher who spoke with the committee during its public workshop had compared costs for a large-scale exome sequencing study using CLIA- and non-CLIA-certified laboratories and estimated a three-fold difference in cost for the data generation alone.[18] As discussed in Chapter 3, opportunity costs associated with CLIA certification also pose barriers for many laboratories. HIPAA Privacy Rule violations, which are enforced by the HHS Office for Civil Rights, can be costly, with monetary penalties as high as $50,000 for each day that the covered entity is in violation (Barnes et al., 2015), putting laboratories without the means to obtain and maintain CLIA certification in the difficult position of having to weigh the relative risks of violating CLIA or HIPAA.

To avoid such conflicts, and in the absence of additional guidance from OCR, some research institutions are interpreting the definition of a designated record set to exclude research results and setting policies accordingly. The rationale is presumably that research results are often not used to make decisions about individuals, which is required in order for it to be considered part of the DRS. Johns Hopkins Medicine, for example, has indicated that, based on its interpretation, a research record is not part of the DRS and only information that is entered into a patient's medical record during research would be part of the DRS and therefore subject to the HIPAA access rule (Johns Hopkins Medicine, 2015). Similarly, New York University's Langone Health System has interpreted the definition of the DRS as excluding research results generated in laboratories not certified by CLIA. This approach, which creates variation across institutions in the ability of research participants to access their results, has been facilitated by ambiguity in the definition of the designated record set and a lack of clear guidance from OCR. The Secretary's Advisory Committee on Human Research Protections (SACHRP, 2015) and other groups have called for clarification of the duties of HIPAA-covered entities to provide results from laboratories that are not CLIA certified and for guidance on how the term DRS should be interpreted.

CONCLUSION: The operationalization of HIPAA access rights to include CLIA-exempt laboratories and those operating under the CLIA research exception creates an insoluble conflict between patients' right to access their research results contained within the DRS and non-CLIA-certified laboratories' prohibition from returning such results under the current CMS interpretation of CLIA.

CONCLUSION: OCR has contributed to the confusion of investigators by failing to define the DRS and, specifically, the status of results generated in research laboratories that are not CLIA certified.

[18] Testimony of Wendy Chung of Columbia University at the public meeting of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on September 6, 2017.

HIPAA and the Common Rule

The Common Rule, codified in separate regulations by 15 federal departments and agencies, is federal policy for the protection of human participants in any research that is conducted, funded, supported, or otherwise subject to regulation by the federal government. The Common Rule outlines the basic provisions for institutional review boards (IRBs), informed consent, and assurances of compliance.[19] Under the Common Rule, IRBs are required to review and approve study protocols involving human participants to ensure that the risks are reasonable relative to the anticipated benefits and that participation is conditioned on the informed consent of research participants. The Common Rule neither explicitly encourages nor explicitly prohibits the return of results to study participants, but pending revisions to the regulation will require investigators to disclose their plans for returning individual research results (i.e., whether results will be returned to participants and, if so, under what conditions). If a research laboratory is (or is part of) a covered entity, participants may be told that their results will not be offered to them, as required by the revisions, even though they will retain a right to access the results under HIPAA if the results are part of the DRS. As discussed in Chapter 5, in such cases participants should be informed of their HIPAA access rights during the informed consent process.

Investigational Device Exemption Regulations and Return of Individual Research Results

FDA regulates, among other things, devices "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals."[20] FDA's investigational device exemption (IDE) offers a regulatory pathway for investigators using an investigational device that has not yet been approved or cleared by FDA for the purposes for which it will be used in a particular study. FDA broadly defines an investigational device as one "that is the object of an investigation"[21] conducted for purposes of determining safety or effectiveness and involving one or more participants (*Federal Register*, 1980).

FDA's IDE process is intended to protect the interests of participants whose clinical care might be affected by the results of investigational devices. If a study proposes to use a laboratory test in a manner that has not been cleared or approved by FDA, the investigators, with oversight from their IRB, must determine whether the IDE regulations apply because the test is an investigational device. If so, investigators must next consider whether the study nevertheless qualifies as exempt from IDE regulations. An investigational device that is subject to the IDE

[19] 45 C.F.R. 46.
[20] 21 U.S.C. § 321(h).
[21] 21 C.F.R. § 812,3(g)(h).

regulations is exempt if it is non-invasive and not used for diagnostic purposes without confirmation of the diagnosis by a "medically established" diagnostic product or procedure. If the study does not qualify as exempt, the investigator must determine whether the device poses "significant risk" (i.e., presents a potential for serious risk to the health, safety, or welfare of a participant)[22] or "non-significant risk." Figure 6-1 shows this decision-making process and the implications for IDE requirements.

The return of research results to research participants may affect the IDE process in at least two ways. First, in the case of studies involving devices, such as whole-genome sequencing, that are being used for purposes not yet cleared or approved by FDA, it appears that the return of results may play a role in determining whether the IDE regulations apply. A National Human Genome Research Institute (NHGRI) webpage focused on IDE regulations states,

> If the investigator does not propose to return results to participants or their physicians, and the results will not otherwise be used to direct or inform the clinical care of that participant, then the investigational device study is exempt from the IDE regulation. (NHGRI, 2017)

Second, the return of research results to research participants may affect the risk classification of a non-exempt investigational device study. This risk classification determines the rigorousness of the requirements necessary to obtain an IDE. An abbreviated process can be used to obtain an IDE for devices that are not significant risk. In determining whether a device poses a significant risk, FDA considers many factors, such as the health status of the population under study and how the information generated by the device will be used in the study, including whether and how results will be returned. In a June 2016 workshop hosted by NHGRI, representatives from FDA explained that the risk of returning investigational device results to healthy volunteers would be considered different from the risks if members of the participant population have a disease or health condition (NHGRI, 2017).[23] The NHGRI resource that reflects information learned from that workshop and the experience of NHGRI grantees describes an example of a significant risk study as one that

> might involve genome sequencing of healthy participants with an intent to return variants of unknown significance (VUS). In this instance, the risk might stem from concern that test results with unknown clinical significance would lead healthy individuals to pursue unnecessary treatments that could expose them to harm. If this study design does not also include appropriate risk-mitigating measures, it could be considered SR [significant risk]. (NHGRI, 2017)

[22] 21 C.F.R. 812.3.

[23] Testimony of Adam Berger of FDA at an open session of the Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories on July 19, 2017.

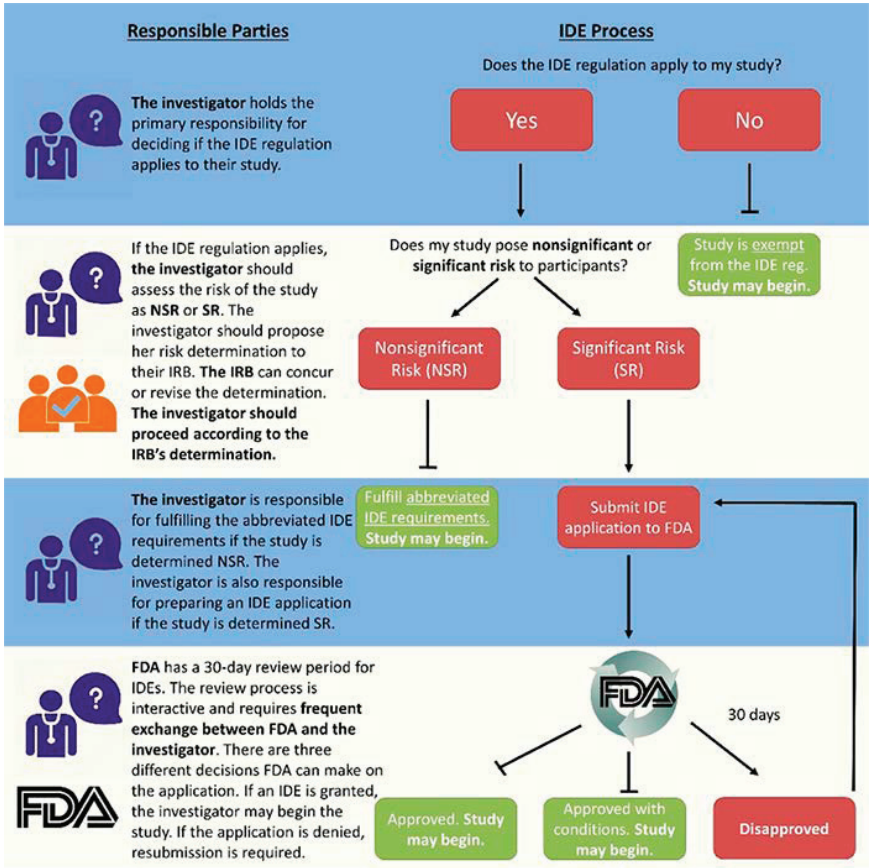

FIGURE 6-1 Investigational device exemption process for research studies.
NOTE: FDA = Food and Drug Administration; IDE = investigational device exemption; IRB = institutional review board; NSR = non-significant risk; SR = significant risk.
SOURCE: NHGRI, 2017.

The committee is aware of only one reported case, the Newborn Sequencing in Genomic Medicine and Public Health program—North Carolina Study, in which the return of research results to healthy volunteers was a key consideration in FDA's determination that investigators needed to pursue a full IDE (NHGRI, 2016). However, the potential for the return of results to trigger additional regulatory hurdles is an additional barrier for investigators considering returning research results and may incentivize them against return.

FDA has not provided binding guidance on the role of the return of individual research results in the IDE process, including the determination of whether

a device is an investigational device or the determination of whether the device poses significant risk. As a result, it is unclear how the IDE regulations actually affect most studies that return results in practice. It is also unclear if and how these analyses will change if investigators return results only in response to individual requests under HIPAA.

CONCLUSION: FDA's interpretation of how the return of individual research results triggers application of the IDE process and affects the risk assessment is unclear. FDA has introduced further confusion by suggesting that the return of individual research results for healthy individuals triggers a significant risk determination, requiring a full IDE.

CONCLUSION: It is unclear how access to individual research results under HIPAA affects FDA's risk assessment for IDEs.

Inconsistent Use of Terminology in Federal Regulations

Terminology that is inconsistent across different regulations can cause unnecessary ambiguity and confusion. The inconsistencies often relate to the process by which laws are written—i.e., different terms with origins in different laws may have the same meaning. In addition to the confusion created by different uses of the term "CLIA exempt," as mentioned above, at least two other examples of terminology are ambiguous or confusing and need to be harmonized across the relevant regulations.

The first relates to terms used to describe the information that individuals can access under CLIA and HIPAA. The original CLIA access rule provided authorized persons access to "test results" generated in CLIA-regulated and CLIA-exempt laboratories. Of note, "authorized persons" did not include the patients themselves (or their personal representative) except in states that explicitly permitted direct patient access. Under the 2014 CLIA access rule, patients and their personal representatives can now access their "completed test reports." The term "completed test report" was not defined, but the preamble to the access rule indicated that test results were complete when "all results associated with an ordered test are finalized and ready for release" (*Federal Register*, 2014, p. 7295). However, how the completed test report differs from the test results that can be accessed by the individuals authorized to order or receive them remains unclear. This ambiguity also contributes to confusion regarding research results that individuals can obtain under the HIPAA access rule, which allows individuals to access their protected health information that is contained within the DRS. The 2014 amendment to the HIPAA Privacy Rule states (in response to a comment) that

laboratory test reports do not become part of the designated record set until they are complete.[24] Some legal scholars have suggested that OCR could clarify that laboratory research results with uncertain clinical significance would not be considered "complete" and thus excluded from the DRS or, alternatively, could issue guidance that research test results are explicitly included in the DRS regardless of their clinical significance (Barnes et al., 2015).

The second terminology issue relates to the description of the identifiability of results. Federal regulations use different terms based on the standards applied when removing the linking information. According to HHS convention, "de-identified" describes results where the linking information has been removed in accordance with HIPAA standards,[25] while "non-identified" refers to results where the linking information has been removed in accordance with the Common Rule, which prescribes standards that are different than HIPAA standards (OHRP, 2016a).[26] Adding further confusion is the use of the term "identifiable sensitive information" in the 21st Century Cures Act in reference to certificates of confidentiality.

CONCLUSION: Inconsistent use of terminology by different regulatory agencies creates unnecessary ambiguity and confusion for investigators, institutions, and research participants.

Discrimination Concerns for Research Participants

The possibility that participants who receive individual research results may face discrimination if the results indicate a previously undiagnosed condition (or a genetic predisposition for a condition) is a concern among both proponents and opponents of the practice. Federal and state laws provide some protections for individuals against discrimination on the basis of disabilities, pre-existing conditions, and genetic information, but gaps remain.

First, the Americans with Disabilities Act (ADA) prohibits discrimination against individuals with disabilities in the areas of employment, public services, and public accommodations.[27] Specifically, employers are prohibited from "discriminating against individuals who (with or without reasonable accommodation) can perform the essential functions of employment positions in hiring, promotion, training, compensation, and other job-related decisions."[28] Addition-

[24] The joint amendment to the CLIA Program and HIPAA Privacy Rule amended 42 C.F.R. § 493.1291; 45 C.F.R. § 164.524.

[25] 45 C.F.R. § 164.514(b).

[26] 45 C.F.R. § 46.101(b)(4) and 45 C.F.R. § 46.102(f) (defining research to involve identifiable private information and describing exemption for research involving existing non-identified data and biospecimens).

[27] See Appendix C, p. 335, Americans with Disabilities Act.

[28] See Appendix C, p. 335, Americans with Disabilities Act.

ally, employers cannot conduct medical examinations or ask questions of job applicants and employees regarding whether they have a disability or the nature or severity of their disability unless the questions are related to the applicant or employee's job.[29] However, employers may require individuals to release their health records after making a conditional offer of employment.

The Genetic Information Nondiscrimination Act of 2008 (GINA)[30] prohibits discrimination in health insurance and employment contexts based on genetic information, which is defined as information about an individual's genetic tests, about the genetic tests of family members, or about the presence of a disease or disorder in family members. Congress's intent in passing GINA was to remove barriers to genetic testing for personal health and research purposes by providing legal protection against the misuse of genetic test results. GINA expanded protections instituted earlier through HIPAA by prohibiting group and individual insurers from using genetic information to set premiums or make eligibility decisions for individuals or groups. The law further prohibits health plans from requesting or requiring genetic testing prior to an individual's insurance enrollment and from requesting, requiring, or purchasing genetic information for underwriting purposes.[31]

GINA similarly limits both access to and use of genetic information by employers (Prince and Berkman, 2012).[32] Thus, employers are prohibited from requesting, requiring, or purchasing genetic information about employees or their family members.[33] Employers also may not use genetic information to make employment decisions (e.g., hiring, firing, promotion, and compensation) or to deprive employees of employment opportunities.[34] Finally, employers must treat the genetic information of their employees as confidential medical records that generally may not be disclosed.[35]

While GINA affords important protections for patients and research participants, it notably does not regulate discrimination based on non-genetic information (e.g., a positive test result for a protein biomarker for Alzheimer's disease) (Arias and Karlawish, 2014). Moreover, GINA is limited to genetic information

[29] See Appendix C, p. 336, Americans with Disabilities Act.

[30] Genetic Information Nondiscrimination Act of 2008, Public Law 110-233, 110th Cong. (May 21, 2008).

[31] 42 U.S.C. § 300gg-4(d).

[32] The Americans with Disabilities Act (ADA) also prohibits discrimination in employment and other contexts but was enacted to protect individuals with disabilities. It is not clear whether an asymptomatic individual with a genetic predisposition to a condition that has not yet manifested would be considered to have a disability under the ADA.

[33] However, it should be noted that the Patient Protection and Affordable Care Act (ACA) seemingly contradicts GINA with respect to the release of genetic information by encouraging employers to offer wellness programs, including diagnostic testing programs, that tie health insurance costs to employee program participation (Public Law 111-148 § 1201).

[34] 42 U.S.C. § 2000ff-1(a)–(b).

[35] 42 U.S.C. § 2000ff-5(a)–(b).

and does not apply to discrimination based on already expressed genetic conditions, although the Patient Protection and Affordable Care Act closed this loophole in health insurance by prohibiting individual and group insurers from denying coverage based on any kind of pre-existing condition.[36] GINA also does not confer protection against the discriminatory use of genetic information by life, disability, or long-term care insurers or in other contexts in which discrimination may occur, such as housing and education. These gaps in GINA's protections may discourage people from participating in biomedical research, particularly when there is the potential to uncover unanticipated findings indicating an increased risk for a health condition (Green et al., 2015).

Most states have sought to augment federal anti-discrimination protections related to genetic information. In a few cases, state laws have focused on preventing discrimination against individuals with specific genetic traits (e.g., sickle cell trait or cystic fibrosis trait), but the majority are more broadly aimed at preventing the discriminatory use of genetic information in employment and insurance decisions. Twenty-four states have enacted laws addressing gaps in GINA's protections by limiting genetic discrimination in life, disability, or long-term care insurance, and California's law further bars discrimination in emergency medical services, housing, mortgage lending, and public education. The implication of this patchwork of statutes is that the protections for research participants who choose to receive their research results will vary by geographic location, and participants will need to understand the anti-discrimination protections in their state.

CONCLUSION: Research participants who choose to receive results from the testing of their biospecimens (or who exercise their right of access under HIPAA) should be informed about the discrimination protections under GINA and the ADA and relevant state laws and what GINA/ADA/state laws do not protect against.

Liability Concerns for Investigators, Laboratories, and Institutions

Survey data have indicated that a fear of legal liability influences investigators' decisions on whether to return individual research results (Ramoni et al., 2013). Concerns regarding the liability associated with not returning results can motivate some investigators to disclose research results to participants, but, at the same time, fears of lawsuits stemming from inaccurate findings or medical mismanagement subsequent to the receipt of results may discourage investigators from returning them.

The legal liability for investigators concerning the return of individual research results most likely appears in the form of tort liability,[37] which falls under

[36] Public Law 111-148 § 1201 (2010) (codified at 42 U.S.C. § 300gg-3).

[37] A tort is a civil wrong (other than breach of contract) for which a remedy may be obtained, usually in the form of damages (Legal Information Institute, 2018).

state law. In the absence of federal regulations or case law directly addressing a researcher's duty to disclose significant research results, investigators and their institutions are left to make difficult decisions about whether and when to return results in the context of significant legal uncertainty surrounding this issue (McGuire et al., 2014).

Concerns Regarding Liability for Disclosure

Several circumstances associated with the return of individual research results may give rise to tort liability. These include

- the disclosure of correct results (of timely interest or utility) to the wrong individual, which might be caused by the improper labeling of biospecimens or results, especially in laboratories without a quality system (this situation could also create liability for non-disclosure—discussed in the next section—if the results are not disclosed to the right individual);
- the disclosure of incorrect results to the right individual, which might be caused by a mishandling of biospecimens, improper test administration, or misinterpretation (e.g., negligent misclassification of variants);
- the disclosure of results to individuals who are not authorized to receive them; and
- failure to update previously disclosed results and to return the updated results.

Although research laboratories are not subject to the same quality requirements as clinical laboratories, they still must maximize the analytic and clinical validity of any results returned to participants. For example, if investigators return erroneous results generated by a research laboratory without indicating that the results need to be verified in a CLIA-certified laboratory before any clinical actions are undertaken, the researchers may be liable to a tort filing. However, even in the case that appropriate warnings regarding the need for confirmatory clinical testing were provided, it is not clear whether this would be sufficient to protect investigators from tort liability (McGuire et al., 2014). This will be decided by courts on a case-by-case basis. For rapidly evolving fields like genomics, further complications arise from continuing changes in the standard of care regarding interpretation and the return of results.

Concerns Regarding Liability for Non-Disclosure

Tort liability related to non-disclosure is most likely to arise as a form of negligence, where an individual owed a duty to another person but breached that duty, and the person was harmed as a result (McGuire et al., 2014). In the return-of-results context, this might involve a case where an investigator or

laboratory failed to return urgent, medically actionable results and the participant was harmed as a result.

Whether one person owes a legal duty to another depends on the nature of their relationship and is highly context specific (Pike et al., 2014). As an example, fiduciary relationships—two-way relationships based on trust—can give rise to a claim of negligence when the fiduciary does not act in the best interests of the principal. However, except in cases where investigators are also a participant's treating physician, the courts have declined to view researchers as fiduciaries of research participants.[38] Nevertheless, precedent suggests that researchers may have a "special relationship" to participants that gives rise to a duty to disclose certain research results (see the *Grimes v. Kennedy Krieger Institute* case described in Appendix C, p. 330, Special relationships).

Whether a special relationship between investigators and participants gives rise to duties that include the return of certain individual research results also depends on the prevailing standard of care. The standard of care can be established by guidance and recommendations to return results, by recognition by scholars and the research community of an ethical obligation to return results, or by a common practice of returning results. Consequently, if the practice of returning results becomes routine, legal scholars have noted, researchers will be legally required to do so (Clayton and McGuire, 2012). Thus far, however, ethics-based recommendations from expert groups have not yet been used to impose legal liability (Wolf, 2012).

Given the concerns regarding legal liability, a staged approach to expanding the practice of returning individual research results (discussed in Chapter 4) may generate forward momentum while allowing the field to test the legal waters and work out the early precedents. As stated by one legal scholar, "to shape ethics and practice around premature conclusions of legal threat would be to thwart an extremely important debate in research ethics and practice" (Wolf, 2012).

CONCLUSION: Perceived liability risks may dampen interest in returning individual results to research participants. However, good faith efforts by investigators to return individual research results with proper warnings and caveats are unlikely to result in legal action for negligence. Delineating standards for the return of individual research results will help to mitigate concerns regarding liability.

[38] There is, however, an open question of whether a laboratory is itself a health care provider with fiduciary obligations. This question is presented in a pending federal lawsuit in South Carolina, *Williams v. Quest Diagnostics*, which is based on allegations that a clinical laboratory returned erroneous genetic test results resulting in the death of an individual who received the wrong treatment (Ray, 2018).

CREATING A REGULATORY ENVIRONMENT BETTER ALIGNED WITH THE BENEFITS AND RISKS OF THE RETURN OF INDIVIDUAL RESEARCH RESULTS

The committee was asked to review the current regulatory requirements and consider whether current regulations are effective in minimizing the risks while maximizing the benefits of returning individual research results. In its assessment of the regulatory environment—described in the sections above—the committee found considerable confusion concerning the legal and regulatory requirements and restrictions pertaining to the return of individual results, causing variable interpretation and action across IRBs and research sites. This confusion stems, in part, from inconsistencies and ambiguities in the regulatory language as well as the potential for conflicts between federal regulations. In some cases, regulations or the institutional interpretations of the regulations are too restrictive, placing institutional protection ahead of participants' right to access health data, while others are not restrictive enough, allowing for the return of results of poor or unsubstantiated quality without appropriate disclaimers to inform participants regarding limitations in the validity and utility of the information they receive. These conflicts appear to result, in part, from opposing values of the federal agencies with oversight in this domain. The statutory responsibilities of CMS and FDA emphasize patient and participant safety, while the promotion of access is a core tenet of OCR's civil rights mandate. Recognizing the critical importance of both sets of values, the committee sees opportunity to strike a balance.

CONCLUSION: Overall the current regulatory environment for the return of individual research results is overly restrictive and characterized by confusion and conflict, unnecessarily impeding participants' access to research results that may have value to them.

CONCLUSION: Inconsistencies in terminology and discrepancies in requirements across different federal regulations relevant to the return of individual research results contribute to the confusion, but could be addressed through an effort to harmonize regulations.

In developing its recommendations on changes to better align the regulatory environment for the return of individual research results with the risks and benefits to individuals, the research enterprise, and society, the committee carefully considered the pros and cons of different approaches as well as the potential downstream effects on the current regulatory framework. The options presented in the sections below are not all mutually exclusive, and, in fact, a combination of approaches may be required to address different concerns.

Considerations for Changes to CLIA Regulations

CLIA regulations serve an important function in ensuring that the clinical results returned to patients are high quality and likely to be accurate. Requiring research laboratories to obtain CLIA certification before returning individual research results similarly increases the likelihood that the research results returned to participants are valid. However, the burdens associated with CLIA certification (e.g., direct costs, human resource requirements) as well as the inconsistencies between some of the CLIA regulations and the functions of a research laboratory create an incentive for investigators to plan not to return results, which, given participants' interest in receiving results, may adversely affect public participation in biomedical research (Crawley, 2001; Hiratsuka et al., 2012; Northington Gamble, 2006). Even in the absence of a plan to return results, investigators and decision makers in their institutions may face a moral dilemma in the event that an unanticipated result generated in a laboratory that is not CLIA certified has implications for the participant's well-being that are so great as to create an ethical imperative to return the result. Moreover, as described above, current conflicting regulatory requirements for CLIA and HIPAA can create legal dilemmas for laboratories that are covered entities, forcing them to choose which of the regulations to intentionally violate in order to comply with the other. Some have suggested that having a plan and allocating funds in the research budget for confirmatory testing in a CLIA-certified laboratory when a need arises to return unanticipated results could help resolve these kinds of dilemmas (Beskow and O'Rourke, 2015; Bookman et al., 2006). However, this assumes that additional samples can be collected from the participant, which is not always possible in research studies, and that a CLIA-certified laboratory is able to validate the research result. For some cutting-edge technologies and novel assays, a validated test in a CLIA-certified laboratory may not be available (Prucka et al., 2015). For example, if the research laboratory is performing a test for a new serum biomarker for a stroke, a CLIA-certified laboratory may not have a validated test for the biomarker. Even when retesting is possible, given the added cost of doing so, the committee does not believe that the possibility of retesting will address the current disincentives for returning research results to participants on a more routine basis. Therefore, the committee considers and describes below proposed changes to the CLIA regulations. In the absence of changes to the CLIA regulations,[39] the committee believes that at the very least HIPAA regulations need to be changed or clarified so that non-CLIA-certified laboratories cannot be compelled to disclose PHI in the DRS of questionable analytic validity that are requested by participants. Potential changes to HIPAA regulations are discussed in the next section.

[39] Of note, analysis of and commentary on changes to the interpretation of CLIA regulations were identified by the sponsors as outside the study scope, so such options are not discussed in this chapter.

On one end of the range of options is a requirement that all testing on human biospecimens (not just those returning results) be conducted in CLIA-certified laboratories. In addition to removing current disincentives to return research results, resolving any possible CLIA–HIPAA conflict, and increasing confidence in the validity of results being returned to participants (both in planned and unplanned return scenarios), such a requirement could help address the broader concerns regarding the quality of research results and the reproducibility in biomedical research. However, the committee did not consider this a viable option, given the likely adverse impacts on many research laboratories, both in terms of the sustainability of costs (particularly for new and smaller laboratories operating earlier in the translational research continuum) and the impacts on innovation. A large number of laboratories conducting research on human biospecimens would require assistance (both financial and technical) for the staff training and operational changes that would be needed to obtain CLIA certification. Institutional core resources could help ameliorate this burden for individual laboratories/investigators, but not all institutions have the capacity to develop this kind of centralized infrastructure. Several groups have concluded that it would be infeasible for all research laboratories that test human biospecimens to become CLIA certified (Barnes et al., 2015; SACHRP, 2016) and such a requirement could disincentivize research on biospecimens, thereby slowing progress in some important research areas (e.g., assay development and novel biomarker identification).

On the other end of the continuum is the option for CMS to amend CLIA regulations so that research results could be returned to participants from any research laboratory without restriction (regardless of whether the laboratory operated under a quality management system and with no requirement for oversight). Although this would remove the current disincentive associated with the burden of CLIA certification for laboratories interested in returning research results, the committee rejected this option because of the potential harms associated with returning results lacking validity, particularly if the results are not accompanied by information conveying the limitations of the reliability and interpretation. The committee also was concerned that this would create a perverse incentive to test human biospecimens for clinical decision making in research laboratories in order to avoid the burden associated with meeting and maintaining the CLIA certification requirements.

Between these two extremes is a third option for CLIA regulatory changes which allows investigators and their institutions greater flexibility in determining the conditions under which returning results is appropriate when they have not been generated in a CLIA-certified laboratory. For the safety reasons discussed in Chapter 3, investigators planning to return research results that are intended for use in clinical decision making should ensure that those results are generated (or verified prior to use and return) in a CLIA-certified laboratory. However, the committee also recognizes that in some scenarios CLIA certification may not be appropriate to the nature of the research conducted by a laboratory and therefore

recommends that the National Institutes of Health (NIH) lead the development of an externally accountable[40] quality management system for research laboratories testing human biospecimens (see Recommendation 2).

The adoption of this standard by research laboratories would adequately support confidence in the analytic validity of research results so that they can be offered to participants, but it would require CMS to revise the CLIA regulations to allow for the return of results from laboratories operating under this research quality management system when the results are not intended for use in clinical decision making (see Box 3-1). To prevent abuse (i.e., by unscrupulous parties seeking to avoid CLIA certification costs and resources even when results are intended to inform clinical decision making) and protect the well-being of research participants, this exception from CLIA requirements would necessitate institutional processes (and the associated infrastructure and resources) for laboratory oversight and risk management. For example, external assessments of a laboratory's quality management system could be reported to the IRB as a condition of protocol approval prior to starting research incorporating the planned return of individual research results not intended for clinical decision making.

Prior to the establishment of an externally accountable quality management system for research laboratories or in cases where investigators did not plan to return results (i.e., unanticipated results or results requested by participants under HIPAA), the proposed CLIA exception could further allow decisions regarding the return of individual research results to be made at the institutional level contingent on an IRB review and approval process (see Recommendation 3). All research results returned to participants would need to be qualified with information that helps recipients understand the limits of the information being returned in order to minimize the risk of harm from a misinterpretation or misapplication of the results.

Considerations for Changes to the HIPAA Access Right

The proposed changes to the CLIA regulations to allow the return of individual research results from laboratories operating under the NIH-defined externally accountable quality management system or following an IRB review and approval process (discussed above and in Chapter 3) would go a long way toward resolving the CLIA–HIPAA conflict. However, it would still leave open the issue that, under the HIPAA access right, laboratories could be compelled to share research results with questionable validity or a high potential for misinterpretation. Some may argue that individuals should still have a right to access their information even if

[40] As discussed in Chapter 3, external accountability requires a system for independent verification (i.e., inspection by external experts without conflict of interest or intractable bias toward any one investigator or perhaps even bias toward the institution) to determine whether laboratories are adhering to quality standards.

it is poor quality, and in regards to other types of information in the DRS, such as physician notes and electronic medical records (EMRs) information, that is the case. However, there is a crucial difference between laboratory results and these other types of protected health information—an individual has no way to know or verify if the laboratory result is accurate or if it even belongs to the individual. By contrast, a patient or patient's caregiver may recognize by himself or herself (or in consultation with the provider) that the information in the EMRs is incorrect. Thus, it is important to have some mechanism for individuals to have confidence in the quality of laboratory test results. Given the inherent uncertainty in research, results with these characteristics may be generated even when laboratories have established quality management systems in place, and investigators and institutions may not feel comfortable returning such results. Therefore, the committee considered additional regulatory changes related to the HIPAA right of access. While cautious about restricting one of the currently available pathways for participants to access their research results, particularly in an environment where results are rarely offered to participants, the committee believes that carefully considered changes are warranted to reduce the risk of harm from the return of research results.

HIPAA's access right applies only to laboratories that are—or are part of—a covered entity and to results that are maintained within the DRS for that entity. Consequently, two[41] different pathways are proposed that restrict the right of access to research results: research laboratories can be legally separated from the HIPAA-covered part of the entity so that they are no longer subject to HIPAA's requirements, or the DRS can be defined to exclude all or some research results.

The legal mechanism for implementing the first approach is the creation of a hybrid entity (Barnes et al., 2015), which is an entity whose business functions include both covered and non-covered functions.[42] Some academic medical centers have elected to become hybrid entities, with research laboratories that do not conduct covered transactions excluded from the covered portion of the entity. Such laboratories could not be compelled to provide access to research results under HIPAA.

However, a number of significant challenges and costs to creating a hybrid entity limit the viability of this approach on a wide scale (Barnes et al., 2015). First, some personnel may be involved with both covered (e.g., health care delivery) and

[41] A third possible approach that has been suggested by some legal scholars is for the federal agencies to exercise enforcement discretion (i.e., not take action against laboratories or institutions that fail to comply with their regulations until the apparent conflict has been resolved) (Barnes et al., 2015). While the committee understands the practicality of this approach in the interim, it believes that the agencies should work to ensure that their regulations do not conflict and not rely on enforcement discretion to resolve apparent conflicts. Additionally, the likely effect of this approach would be that institutions would continue to interpret the regulations in their own way, resulting in inequitable access for research participants.

[42] 45 C.F.R. § 164.103, 45 C.F.R. § 164.105(a)(2)(iii).

non-covered (e.g., some research[43]) functions, making separation of the subparts difficult to define. The conduct of covered transactions by the non-covered part of the hybrid entity could result in a fine from the HHS OCR. For a fee, legal and other consultants can help institutions properly separate components into covered and non-covered elements. Second, in accordance with the HIPAA Privacy Rule, institutions would need to ensure that information from the covered part of the entity is shared with the non-covered part in the same way that information from any two separate entities is shared. This would necessitate separate information systems, which conflicts with the proposed use of the medical EHR for communication of research results noted above. Hybrid entities cannot have a unified electronic record system. In addition to the infrastructure costs associated with separate information systems, creating a hybrid entity restricts data sharing across covered and non-covered components[44] (Barnes et al., 2015) and could thereby impede some kinds of research—e.g., research involving the review and analysis of medical records cannot be conducted by laboratories in the non-covered part of the entity. Moreover, while the creation of hybrid entities can be done on an institution-by-institution basis, no regulatory mechanism universally excludes research laboratories from the covered portion of an entity. Thus, while this approach may make sense for some individual institutions, the committee does not consider it to be a viable option for addressing the issues with HIPAA access to results of questionable validity and its potential conflict with the CLIA requirements.

An alternative approach that could have broader reach if implemented by OCR is to more explicitly define what is and is not included in the DRS. Defining the DRS so that it does not include research results—specifically those results not intended for clinical decision making[45]—would prevent laboratories from being compelled to disclose such results when requested by participants (although investigators and institutions could still decide to return the results if they were generated in a laboratory with an accepted externally accountable quality management system or if the disclosure was reviewed through an independent process and approved by the IRB per Recommendation 3). The committee notes that some research institutions are already taking this approach, but by each institution documenting its interpretation of what OCR intends to be included in the DRS in its own way, different standards are being created at different institutions, resulting in inconsistent and inequitable access to research results for participants.

[43] Some research, including some clinical trials, can involve covered transactions such as billing and therefore could not be conducted by the non-covered portion of a hybrid entity.

[44] Except as permitted by HIPAA—for example, with a valid patient authorization.

[45] Research results that are also used in clinical decision making (e.g., results from a clinical trial conducted in a health care setting to evaluate the comparative effectiveness of medical treatments) would not be excluded from the designated record set and could be accessed by participants upon request under HIPAA.

Although defining the DRS to exclude all research results not intended for clinical decision making would resolve the issues of access to unreliable results and the potential CLIA–HIPAA conflict, this approach is unnecessarily restrictive since it also impedes access to high-quality research results that may have value to participants. Additionally, the fact that HIPAA excludes the right of access for protected health information only during the duration of the research study suggests that OCR did intend for research results to be part of the DRS once a study has reached completion. Instead, the committee favors a more inclusive approach to defining the DRS that would preserve access to individual research results generated in CLIA-certified laboratories and laboratories with a quality management system consistent with Recommendation 2 (see Figure 6-2). This approach reduces the risks (to participants and investigators) from returning unreliable results while maximizing access to reliable research results.

Recommendation 12: Revise and Harmonize Regulations to Support the Return of Individual Research Results.

Regulators and policy makers should revise and harmonize the relevant regulations in a way that respects the interests of research participants in obtaining individual research results and appropriately balances the competing considerations of safety, quality, and burdens on the research enterprise.

Specific actions that should be taken include

- **A. Because the designated record set (DRS) is intended to include information used to make decisions about individuals, those decisions should be based on test results that are of sufficient quality to be valuable for decision making. Accordingly, the Office for Civil Rights (OCR) of the Department of Health and Human Services (HHS) should define the DRS to include only individual research results generated in a CLIA-certified laboratory or under the externally accountable quality management system for research laboratories (see Recommendation 2);**
- **B. OCR should require all HIPAA-covered entities that conduct research on human biospecimens to develop a plan that is reviewed and approved by the IRB for the release of individual research results in the designated record set to participants in a responsive manner when requested under HIPAA;**
- **C. CMS should revise CLIA regulations such that when there is a legal obligation under the HIPAA access right to return individual research results, a laboratory will not be considered in violation of CLIA and need not obtain CLIA certification before satisfying this legal obligation;**
- **D. CMS should revise CLIA regulations to allow research results to be returned from a non-CLIA-certified laboratory when they are not**

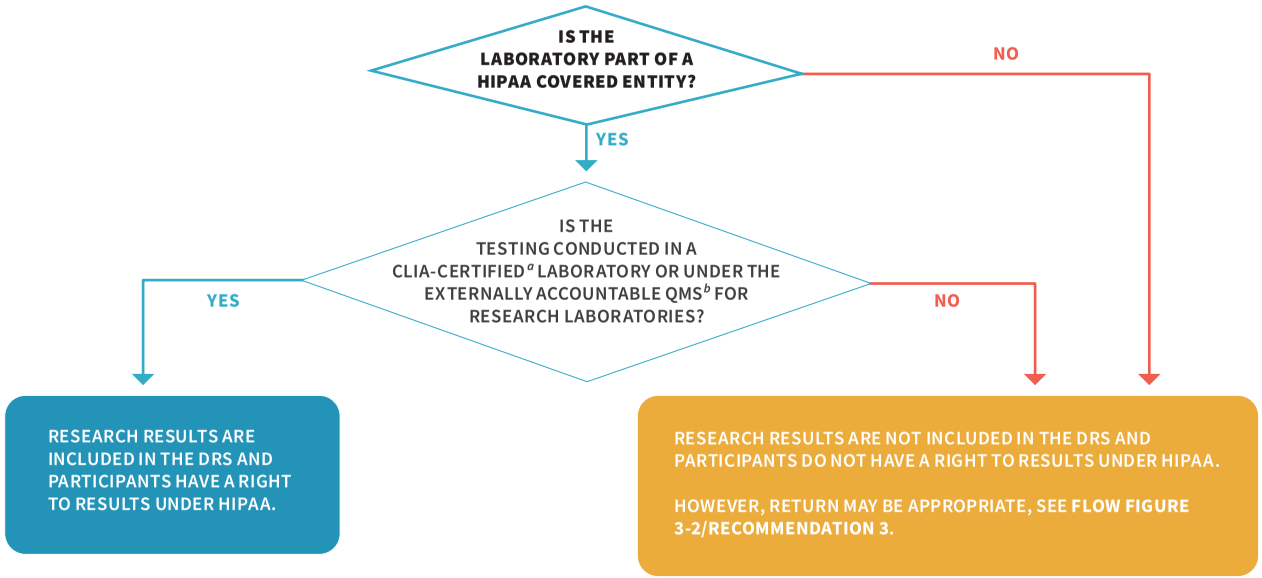

FIGURE 6-2 Determining whether participants have the right to access their individual research results under HIPAA.

[a] CLIA-certified includes tests run in a CLIA-certified, -accredited, or -waived laboratory.

[b] See Recommendation 2.

NOTE: CLIA = Clinical Laboratory Improvement Amendments of 1988; DRS = designated record set; HIPAA = Health Insurance Portability and Accountability Act of 1996; NIH = National Institutes of Health; QMS = quality management system.

intended for clinical decision making in the study protocol (as defined in Box 3-1) and the laboratory conducts its testing under the quality management system with external accountability or the IRB has approved the return of results (as described in Recommendation 3);

E. CMS and OCR should harmonize the definitions of the following terms, providing a clear explanation and justification for any differences or discrepancies: "test report" and "completed test report" (CLIA), and "PHI in the designated record set" (HIPAA);

F. OCR, OHRP, and NIH should harmonize the definitions of the following terms, providing a clear explanation and justification for any differences or discrepancies: "de-identified" (HIPAA), "non-identified" (Common Rule), and "identifiable sensitive information" (21st Century Cures Act regarding certificates of confidentiality);

G. HHS (including CMS, FDA, NIH, OHRP) should ensure that all regulations, policies, and guidance relevant to human research refer to research "participants," rather than research "subjects," in accordance with the ethical principles of autonomy and respect for persons; and

H. FDA should clarify and provide additional guidance that if a device is not exempt from investigational device exemption (IDE) regulations, disclosure of results in many circumstances, including to healthy volunteers, will not necessarily entail significant risk, and FDA should clarify when it will consider the return of individual research results to entail significant risk. Additionally, FDA should provide guidance to IRBs on how to determine significant risk if the device is not exempt from IDE regulations.

FINAL THOUGHTS

The recommendations in this report, if followed, will result in substantial and potentially controversial changes to the research regulations and the research enterprise involving research with human biospecimens. The opportunity for change is due to the evolving relationship between investigators and participants, but more specifically to an assessment of the benefits and risk of results disclosure. The need for higher standards of quality in many research laboratories is clearly illustrated in this report and in our recommendations. Yet, despite the inherent limitations in the validity and reliability of many research results, our assessment is that the risks associated with the communication of results have been overstated, particularly for the many research projects that are unlikely to yield highly sensitive or clinically impactful results. Furthermore, the benefits to individual participants and to the research enterprise of results disclosure have been understated. Therefore, we are recommending that the absolute standard—that is, that

all disclosed results must be generated in a CLIA-certified laboratory—should be replaced with a process-oriented standard, meaning that a peer-review process can be used in some circumstances to weigh competing considerations regarding the return of individual results. We recommend that such a process take into account, on a case-by-case basis, the values of the participants, the risks and benefits of the return of particular results, the quality of the research laboratory, and the feasibility for investigators to pursue this course. Moving away from an absolute standard has risks, but we believe that the risks can be mitigated through improvements in laboratory quality, a case-by-case assessment of the risks and benefits, and the promotion and development of communication strategies to help place results in the proper context for participants. The committee believes that the benefits of this more nuanced approach will greatly exceed the adverse impacts and costs.

The committee is well aware that more frequent return of individual research results will create new demands on the research and clinical enterprise. Many institutions and researchers currently lack the experience and resources to return individual research results in a deliberate and effective manner. The committee does not expect that the consistent and widespread return of individual research results will happen overnight. However, the committee foresees an evolving set of responsibilities and offers recommendations that it believes will help stakeholders prepare for these added responsibilities and develop the necessary expertise over time.

At a broader level, the justification for fundamental changes in the research landscape is found in our evolving understanding of the ethics of human participant research (which should be reflected in the language of federal regulations—see Recommendation 12G above) as well as to our recognition that failures to support transparency and to earn respect and trust from individuals in the community are hampering the conduct of science. The vision is that a dedicated commitment to collaboration will better honor participants, benefit science, and promote the welfare of society. The standards and practices related to the return of individual results are but one set of elements in this evolving landscape. But the return of individual research results is a tangible, measurable piece that we know is valued by participants and is feasible in many more circumstances than are reflected in current practice. Our hope is that this report will promote the return of individual research results through selected changes in research regulations, the use of quality systems that improve the quality of research results, and through the commitment of all stakeholders (see Table 6-3) to innovative, collaborative processes in the planning and conduct of research.

TABLE 6-3 Recommendations by Stakeholder[a]

STAKEHOLDER	RECOMMENDED ACTION
HHS	**RECOMMENDATION 12G** – Chapter 6 Refer to research volunteers as *participants*, not *subjects* in all regulations relevant to human research
CMS	**RECOMMENDATIONS 12C and D** – Chapter 6 Revise CLIA regulations to allow for the return of individual research results from non-CLIA-certified laboratories when results are requested under the HIPAA access right and when the quality of results has been established and they are not intended for use in clinical decision making
	RECOMMENDATION 12E – Chapter 6 Work with OCR to harmonize definitions of key terms relevant to the return of individual research results in the federal regulations
FDA	**RECOMMENDATION 12H** – Chapter 6 Clarify and provide additional guidance regarding how the return of individual research results affects IDE requirements for research studies
NIH	**RECOMMENDATION 2** – Chapter 3 Lead an interagency effort with nongovernmental stakeholders to develop standards for a quality management system for research laboratories testing human biospecimens

continued

TABLE 6-3, Continued

	RECOMMENDATION 12F – Chapter 6 Work with OCR and OHRP to harmonize the definitions of key terms relevant to the return of individual research results in the federal regulations
OCR	**RECOMMENDATION 12A** – Chapter 6 Revise the definition of the designated record set (DRS)
	RECOMMENDATION 12B – Chapter 6 Require HIPAA-covered entities that conduct research on human biospecimens to develop a plan for the release of individual research results in the DRS when requested under HIPAA
	RECOMMENDATIONS 12E and F – Chapter 6 Work with CMS, OHRP, and NIH to harmonize definitions of key terms relevant to the return of individual research results in the federal regulations
OHRP	**RECOMMENDATION 12F** – Chapter 6 Work with OCR and NIH to harmonize definitions of key terms relevant to the return of individual research results in the federal regulations
Research sponsors and funding agencies	**RECOMMENDATION 4** – Chapter 3 Ensure adequate resources and infrastructure to generate high-quality individual research results
	RECOMMENDATION 5 – Chapter 4 Engage community and participant representatives in the development of policy and guidance related to the return of individual research results

	RECOMMENDATION 7 – Chapter 4 Ensure planning for the return of individual research results in applications for funding
	RECOMMENDATION 11 – Chapter 5 Support research to expand the empirical evidence base relevant to the return of individual research results
Research institutions	**RECOMMENDATION 1** – Chapter 2 Consider whether and how to return individual research results on a study-specific basis
	RECOMMENDATION 3 – Chapter 3 Ensure the high quality of individual research results that are returned to participants
	RECOMMENDATION 4 – Chapter 3 Ensure adequate resources and infrastructure to generate high-quality research results
	RECOMMENDATION 5 – Chapter 4 Enable and facilitate investigator access to relevant community and participant networks, resources, and training
	RECOMMENDATION 8 – Chapter 4 Develop policies and procedures that support the assessment of plans for the return of individual research results, and ensure that IRBs and research teams have or have access to the necessary expertise and resources to assess plans

continued

TABLE 6-3, Continued

Research institutions	**RECOMMENDATION 10** – Chapter 5 Enable the understanding of individual research results by research participants
IRBs	**RECOMMENDATION 3** – Chapter 3 Ensure the high quality of individual research results that are returned to participants
	RECOMMENDATION 7 – Chapter 4 Review the return-of-results plan and ensure the consent process aligns with it
Investigators	**RECOMMENDATION 1** – Chapter 2 Consider whether and how to return individual research results on a study-specific basis
	RECOMMENDATION 5 – Chapter 4 Seek information on participant needs, preferences, and values related to return of individual research results
	RECOMMENDATION 6 – Chapter 4 Include plans for return of individual research results in research protocols
	RECOMMENDATION 9 – Chapter 5 Ensure transparency regarding return of individual research results in the consent process

	RECOMMENDATION 10 – Chapter 5 Enable the understanding of individual research results by research participants
Participants	**RECOMMENDATION 5** – Chapter 4 Engage researchers to ensure that participant needs, preferences, and values are incorporated in decision making about the return of individual research results

[a] An interactive version of this table can be found at http://resources.nationalacademies.org/ReturnofResults/index.html (accessed August 13, 2018).

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A

Study Approach and Methods

In response to a request by the Centers for Medicare & Medicaid Services, the Food and Drug Administration, and the National Institutes of Health, the National Academies of Sciences, Engineering, and Medicine's Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories was charged with reviewing and evaluating the ethical, social, regulatory, and operational issues regarding the return of individual-specific research generated in laboratories involved in research on human biospecimens. The committee's final report will include a review and evaluation of available evidence, current practices, potential benefits and harms, the regulatory environment for returning individual research results to participants, and the ethical considerations involved in providing or denying access to individual research test results.

COMMITTEE EXPERTISE

The National Academies formed a committee of 15 experts to conduct a 14-month study to deliberate and respond to the Statement of Task. The committee was composed of individuals with expertise in bioethics, legal and regulatory practice, research and laboratory practice, health communication, health literacy, decision science, and patient and community advocacy.

MEETINGS AND INFORMATION-GATHERING ACTIVITIES

The committee deliberated from July 2017 to May 2018, during the course of which it held five in-person meetings (July, September, October, December, and February). The July, September, October, and December meetings included

portions open to the public, and there was a public webinar held in December 2017 as well. The open session agendas appear in Appendix B. The committee meeting in February 2018 was held in closed session.

To inform its deliberations the committee gathered information through a variety of mechanisms: (1) one 2-day workshop with open public sessions; (2) one 90-minute webinar in December discussing laboratory standards for regulated and non-regulated biomedical laboratories; (3) two open public-comment session during its September and October meetings; (4) one 2-hour informal interview session with participant and community representatives at the December meeting; (5) literature reviews of the scientific, ethical, and social issues and other pertinent background research; (6) solicitation and consideration of written statements from stakeholders and members of the public through the committee's Current Projects System website and by coordinated e-mail outreach; and (7) personal communication between committee members and staff and individuals who have been directly involved in or have special knowledge of the issues under consideration.

SOLICITATION FOR PUBLIC COMMENT

The committee proactively solicited a call for public comments in order to capture the diverse perspectives on the current evidence base and on practices related to the return of individual research results generated in laboratories that perform tests on human biospecimens. The comments were solicited through internal listservs at the National Academies. There was also an external solicitation carried out by the National Academies communications office, which tweeted a call for public comments through the Health and Medicine Division (HMD) and National Academies Twitter accounts and e-mailed individuals who had signed up to receive updates on the following topics: aging; biomedical and health research; children and families; diseases; environmental health; global health; health care workforce; health services, coverage, and access; public health; select populations and health disparities; veterans' health; and women's health. This included the Board on Health Care Services and the Board on Health Sciences Policy as well as the HMD's forums and roundtables which distributed the call for comments to the internal membership and external listservs. The forums and roundtables included

- Forum on Aging, Disability, and Independence
- Forum on Drug Discovery, Development, and Translation
- Forum on Microbial Threats
- Forum on Neuroscience and Nervous System Disorders
- Forum on Regenerative Medicine
- National Cancer Policy Forum
- Roundtable on Environmental Health Sciences, Research, and Medicine

- Roundtable on Genomics and Precision Health
- Roundtable on Health Literacy
- Roundtable on Population Health Improvement
- Roundtable on Quality Care for People with Serious Illness
- Roundtable on the Promotion of Health Equity

Staff also sent the call for public comments to the principle investigators of the 60 universities affiliated with the Clinical and Translational Science Awards (CTSA) consortium. These included

1. Albert Einstein College of Medicine (partnering with Montefiore Medical Center)
2. Boston University
3. Case Western Reserve University
4. Children's National Medical Center
5. Columbia University
6. Duke University
7. Emory University (partnering with Morehouse School of Medicine and Georgia Institute of Technology)
8. Georgetown University with Howard University
9. Harvard University
10. Indiana University School of Medicine (partnering with Purdue University and the University of Notre Dame)
11. Johns Hopkins University
12. Mayo Clinic
13. Medical College of Wisconsin
14. Medical University of South Carolina
15. Mount Sinai School of Medicine
16. New York University School of Medicine
17. Northwestern University
18. The Ohio State University
19. Oregon Health & Science University
20. Penn State Milton S. Hershey Medical Center
21. The Rockefeller University
22. Scripps Research Institute
23. Stanford University
24. Tufts University
25. The University of Alabama at Birmingham
26. University of Arkansas for Medical Sciences
27. University of California, Davis
28. University of California, Irvine
29. University of California, Los Angeles
30. University of California, San Diego

31. University of California, San Francisco
32. The University of Chicago
33. University of Cincinnati
34. University of Colorado Denver
35. University of Florida
36. University of Illinois at Chicago
37. The University of Iowa
38. University of Kansas Medical Center
39. University of Kentucky Research Foundations
40. University of Massachusetts Worcester
41. University of Michigan
42. University of Minnesota
43. University of New Mexico Health Sciences
44. University of North Carolina at Chapel Hill
45. University of Pennsylvania
46. University of Pittsburgh
47. University of Rochester School of Medicine and Dentistry
48. University of Southern California
49. The University of Texas Health Science Center at Houston
50. The University of Texas Health Science Center at San Antonio
51. The University of Texas Medical Branch
52. The University of Texas Southwestern Medical Center at Dallas
53. The University of Utah
54. University of Washington
55. University of Wisconsin–Madison
56. Vanderbilt University–CTSA Coordinating Center (partnering with Meharry Medical College)
57. Virginia Commonwealth University
58. Washington University
59. Weill Cornell Medical College (partnering with Hunter College)
60. Yale University

In all, the solicitation of comments reached more than 25,000 individuals. We received 35 comments for committee consideration.

SOLICITATION OF PARTICIPANT AND COMMUNITY REPRESENTATIVES

To enhance its understanding of the diverse perspectives among research participants on issues relevant to the return of individual research results, the committee solicited nominations for interviewees from research participant networks (e.g., National Patient-Centered Clinical Research Network [PCORNet]), community advisory boards (e.g., the Yale community advisory board), patient advocacy groups, and researcher networks (e.g., CTSA advisory boards), which

identified individuals who were well suited to participate in informal interviews with the committee. Committee members also sent targeted e-mails to contacts asking for recommendations about representatives from priority populations. The contacted organizations included

- AIDS Clinical Trials Group
- AIDS Research Consortium of Atlanta
- AIDS Vaccine Advocacy Coalition (New York City)
- *All of Us* institutional review board
- Black AIDS Institute (Louisiana)
- Centers of Excellence on Minority Health and Health Disparities, National Institutes of Health
- Community Advisory Board, Yale University
- Community–Campus Partnerships for Health (CCPH)
- Community Research Group (District of Columbia)
- CTSA (Clinical and Translational Science Awards) Collaboration and Engagement Domain Task Force
- Genetic Alliance
- Healthy African American Families
- HIV Prevention Trials Network
- HIV Vaccine Trials Network
- International Maternal Pediatric Adolescent AIDS Clinical Trials
- Jackson Heart Study
- National Minority AIDS Council (District of Columbia)
- National Patient-Centered Clinical Research Network (PCORNet)
- NCATS (National Center for Advancing Translational Sciences) Council Subcommittee on Patient Engagement
- PACER—Partners for the Advancement of Community-Engaged Research
- Rural and Underserved Health Research Center, University of Kentucky
- SisterLove (Atlanta)
- Treatment Action Group (New York City)

The committee received 11 nominations and selected 6 for interviews based on the following criteria: (1) personal experience with topic, (2) experience with engaging population of interest or general knowledge of groups' perspectives on the topic, and (3) represents population or group determined to be a priority for project. Those nominated individuals who were not selected for interviews were invited to provide written comments to the committee.

The committee conducted five interview-style phone calls with research participants during the December committee meeting. This was done in a public session format, meaning that the calls were posted on the committee website 10 days before they occurred, and the full committee and public was able to listen in.

The interviews were conducted by one committee member with one participant. Interviews lasted approximately 20 minutes.

PUBLIC COMMENTS AND CONTRIBUTIONS

- Douglas A. Beigel, COLA
- Adam Berger, Food and Drug Administration
- Leslie Biesecker, National Human Genome Research Institute
- Angela Bradbury, University of Pennsylvania
- Christopher R. Cogle and Yulia Strekalova, University of Florida
- College of American Pathologists
- Carolyn Compton, Arizona State University
- Nancy J. Cox, American Society of Human Genetics
- Rebecca Davies, University of Minnesota
- Stephanie Devaney, National Institutes of Health
- Karen Dyer, Centers for Medicare & Medicaid Services
- Barbara J. Evans, University of Houston
- Mary E. Freivogel, National Society of Genetic Counselors
- Gail Jarvik, Clinical Sequencing Evidence-Generating Research Consortium
- Joseph P. Kim, Eli Lilly and Company
- Memorial Sloan Kettering
- Federico A. Monzon, Association for Molecular Pathology
- Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard
- Sally Okun, PatientsLikeMe
- Project Baseline
- Randy Querry, American Association for Laboratory Accreditation
- Carlos Quijada, The University of Utah S.J. Quincy School of Law
- Mark E. Sobel, American Society of Investigative Pathologists
- Greta Lee Splansky, Framingham Heart Study
- Julie Anne Zawiska, Merck & Co., Inc.

LITERATURE AND PRESS REVIEW

The committee and staff conducted a series of literature searches that concentrated on journals found in the following databases: Embase, Medline, Cochrane Databases of Systematic Reviews, PubMed, Scopus, Web of Science, Lexis, the Department of Energy, the Environmental Protection Agency, Greenfile, Proquest, and Science.gov. The articles obtained by use of the search terms were reviewed for their relevance to the committee's charge. Search parameters for three of the committee's literature searches are detailed below, This does not represent an exhaustive list of the research conducted. Other targeted literature reviews were

conducted throughout the committee's deliberations as novel issues arose and research gaps were identified.

Return of Results in Practice

Search Parameters:
- Date range: 2005 to present
- International, English only

Databases:
- Embase
- Medline
- Cochrane Databases of Systematic Reviews
- PubMed
- Web of Science
- Scopus

Search Strategy:
Research participant
- Search terms: human experimentation, participant decision making, research participants, participant perspectives, study participants

Return of research results
- Search terms: individual research results, methods of returning research results, research findings, individual research results, return of results

Additional terms of interest
- Search terms: Native Americans, American Indians, attitudes, benefit, clinical care choices, decision making, end of life, harm, opinions, palliative care, privacy, risk, stigma, terminal care, therapeutics, treatment, trust, value, vulnerable populations, human rights, Helsinki Declaration

Legal and Operational Considerations for Research Laboratories

Search Parameters:
- Date range: 2005 to present
- International, English only

Databases:
- Scopus
- Web of Science
- Lexis Law Reviews

Search Strategy:

- TITLE (laboratories OR laboratory OR "biomedical laboratories" OR "clinical laboratory services" OR "research laboratories" OR "research laboratory" OR "CLIA-excepted laboratory" OR "CLIA-exempt laboratories") AND
- TITLE-ABS-KEY ("CLIA accreditation" OR "cost of accreditation" OR accreditation OR "operational barriers" OR "confirmation of results" OR "confirmation of results" OR "confirmation of results in CLIA-certified laboratories" OR "clinical laboratory improvement amendments") AND PUBYEAR AFT 2004

Return of Results in the Environmental Health Field

Search Parameters:

- Date range: 2000 to present
- International, English only

Databases:

- Department of Energy
- Environmental Protection Agency
- Greenfile
- Proquest
- Science.gov
- Scopus
- Web of Science

Search Strategy:

Research participant perspectives

- TITLE-ABS-KEY ("individual research results" OR "research findings" OR "research results" OR "return of individual research results" OR "return of results" OR "disclosure of research results") AND
- TITLE-ABS-KEY ("research participants" OR "research participants perspectives" OR "study participants" OR subjects) AND
- TITLE-ABS-KEY ("american indians" OR indians OR attitudes OR benefit OR "clinical care choices" OR "decision making" OR "end of life" OR harm OR "native americans" OR opinions OR "palliative care" OR privacy OR risk OR stigma OR "terminal care" OR therapeutics OR treatment OR trust OR value OR "vulnerable populations")

Return of research results

- ts=("individual research results" OR "research findings" OR "research results" OR "return of individual research results" OR "return of results" OR "disclosure of research results") AND

- ts=("research participants" OR "research participants perspectives" OR "study participants" OR subjects) AND
- ts=("american indians" OR indians OR attitudes OR benefit OR "clinical care choices" OR "decision making" OR "end of life" OR harm OR "native americans" OR opinions OR "palliative care" OR privacy OR risk OR stigma OR "terminal care" OR therapeutics OR treatment OR trust OR value OR "vulnerable populations") Indexes=SCI-EXPANDED, SSCI, BKCI-S, BKCI-SSH Timespan=2000-2017

B

Public Agendas

Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories

First Committee Meeting

July 19, 2017
National Academies Keck Building
500 Fifth Street, NW, Washington, DC 20001

AGENDA

OPEN SESSION

1:00–1:15 p.m.	Opening Remarks to Public Audience *Jeffrey Botkin*, Committee Chair
1:15–2:00 p.m.	Presentation by Sponsors: *Stephanie Devaney*, National Institutes of Health *Adam Berger*, Food and Drug Administration *Karen Dyer*, Centers for Medicare & Medicaid Services
2:00–2:45 p.m.	Sponsor Q&A with Committee Moderator: *Jeffrey Botkin*, Committee Chair
2:45 p.m.	ADJOURN Open Session

Second Committee Meeting

September 6–7, 2017
National Academy of Sciences Building
2101 Constitution Avenue, NW, Washington, DC 20148

AGENDA

OPEN SESSION

Day 1: September 6, 2017

8:30–8:45 a.m.	Welcome and Opening Remarks *Jeffrey Botkin*, Committee Chair
8:45–10:15 a.m.	Session 1: Participant and Community Perspectives Moderator: *Gregg Gonsalves*, Committee Member *Fran Visco*, President, National Breast Cancer Coalition *Ellen Wagner*, Board of Directors, Parent Project Muscular Dystrophy *Chioma Nnaji*, Program Director, Multicultural AIDS Coalition
10:15–10:30 a.m.	BREAK
10:30 a.m.–12:00 p.m.	Session 2a: Perspectives of Researchers and Laboratorians Moderator: *Debra Leonard*, Committee Member *Wendy Chung*, Professor of Pediatrics and Medicine, Columbia University *Carolyn Compton*, Professor of Life Sciences, Arizona State University *Jessica B. Langbaum*, Principal Scientist, Banner Alzheimer's Institute *Lea C. Harty*, BioBank Biological Materials Custodian, Pfizer Inc., Representative of the Industry Pharmacogenomics Working Group
12:00–12:30 p.m.	LUNCH
12:30–1:15 p.m.	Session 2b: Successes and Challenges—CSER and eMERGE Moderator: *Steven Joffe*, Committee Member (resigned from the committee on September 26, 2017)

Rex Chisholm, Vice Dean for Scientific Affairs and Graduate Education, Adam and Richard T. Lind Professor of Medical Genetics, Feinberg School of Medicine, Northwestern University, eMERGE
Gail Jarvik, Head, Division of Medical Genetics, University of Washington, CSER/eMERGE

1:15–2:45 p.m. Session 2c: Experiences to Date of Returning Results from Different Health Care Institutions
Moderator: *Chester Brown*, Committee Member
Febe Wallace, Director of Primary Care, Cherokee Health Systems
Ronald Przygodzki, Director, Genomic Medicine Implementation, Department of Veterans Affairs, Office of Research & Development
Joanne Murabito, Research Center Director, Framingham Heart Study
Adam Buchanan, Clinical Investigator I, Geisinger Health System

2:45–3:00 p.m. BREAK

3:00–4:30 p.m. Session 3: Laws and Regulations Governing the Return of Results
Moderator: *Jeffrey Botkin*, Committee Chair
Susan M. Wolf, McKnight Presidential Professor of Law, Medicine & Public Policy; Faegre Baker Daniels Professor of Law; Professor of Medicine; University of Minnesota Law School, Medical School, and Consortium on Law and Values in Health, Environment & the Life Sciences
David J. Peloquin, Associate, Ropes & Gray LLP
Sally Howard, Head of Regulatory Affairs and Policy and Chief Privacy Officer, Human Longevity, Inc.

4:30–6:00 p.m. Session 4: Institutional Management and Oversight
Moderator: *Rhonda Kost*, Committee Member
Leslie G. Biesecker, Chief, Medical Genomics and Metabolic Genetics Branch, National Institutes of Health, National Human Genome Research Institute
Alexis Carter, Physician Informaticist, Children's Healthcare of Atlanta, Representative from College of American Pathologists

Mark Sobel, Executive Officer, American Society for Investigative Pathology
Heather Pierce, Senior Director, Science Policy and Regulatory Counsel, Association of American Medical Colleges

6:00 p.m. ADJOURN

DAY 2: September 7, 2017

8:00–8:15 a.m. Welcome and Opening Remarks
Jeffrey Botkin, Committee Chair

8:15–9:45 a.m. Session 5: Communicating Results to Meet User Needs
Moderator: *Consuelo Wilkins*, Committee Member
Sally Okun, Vice President for Policy and Ethics, PatientsLikeMe
Julia Wynn, Senior Genetic Counselor and Clinical Research Manager, Columbia University Medical Center
Sara Czaja, Leonard M. Miller Professor in the Departments of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine (participating via WebEx)
John Wilbanks, Chief Commons Officer, Sage Bionetworks

9:45–10:00 a.m. BREAK

10:00–11:00 a.m. Session 6: A Discussion with Workshop Panelists
Moderator: *Jeffrey Botkin*, Committee Chair
Gail Javitt, Member of the Firm in the Health Care and Life Sciences Practice, Office of Epstein Becker Green (participating via WebEx)
Leslie G. Biesecker, Chief, Medical Genomics and Metabolic Genetics Branch, National Institutes of Health, National Human Genome Research Institute
Ellen Wagner, Board of Directors, Parent Project Muscular Dystrophy

11:00–11:30 a.m. Public Comment
Moderator: *Jeffrey Botkin*, Committee Chair

11:30 a.m. ADJOURN

Third Committee Meeting
Public Workshop

October 24, 2017
National Academies Keck Building
500 Fifth Street, NW, Washington, DC 20001

AGENDA

OPEN SESSION

1:00–2:30 p.m.	Basic and Translational Researcher Panel (non-genetic genomics) Moderator: *Suzanne Bakken*, Committee Member *Nicholas Newman*, Department of Pediatrics, Cincinnati Children's Hospital Medical Center *Theresa Powell*, University of Colorado Anschutz Medical Campus
4:30–5:30 p.m.	Public Comment Session
5:30 p.m.	ADJOURN Open Session

Public Webinar

December 7, 2017
90-Minute Webinar

2:00–3:30 p.m.	Quality Standard for Regulated and Non-Regulated Biomedical Research Laboratories Moderator: *Debra Leonard*, Committee Member *Rebecca Davies*, University of Minnesota *Randy Querry*, American Association for Laboratory Accreditation

Fourth Committee Meeting

Community and Participant Perspectives—Public Webinar

December 11, 2017
Arnold and Mabel Beckman Center
100 Academy Drive, Irvine, CA

3:30–6:30 p.m. Community and Participant Perspectives—Public Webinar
John Molina, Native Health, Phoenix
Sonja Fuqua, Jackson Heart Study Participant and Community Health Advisor
Crispin Goytia-Vaquez, Mount Sinai Centers for Community and Academic Research Partnerships
Matthew Rose, National Minority AIDS Council
Lisa Schlager, Facing Our Risk of Cancer Empowered
Stephen Mikita, Aspirin in Reducing Events in the Elderly

C

Analysis of Legal and Regulatory Landscape Relevant to Return of Individual Results Generated from Biospecimens in Research[1]

[1] A white paper commissioned by the National Academies of Sciences, Engineering, and Medicine's Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, written by Christi J. Guerrini, J.D., M.P.H., Baylor College of Medicine.

EXECUTIVE SUMMARY

This memorandum describes the U.S. legal and regulatory landscape relevant to the return of individual results generated from biospecimens in research.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) requires certification (or waiver of certification) of all laboratories, which are defined as facilities where human specimens are examined for the purpose of providing information for diagnosis, prevention, treatment, or health assessment. However, research laboratories need not become certified so long as they do not report results to tested individuals, their physicians, or researchers, where the results could be used for diagnostic, preventative, treatment, or health assessment purposes.

Since 2000, the Health Insurance Portability and Accountability Act (HIPAA) has provided individuals with a right of access to inspect and obtain a copy of their protected health information that is contained within a designated record set, which is defined broadly as any record used by covered entities to make any kind of decision about individuals. So defined, the designated record set may include laboratory test reports and related information. Research laboratories are HIPAA-covered entities if they electronically conduct at least one billing-related transaction or function as part of a larger covered entity, such as a hospital or academic medical center.

Before 2014, all laboratories, including research laboratories, were not only exempted by HIPAA from compliance with the right of access, but also were prohibited by CLIA from returning laboratory test results directly to tested individuals unless explicitly authorized to do so by state law. In 2014, however, both CLIA and HIPAA were amended to require all HIPAA-covered laboratories, including HIPAA-covered research laboratories, to comply with the right of access.

It is generally recognized that these amendments have created a dilemma for research laboratories that are covered by HIPAA but not certified by CLIA. To comply with the expanded access rules, these laboratories must now return test reports and related information contained within designated record sets when individuals request them to do so, but research laboratories cannot do so without becoming CLIA-certified. Yet, CLIA certification is time consuming and expensive, and it may be unrealistic to require all research laboratories to become CLIA-certified in order to comply with HIPAA. Some institutions have responded to this dilemma by adopting policies that interpret the designated record set to exclude some research-related information or by making case-by-case determinations to return certain research results even if generated by laboratories that are not CLIA-certified.

The return of research results is also relevant to regulations for the protection of research participants. These include the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) and relevant regulations adopted by the Food and Drug Administration (FDA). Neither set of regulations explicitly allows or prohibits the return of results to study participants. However, they both require that, where appropriate, research participants be informed of significant findings that may relate to participants' willingness to continue participation. Moreover, pending revisions to the Common Rule will require that plans to return results be provided as an element of informed consent in some circumstances. In practice, when a study protocol includes a plan to return results, an institutional review board (IRB) will review the plan to ensure its benefits outweigh its risks. While IRBs can prohibit investigators from

returning results, however, they cannot block access when study participants request results under HIPAA.

The return of individual research results is relevant to other FDA regulations related to the agency's responsibility to protect and promote public health by ensuring the safety and effectiveness of medical drugs and devices, which include laboratory tests. First, the return and subsequent use of results generated by laboratory-developed tests (LDTs) have factored into FDA interest in abandoning its policy of enforcement discretion of LDTs. The return of results directly to consumers also has played a role in FDA regulation of specific genetic tests. Further, FDA regulation of investigational devices, including laboratory tests, depends in part on whether and how results from such devices will be returned. Finally, the communication of interpreted research results in some cases may constitute prohibited promotion of devices.

In general, state courts have not viewed research results, including data generated from genetic tests, as legal property belonging to research participants. However, in the context of genetics, some states, including Colorado and Alaska, have enacted statutes that explicitly recognize property rights of individuals in their test results. Individuals can also privately agree to allocate rights in test results that are different from default legal rules.

The return of research results may give rise to tort liability under state law for researchers and laboratories. Tort liability associated with the return of research results can generally be categorized as non-disclosure liability or disclosure liability; the most probable cause of action for both is negligence. In general, individuals owe a duty of reasonable care under the circumstances, but tort law imposes no affirmative duties to act for another's benefit and individuals are not required to warn others of impending harm. A number of factors can overcome this general tort law notion that individuals do not owe others affirmative duties, however, including the existence of a fiduciary relationship or other "special relationship," as well as contractual obligations. While physicians are held to be fiduciaries of their patients, researchers are generally not viewed as fiduciaries of their research participants. Nevertheless, in some cases, researchers have been held to have a "special relationship" with their research participants giving rise to affirmative duties. Whether those duties include the return of certain test results depends on the prevailing standard of care.

Researchers who return results must do so consistent with the standard of care and regulatory requirements. Many kinds of actions associated with the return of research results may give rise to tort liability, including disclosure of incorrect results as a result of, e.g., improper test administration. Meanwhile, disclosure of results to individuals who are not authorized to receive them may give rise to negligence claims where, among other things, the tested individual suffered discrimination as a result.

There is a complex web of federal and state laws that address unwanted access to and discriminatory use of health information. Two major federal statutes are the Genetic Information Nondiscrimination Act (GINA), which limits access to and use of genetic information in health insurance and employment contexts, and the Americans with Disabilities Act (ADA), which limits discrimination against individuals with disabilities in employment, public services, and public accommodations contexts. However, GINA and the ADA do not preempt state laws that provide equal or greater protection, and over the years, many state anti-discrimination statutes have been enacted that vary widely in scope and applicability. The majority of states have enacted laws that regulate employment and/or insurance discrimination based upon genetic test results or genetic status, and some also regulate genetic discrimination by life, disability, or long-term care insurers.

INTRODUCTION

I. Background

A. Legal Landscape

This memorandum describes the U.S. legal and regulatory landscape relevant to the return of individual results generated from biospecimens in research. Black's Law Dictionary defines "law" broadly as "[t]he body of authoritative grounds of judicial and administrative action."[1] The *legal landscape* of a particular issue therefore encompasses the collective legal rules and practices that are followed when deciding controversies relevant to that issue.

The legal landscape consists of: federal and state constitutions (constitutional law); federal and state statutes (statutory law); federal and state regulations and administrative practices (administrative law); and laws and principles derived from federal and state judicial decisions (common law).

B. Regulatory Landscape

The legal landscape relevant to a particular issue necessarily includes its regulatory landscape. The *regulatory landscape* refers to the regulations adopted and practices followed by administrative agencies, such as the Department of Health and Human Services (HHS).

Within the regulatory landscape, agency action can be classified as rulemaking or adjudication.[2] Focusing on rulemaking, many agencies are authorized to issue what are known as *legislative rules* that grant legal rights to or impose legally binding obligations on regulated parties.[3] Legislative rules must be issued in accordance with notice-and-comment procedures.[4] Examples of legislative rules include regulations implementing the CLIA and the Health Insurance Portability and Accountability Act (HIPAA).

Final legislative rules are codified in the Code of Federal Regulations.[5] They are also published in the Federal Register and are typically preceded by a preamble that describes the regulatory changes taking effect.[6] Although a preamble cannot control the meaning of a regulation and so does not itself have the force of law,[7] courts have recognized that a preamble may serve as evidence of "contemporaneous agency intent" regarding the meaning and operation of the regulation.[8]

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[1] BLACK'S LAW DICTIONARY (10th ed. 2014) ("law").
[2] CHARLES H. KOCH, JR. & RICHARD MURPHY, 3 ADMIN. L. & PRAC. § 2.10 (3d ed. 2017).
[3] JAMES T. O'REILLY, ADMINISTRATIVE RULEMAKING § 2:3 (2017 ed.).
[4] *See* KOCH & MURPHY, *supra* note 2, at § 4.10.
[5] *See id*. at § 1:21.
[6] *See* O'REILLY, *supra* note 3, at §§ 10.1, 12.1.
[7] *See id*. § 10.2. However, an agency's own procedural rules may give a Federal Register preamble more authority. *See, e.g.*, 21 C.F.R. § 10.85(d)-(e) (2017) (providing that a Federal Register preamble to a final Food and Drug Administration rule constitutes an advisory opinion that FDA is obligated to follow until it is amended or revoked).
[8] Wyo. Outdoor Council v. U.S. Forest Serv., 165 F.3d 43, 53 (D.C. Cir. 1999) ("Although the preamble does not 'control' the meaning of the regulation, it may serve as a source of evidence concerning contemporaneous agency intent."); *see also* City of Las Vegas, Nev. v. Fed. Aviation Admin. 570 F.3d 1109, 1117 (9th Cir. 2009) ("When a regulation is ambiguous, we consult the preamble of the final rule as evidence of context or intent of the agency promulgating the regulations.").

In addition to legislative rules, agencies may adopt *procedural rules* directed at organizing and improving their operations and *interpretive rules* that interpret a statute or another rule.[9] Because both procedural and interpretive rules do not create new duties, rights, or obligations, they may be issued without following notice-and-comment procedures.[10] Finally, and similar to interpretive rules, *general policy statements* (sometimes set forth in or labeled as guidance documents, guidelines, or manuals) are announcements to advise the public prospectively of the manner in which an agency proposes to exercise its discretionary powers.[11] Like an interpretive rule, a general policy statement does not purport to establish a binding norm and so does not have the force of law.[12] Nevertheless, courts hold that it is prudent to give deference to interpretive rules and policy statements.[13]

C. Legal Hierarchy

The U.S. legal system functions as a hierarchy that dictates how different categories of law rank in authority. The U.S. Constitution is the supreme law of the land.[14] Because no federal or state law may contradict it, federal constitutional law represents the highest legal authority.[15] Second in rank is federal statutory law, which is enacted by Congress and must be followed by the states, and third is federal regulations that interpret federal statutes.[16] The lowest legal authority in the federal system is federal common law.[17]

In the event of a conflict between a federal law and state law, the federal law preempts the state law.[18] However, states can generally offer greater protections than federal law, and when this occurs, there is no conflict and state law controls.[19] Moreover, state laws generally can address issues that are not addressed by federal law so long as they do not violate the U.S. Constitution or the state's constitution.[20]

At the state level, the highest legal authority is the state's constitution, followed by state statutes, state regulations, and, finally, state common law.[21]

D. Conceptual Distinctions

At the outset, it is important to acknowledge certain conceptual distinctions that are relevant as a legal, practical, or technical matter to this analysis. First, there is a generally

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[9] *See* O'REILLY, *supra* note 3, at §§ 2.4-2.5.
[10] *See id*.
[11] *See id*. § 2.6.
[12] *See id*.
[13] *See* KOCH & MURPHY, *supra* note 2, at § 10:22.
[14] *See* 16 C.J.S. *Constitutional Law* § 9 (2017).
[15] *See id*.
[16] *See* 2 AM. JUR. 2D *Administrative Law* § 218 (2d ed. 2017).
[17] Kent Greenawalt, *The Rule of Recognition and the Constitution*, 85 MICH. L. REV. 621, 628 (1987) (describing legal hierarchy); Michael J. Glennon, *Raising the* Paquete Habana*: Is Violation of Customary International Law by the Executive Unconstitutional?*, 80 NW. U. L. REV. 321, 334 (1985) (same).
[18] *See* 16A AM. JUR. 2D *Constitutional Law* § 232.
[19] *See id*. § 231.
[20] *See id*. § 11.
[21] *See* Greenawalt, *supra* note 17, at 628.

recognized distinction between *research* and *clinical care*.[22] Research is focused on the production of generalizable knowledge, where the responsibility of researchers is to preserve the integrity of the research process.[23] While researchers are obligated to minimize harms to participants, they do not have a duty to optimize participants' health.[24] By contrast, the responsibility of clinicians is to provide care directed to the best interests of patients.[25]

The distinction between research and clinical care is central to laws and responsibilities relevant to the conduct of research and medical practice.[26] In addition, the distinction is used for practical purposes to classify, e.g., results of laboratory tests of biospecimens as research results or clinical results and laboratories that perform such tests as research or clinical laboratories.

Distinctions can also be made between the kinds of information generated by laboratory tests. These include *uninterpreted raw data* and *interpreted findings*. In the context of a genetic test, uninterpreted raw data are sequencing data, whereas an interpreted finding might be information that the test identified a genetic variant that increases one's risk of developing a particular disease or condition.[27] For the sake of simplicity, this analysis will refer to the spectrum of information generated by laboratory tests of biospecimens generally as "results" except where finer distinctions are required.

In a research context, test results may be relevant to primary study aims or they may describe incidental or additional findings.[28] Research results can further be distinguished based on whether they pertain to individual research participants or are aggregated and reported as general study results,[29] as well as when the results are generated in research—at baseline, while the research is in process, or at study end.[30] Further, test results may be those that are originally generated (and possibly also reported), or they may be results that are later revised to correct errors or reflect new knowledge.[31]

Test results may be linked (or not) to research participants according to different standards. Thus, *de-identified* results can be linked to specific individuals but information that would identify those individuals with the results has been removed in accordance with HIPAA

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[22] *See, e.g.*, Susan M. Wolf, *The Role of Law in the Debate Over Return of Research Results and Incidental Findings: The Challenge of Developing Law for Translational Science*, 13 MINN. J. L. SCI. & TECH. 435, 443-44 (2012) (noting that the traditional architecture of health law and bioethics has "largely accepted and built upon a dichotomy between the two spheres" of research and clinical care).

[23] *See* Wylie Burke, Barbara J. Evans & Gail P. Jarvik, *Return of Results: Ethical and Legal Distinctions Between Research and Clinical Care*, AM. J. MED. GENETICS SEMINARS MED. GENETICS 105, 106 (2014).

[24] *See id*.

[25] *Id*.

[26] *See* Wolf, *supra* note 22, at 443-44. However, Prof. Wolf explains that the traditional "wall" between research and clinical care is starting to resemble a membrane as research insights increasingly move into clinical practice. *Id*. at 443-45. For a discussion of the relevance of the clinical care-research distinction to tort liability, see Part IX, *infra*.

[27] *See* Adrian Thorogood et al., *APPLaUD: Success for Patients and Participants to Individual Level Uninterpreted Genomic Data*, 12 HUMAN GENOMICS 7, 7-8 (2018) (distinguishing uninterpreted raw data from interpreted results); Anna Middleton et al., *Potential Research Participants Support the Return of Raw Sequence Data*, 52 J. MED. GENETICS 571, 571 (2015) (same).

[28] *See* Barbara J. Evans, *The First Amendment Right to Speak About the Human Genome*, 16 U. PA. J. CONST. L. 549, 555-56 (2014).

[29] *See* SACHRP, JULY 21, 2016 SACHRP LETTER TO THE HHS SECRETARY, ATTACHMENT B: RETURN OF INDIVIDUAL RESEARCH RESULTS (passed May 19, 2016).

[30] *See id*.

[31] *See generally* Part IX.B, *infra* (discussing tort liability for failing to update or correct previously disclosed results).

standards.[32] *Non-identified* results can also be linked to known individuals but identifying information has been removed in accordance with the Federal Policy for the Protection of Human Subjects (also known as the Common Rule), which prescribes standards that are different than HIPAA standards.[33] *Re-identified* results are de-identified or non-identified results whose links to known individuals have been restored.

Finally, distinctions can be made regarding to whom test results are returned. Depending on applicable laws, results can be returned to the individuals whom they describe, their relatives, or other authorized persons.[34] Distinctions also can be made between returning results when the individuals to whom they pertain are alive versus deceased, as well as when the individuals, if alive, are capacitated versus incapacitated.[35]

REGULATORY LANDSCAPE

II. CLIA

A. Scope

The Centers for Medicare & Medicaid Services (CMS) is responsible for administering the regulatory standards governing laboratories known as CLIA.[36] CLIA establishes quality standards for laboratories to ensure the accuracy, reliability, and timeliness of individual test results.

CLIA defines regulated "laboratories" as any:

> [F]acility for the . . . examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.[37]

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[32] *See* 45 C.F.R. § 164.514(b) (2017) (prescribing standards for de-identification under HIPAA).

[33] *See id*. §§ 46.101(b)(4), 102(f)(2) (defining research regulated by the Common Rule as involving "identifiable private information" and describing a regulatory exemption for research involving existing non-identified data and biospecimens); OHRP, CODED PRIVATE INFORMATION OR SPECIMENS USE IN RESEARCH, GUIDANCE (Oct. 16, 2008), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html (describing standards for non-identification by coding). The convention of referring to data and biospecimens that are not identifiable according to Common Rule standards as "non-identified" is explained in the Federal Policy for the Protection of Human Subjects: Notice of Proposed Rulemaking, 80 Fed. Reg. 53,933, 53,942-43 (Sept. 8, 2015) ("Consistent with historical interpretation of identifiable private information under the Common Rule, the terms 'non-identified' or 'non-identifiable' are used throughout this [notice] to signify biospecimens or data that have been stripped of identifiers such that an investigator cannot readily ascertain a human subject's identity.").

[34] *See generally* Susan M. Wolf et al., *Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations*, 43 J. L. MED. ETHICS 440 (2015).

[35] *See id*. at 453-59.

[36] FDA and the Centers for Disease Control and Prevention also have responsibilities related to CLIA. *See* FDA, *Clinical Laboratory Improvement Amendments (CLIA)*, FDA.GOV, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm (last updated March 22, 2018).

[37] 42 C.F.R. § 493.2 (2018).

CLIA requires certification (or waiver of certification) of all laboratories, so defined, except "CLIA exempt" laboratories,[38] which have been licensed by a state that has enacted laws relating to CMS-approved laboratory requirements "that are equal to or more stringent than CLIA requirements."[39] As discussed in Part III, *infra*, CMS has approved the licensure programs of Washington and New York. Licensed laboratories in these states therefore qualify as "CLIA exempt."

CLIA further provides that its rules do not apply to "components or functions" of certain laboratories that are referred to as "exceptions."[40] For purposes of this analysis, the most important CLIA exception covers:

> Research laboratories that test humans but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.[41]

CMS has interpreted this provision to mean that "only those facilities performing research testing on human specimens that **do not report patient-specific results** may qualify to be excepted from CLIA certification."[42] If a research laboratory intends to report individual-level results, and those results "will be or could be" used to diagnose, treat, prevent, or assess human health, the laboratory must first obtain CLIA certification.[43] In practice, CMS has taken the position that a research laboratory may not report individual-level research results to any person or entity, where "[t]he results are available to be used for health care for individual patients," unless the laboratory is CLIA-certified.[44] Thus, a research laboratory may not report individual-level test results to tested individuals or their clinicians unless it is CLIA-certified.[45] Further, a research laboratory may not report individual-level test results to investigators where those results could be used in the treatment of research participants, which includes assignment of participants to control and treatment arms.[46]

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[38] *Id*. § 493.3(a).
[39] *Id*. § 493.2.
[40] *Id*. § 493.3(b).
[41] *Id.* § 493.3(b)(2).
[42] CMS, *Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations*, CMS.GOV, https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf (last updated Dec. 10, 2014) (emphasis in original).
[43] *Id*.
[44] *See* Penelope Meyers, *CLIA and Research Results, Presentation to the Secretary's Advisory Committee on Human Research Protections* (Mar. 8, 2011), *available at* http://wayback.archive-it.org/org-745/20150824191143/http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-11/rirr_by_p_meyers.pdf [hereinafter Meyers, SACHRP Presentation]. Moreover, it is CMS's position that research laboratories returning results cannot avoid the requirement of CLIA certification by including disclaimers that, e.g., the testing was conducted in a research setting and/or the clinical meaning of the results is unknown. Telephone communication with Penelope Meyers, Technical Director, Division of Laboratory Services, CMS (Nov. 16, 2017). *Accord* David H. Ledbetter & W. Andrew Faucett, *Issues in Genetic Testing for Ultra-Rare Diseases: Background and Introduction*, 10 GENETICS MED. 309, 310 (2008) (noting the misconception that CLIA allows research laboratories to return results that might be used to impact diagnosis, management, or decision making by patients or their physicians if they are "simply qualif[ied] with statements (verbal or written) that testing was done on a research basis").
[45] Telephone communication with Penelope Meyers, *supra* note 44.
[46] *See id*.; Meyers, SACHRP Presentation, *supra* note 44.

Table C-1 summarizes these three categories of laboratories: laboratories regulated by CLIA and requiring CLIA certification; "CLIA-exempt" laboratories; and research laboratories that are "exceptions" to CLIA.

TABLE C-1 CLIA Categories of Laboratories

	CLIA Definition	CLIA Certification
Laboratories regulated by CLIA	"[F]acilit[ies] for the . . . examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings"	Yes
CLIA-exempt	Laboratories licensed by states that have "enacted laws relating to CMS-approved laboratory requirements that are equal to or more stringent than CLIA requirements"	No, but subject to, CMS-approved, state regulations
Research laboratories	Facilities "that test humans but do not report patient-specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of, the health of individual patients"	No

Laboratories may obtain waivers from CLIA to the extent that they perform only tests that: are so simple and accurate that the likelihood of error is negligible; pose no reasonable risk of harm if performed incorrectly; or are cleared by the FDA for home use.[47]

With respect to genetic testing, there has been a trend in recent years of unbundling collection of biospecimens and test administration from data interpretation.[48] Because CLIA is limited to regulation of laboratories, legal scholars have noted that it should not extend to firms offering only interpretation services.[49] CMS is currently considering its position on this issue.[50]

B. Original Access Rule

Until 2014, CLIA restricted the disclosure of laboratory test results as follows:

> [T]est results must be released only to authorized persons and, if applicable, the individual responsible for using the test results and the laboratory that initially requested the test.[51]

CLIA defines an "authorized person" as "an individual authorized under State law to order tests or receive test results, or both."[52] Thus, until 2014, laboratories were legally permitted to release

[47] *See* 42 C.F.R. § 493.15.
[48] *See* Margaret A. Curnutte, Karen L. Frumovitz, Juli M. Bollinger, Amy L. McGuire & David L. Kaufman, *Development of the Clinical Next-Generation Sequencing Industry in a Shifting Policy Climate*, 32 NATURE BIOTECH. 980, 981-82 (2014).
[49] *See* Gail H. Javitt & Katherine Strong Carner, *Regulation of Next Generation Sequencing*, 42 J. L. MED. & ETHICS 9, 15-16 (2014 supp.).
[50] Telephone communication with Karen Dyer, Director, Division of Laboratory Services, CMS (Dec. 14, 2017).
[51] 42 C.F.R. § 493.1291(f) (effective to April 6, 2014).
[52] *Id.* § 493.2 (effective to July 10, 2014).

results only to health care providers, ordering laboratories, and persons authorized by state law to order tests or receive test results. In states that did not provide for direct access to laboratory test results, individuals were required to request and obtain their results through their ordering providers.[53]

C. New Access Rule

Seeking to harmonize the existing CLIA access rule with revisions to the HIPAA access rule (see Part IV, *infra*), in 2014, HHS amended CLIA to expand individuals' access to their laboratory test results. HHS did so by retaining the original CLIA access rule and adopting a new provision that:

> Upon request by a patient (or the patient's personal representative), the laboratory may provide patients, their personal representatives, and those persons specified under [the HIPAA access rule], as applicable, with access to completed test reports. . . .[54]

The new rule does not define a "completed test report," although HHS explained in the Federal Register preamble to the new access rule that it considers test results to be "complete" when "all results associated with an ordered test are finalized and ready for release."[55] HHS further clarified that laboratories are not required to provide any interpretation of the test reports that they provide upon request.[56]

The new rule provides that the return of completed test reports is discretionary ("may") in the identified circumstances. Thus, to the extent that the return of completed test reports to individuals would conflict with a state law that prohibits disclosure without provider consent, the state law controls unless it is preempted by another federal law, such as HIPAA (see Part IV, *infra*).

Today, both the original and new CLIA access rules apply to all requests for access to results of tests performed by CLIA-regulated laboratories. Table C-2 describes key distinctions between the rules.

TABLE C-2 Original Versus New CLIA Access Rule*

	Original Access Rule	New Access Rule
Who may request access?	N/A	• Patients • Patients' personal representatives
Who may obtain access?	• Individuals responsible for using test results • Laboratories initially requesting results	• Patients • Patients' personal representatives • Individuals designated by requestors (as provided in HIPAA)

[53] *See* CMS, Memorandum from Thomas Hamilton, Director, Survey and Certification Group, CMS, to State Survey Agency Directors, Ref: S&C:14-11-CLIA (Feb. 7, 2014), *available at* https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-14-11.pdf.
[54] 42 C.F.R. § 493.1291(l) (2017).
[55] CLIA Program and HIPAA Privacy Rule, 79 Fed. Reg. 7290, 7295 (Feb. 6, 2014).
[56] *Id*. at 7293.

	• Individuals authorized by state law to order tests • Individuals authorized by state law to receive test results	
What may be obtained?	"Test results"	"Completed test reports"

NOTE: * *Both the original and new CLIA access rules are legally in effect.*

D. Enforcement

CMS is authorized to enforce CLIA. Its principal enforcement mechanism is the suspension, limitation, or revocation of a laboratory's CLIA certificate, which also can result in cancellation of a laboratory's approval to receive Medicare payments for its services.[57] For research laboratories that are not CLIA-certified, CMS generally has two enforcement options: (1) impose a civil money penalty of $50–$10,000 per day of noncompliance or per violation, depending on whether the deficiency poses an "immediate jeopardy"; or (2) file a civil lawsuit to enjoin continuation of any activity that CMS has reason to believe constitutes a "significant hazard to the public health."[58]

CMS publishes a Laboratory Registry every year identifying laboratories and individuals that have been sanctioned for CLIA violations.[59] Based on these registries, there do not appear to have been any actions taken against laboratories that involved the return of research results. Further, a search of CMS's website did not identify any published hearing decisions involving research laboratories.[60]

Otherwise, there are few known instances in which CMS has used less formal mechanisms to enforce CLIA against research laboratories that returned or planned to return individual-level test results. The most recent such instance involved ORIG3N, a direct-to-consumer (DTC) genetic testing firm that offers genetic tests purporting to identify genetic variants associated with intelligence, athleticism, and metabolism.[61] After ORIG3N announced plans to give away tests at a Baltimore Ravens game in September 2017, CMS intervened to examine whether those tests are subject to CLIA.[62] ORIG3N claimed to be outside the scope of CLIA as a "research laboratory that does not provide patient specific results," but instead provides results to "customers."[63] CMS rejected this characterization, however, and concluded that ORIG3N is subject to CLIA because it provides information for health assessment purposes, and CMS directed ORIG3N to apply for certification.[64]

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[57] 42 U.S.C. § 263a(i)(1); 42 C.F.R. §§ 493.1806(a)-(b), 493.1840(a)-(b), 493.1842(a).
[58] 42 U.S.C. §§ 263a(h)(1)-(2), § 263a(j); 42 C.F.R. §§ 493.1806(c)(3)-(d), 493.1834(c)-(d), 493.1846; *see also* telephone communication with Karen Dyer, *supra* note 50.
[59] *See* CMS, *Laboratory Registry*, CMS.GOV, https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Laboratory_Registry.html (last modified Apr. 28, 2017).
[60] *See* CMS, *CLIA-Related Hearing Decisions*, CMS.GOV, https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Hearing-Index-August-14-2017.pdf (current through Aug. 14, 2017).
[61] ORIG3N, https://orig3n.com/?gclid=Cj0KCQiA0vnQBRDmARIsAEL0M1nAUesRebAYPjT6btWL3udxNIvQ2Xu8OjtyVe2AqFJadSfYqpLR6f0aAqUwEALw_wcB (last visited Jan. 11, 2018).
[62] *See* Jeff Barker, "*DNA Day" Planned for Ravens' Game Undergoes Federal and State Scrutiny*, BALT. SUN, Sept. 18, 2017, http://www.baltimoresun.com/business/bs-bz-ravens-dna-day-20170918-story.html.
[63] Letter from Karen Dyer, Director, Division of Laboratory Services, CMS, to Kate Blanchard, Chief Operating Office, ORIG3N (Oct. 30, 2017) (on file with author) (summarizing ORIG3N's asserted position).
[64] *Id*.

III. State Laws Equivalent to CLIA

CMS has determined that the laboratory licensure programs of Washington and New York are equivalent to CLIA requirements and so laboratories in these states can qualify as "CLIA exempt."[65]

A. Washington

Washington law regulates "medical test sites," defined as any facility or site "which analyzes materials derived from the human body for the purposes of health care, treatment, or screening."[66] Washington provides exceptions for two kinds of facilities, neither of which is relevant to this analysis.[67] When asked whether research laboratories are considered medical test sites that require certification, an official with the Washington State Department of Health explained that if a research laboratory "is giving out results that get to patients and/or providers," the testing will be considered clinical testing by a medical test site subject to state regulation.[68] In this respect, Washington's rule prohibiting the return of research results generated by unlicensed laboratories is identical to the CLIA prohibition.[69]

The default access rule in Washington requires that "test reports" be released to "authorized persons or designees," defined as individuals allowed by state law to order tests or receive test results. [70] After the new CLIA access rule was enacted, Washington adopted a similar provision that test reports may be released to patients and their personal representatives.[71]

B. New York

New York law regulates "clinical laboratories" located in New York or that accept specimens from New York.[72] New York's definition of clinical laboratories is similar to CLIA's definition of laboratories except that New York's regulations also encompass laboratory testing for forensic and identification purposes.[73]

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[65] *See* CMS, *List of Exempt States Under the Clinical Laboratory Improvement Amendments (CLIA)*, CMS.GOV, https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/ExemptStatesList.pdf (last visited Jan. 12, 2018).
[66] WA. REV. CODE ANN. §§ 70.42.005, 70.42.010(8) (West 2017); WASH. ADMIN. CODE §§ 246-338-001, 246-338-010(25) (2017).
[67] *See* WASH. ADMIN. CODE § 246-338-010(25).
[68] E-mail from Susan Walker, Program Manager, Laboratory Quality Assurance, Washington State Department of Health, to author (Sept. 14, 2017) (on file with author).
[69] Telephone communication with Susan Walker, Program Manager, Laboratory Quality Assurance, Washington State Department of Health (Nov. 2, 2017).
[70] WASH. ADMIN. CODE §§ 246-338-010(2), 246-338-070(3)(b).
[71] *See id*. § 246-338-070(3)(c).
[72] *See* N.Y. PUB. HEALTH LAW §§ 570, 571(1), 572 (McKinney 2017).
[73] *See id*. § 571(1) (defining "clinical laboratory" to include examination for the purpose of "obtaining information" for health assessment and identification purposes); NY STATE DEP'T OF HEALTH WADSWORTH CENTER, CLINICAL LABORATORY EVALUATION PROGRAM: A GUIDE TO PROGRAM REQUIREMENTS AND SERVICES 3 (rev. Jan. 2017) [hereinafter NY STATE PROGRAM GUIDE] (providing that "[c]linical laboratories located in New York State, and laboratories conducting clinical or forensic testing on specimens originating in New York State regardless of location, must hold a New York State Department of Health clinical laboratory permit").

Like CLIA, New York provides an exception for facilities that "perform laboratory tests solely for research purposes."[74] In its Clinical Laboratory Evaluation Program's Guide to Program Requirements and Services, the New York Department of Health clarified the clinical-research laboratory distinction as follows:

> Research testing is considered clinical in nature if a patient-identified result is generated. This would include results used to make clinical decisions for patient management under an IRB-approved research protocol or clinical trial.[75]

If a result is obtained during the course of research testing that a laboratory feels ethically compelled to report to a clinician or research participant, the laboratory must obtain a New York clinical laboratory permit prior to reporting.[76] In practice, New York's rule prohibiting the return of research results generated by unlicensed laboratories is comparable to the CLIA prohibition.[77]

The default access rule in New York restricts the reporting of test results of specimens "submitted for evidence of human disease or medical condition" to three categories of individuals: physicians, their agents, and persons legally authorized "to employ the results thereof in the conduct of [their] practice or in the fulfillment of [their] official duties."[78] After the new CLIA access rule was enacted, New York adopted a similar provision that test reports may be released to patients.[79]

IV. HIPAA

A. Scope

HIPAA applies to three categories of individuals and entities: health plans, health care clearinghouses, and health care providers who transmit "any health information in electronic form" to carry out certain activities related to furnishing, billing, or receiving payment for health care.[80] Such covered transactions include sending claims to health plans to inquire about eligibility to receive health care or to request payment for medical services.[81] The privacy and

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[74] *See* N.Y. PUB. HEALTH LAW § 580(2).
[75] NY STATE PROGRAM GUIDE, *supra* note 73, at 4; *see also* NY State Dep't of Health, *Test Approval: LDTs used in Clinical Trials*, WADSWORTH.ORG, https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval (last visited Jan. 12, 2018) ("Examples of testing performed for participant management include those that influence enrollment (exclusion or inclusion), safety, or dosing.").
[76] NY State Dep't of Health, *Test Approval: LDTs used in Research Testing*, WADSWORTH.ORG, https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval (last visited Jan. 12, 2018).
[77] Telephone communication with Stephanie Shulman, Director, New York Clinical Laboratory Program (Nov. 14, 2017).
[78] N.Y. COMP. CODES R. & REGS. tit. 10, § 58-1.8 (2018).
[79] *Id*.
[80] 42 U.S.C. §§ 1320d-1(a), 1320d-2(a) (2018); 45 C.F.R. § 160.103 (2018); *see also* CMS, *Administrative Simplification: Covered Entity Guidance*, CMS.GOV, https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/HIPAA-ACA/Downloads/CoveredEntitiesChart20160617.pdf (last visited Jan. 16, 2018) [hereinafter CMS, *Administrative Simplification*] (summarizing covered transactions).
[81] *See* 42 U.S.C. § 1320d-2(a)(2) (listing covered transactions); 45 C.F.R. §§ 162.1101, 162.1201 (defining transactions relevant to "health care claims or equivalent encounter information" and "eligibility for a health plan"). *See also* CMS, *Administrative Simplification*, *supra* note 80; CMS, *Transactions Overview*, CMS.GOV, https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/Transactions/TransactionsOverview.html (last modified July 26, 2017).

security regulations that implement HIPAA also extend to "business associates" of covered entities.[82] A business associate is any person who creates, receives, maintains, or transmits protected health information (PHI) on behalf of a covered entity or provides services to a covered entity that includes disclosure of PHI.[83] PHI is defined as individually identifiable health information, which is any information (including genetic information) that: (1) is created or received by a covered entity or employer; (2) "relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual"; and (3) identifies or could be used to identify the individual.[84]

Research laboratories are HIPAA-covered entities in two situations. The first is when they electronically conduct a covered transaction.[85] HHS has emphasized that the conduct of a single covered transaction will transform a laboratory into a covered entity "with respect to all protected health information that it creates or maintains," not just the individuals or information associated with the covered transaction.[86]

The second situation in which research laboratories are covered entities is when they function as part of larger covered entities. Thus, research laboratories that operate within HIPAA-covered hospitals, medical centers, or medical schools may also be covered by HIPAA by virtue of these relationships.[87] However, a covered entity may elect to become a "hybrid entity," which is defined as a covered entity whose business activities include both covered and non-covered functions.[88] When a covered entity elects to become a hybrid entity, it must ensure that its designated health care components that perform covered functions do not disclose PHI to other components except as permitted by HIPAA.[89] This becomes difficult in the case of a clinician-investigator who is an employee of and performs duties for both a health care component and a non-covered component of a hybrid entity.[90] In the end, hospitals, medical centers, and medical schools often do not elect hybrid entity status and designate their research laboratories as non-covered components because of the operational complexities and high transaction costs associated with doing so successfully.[91]

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[82] *See* 45 C.F.R. §§ 162.923(c), 164.302, 164.500(c).
[83] *Id*. § 160.103.
[84] *Id*.
[85] *See supra* notes 80-81 and accompanying text.
[86] CLIA Program and HIPAA Privacy Rule, 79 Fed. Reg. 7290, 7291 (Feb. 6, 2014).
[87] *See* Barbara J. Evans, Michael O. Dorschner, Wylie Burke & Gail P. Jarvik, *Regulatory Changes Raise Troubling Questions for Genomic Testing*, 16 GENETICS MED. 799, 801 (2014) (explaining that a research laboratory may "fall under HIPAA because of its business organizational arrangements (for example, if it is part of a HIPAA-covered academic medical center)").
[88] *See* 45 C.F.R. §§ 164.103, 164.105(a)(2)(iii)(D).
[89] *See id*. § 164.105(a)(2)(ii). Health care components include every component that "would meet the definition of a covered entity or business associate if it were a separate legal entity." *Id*. § 164.105(a)(2)(iii)(D).
[90] *See id*. § 164.105(a)(2)(ii)(C); telephone communication with Mark Barnes, Partner, Ropes & Gray LLP (Nov. 15, 2017).
[91] Telephone communication with Mark Barnes, *supra* note 90. Further, if a research laboratory functions as a business associate to a hospital, medical center, or medical school that has elected hybrid entity status, it must be designated a covered health care component. *See* 45 C.F.R. § 164.105(a)(2)(iii)(D); *see also* Modifications to the HIPAA Privacy, Security, Enforcement, and Breach Notification Rules Under the Health Information Technology for Economic and Clinical Health Act and the Genetic Information Nondiscrimination Act, 78 Fed. Reg. 5566, 5588 (Jan. 25, 2013) (explaining that the final rule "requires that the health care component of a hybrid entity include all business associate functions within the entity"); telephone communication with David Peloquin, Associate, Ropes & Gray LLP (Nov. 22, 2017).

B. Original Access Rule

Since 2000, HIPAA regulations have included a rule that individuals have a "right of access" to inspect and obtain a copy of their PHI that is maintained within a "designated record set" for as long as the PHI is maintained in the designated record set.[92] A designated record set is defined as a "group of records" maintained by or for a covered entity that includes medical, claims, and billing records, as well as any other record "[u]sed, in whole or in part, by or for the covered entity to make decisions about individuals."[93] HHS has interpreted this definition broadly to mean that the designated record set includes all "records that are used to make decisions about any individuals, whether or not the records have been used to make a decision about the particular individual requesting access."[94] Further, qualifying "decisions" include but are not limited to health care decisions "because other decisions by covered entities can also affect individuals' interests."[95]

Before 2014, the HIPAA access rule provided an exception for HIPAA-covered laboratories. Specifically, two provisions excluded from access any PHI maintained by:

(1) Laboratories "[s]ubject to [CLIA], to the extent the provision of access to the individual would be prohibited by law"; and
(2) Laboratories "[e]xempt from [CLIA], pursuant to 42 C.F.R. § 493.3(a)(2)" (which refers to "CLIA-exempt" laboratories).[96]

The first provision excluded CLIA-regulated laboratories because at that time CLIA prohibited the return of results to individuals except in states that explicitly authorized such returns (see Part II, *supra*). The second provision excluded "CLIA-exempt" laboratories regulated by New York and Washington. Importantly, however, in the preamble to the original access rule, HHS interpreted the second provision excluding laboratories "[e]xempt from [CLIA], pursuant to 42 C.F.R. § 493.3(a)(2)" to also include research laboratories—even though research laboratories are excluded from CLIA under a different regulatory section.[97] HHS explained that this interpretation was necessary because if research laboratories are "subject to the access requirements of this regulation, such entities would be forced to meet the requirements of CLIA from which they are currently exempt."[98] "To eliminate this additional regulatory burden," HHS viewed research laboratories as excluded from the HIPAA access requirement.[99]

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[92] 45 C.F.R. § 164.524(a).
[93] *Id*. § 164.501. A "record," in turn, is defined as any "item, collection, or grouping of information" that includes PHI and is "maintained, collected, used, or disseminated by or for a covered entity." *Id*.
[94] Standards for Privacy of Individually Identifiable Health Information, 65 Fed. Reg. 82,462, 82,606 (Dec. 28, 2000).
[95] *Id*.
[96] 45 C.F.R. § 164.524(a)(1)(iii) (effective to April 7, 2014).
[97] Standards for Privacy of Individually Identifiable Health Information, 65 Fed. Reg. at 82,485. Dr. Evans and colleagues argue that CMS forgot this history when it eliminated the exception that kept "CLIA-exempt" laboratories from having to comply with the HIPAA access rule, thereby inadvertently putting "HIPAA-covered, non-CLIA laboratories squarely in the crosshairs of individuals' new § 164.524 access right." Evans et al., *supra* note 87, at 801.
[98] Standards for Privacy of Individually Identifiable Health Information, 65 Fed. Reg. at 82,485 (referring to the CLIA "exemption" for research laboratories under 42 C.F.R. § 493.3(a)(2)).
[99] *Id.* Research laboratories might also have been indirectly excluded by the terms of the first provision. In the view of CMS, research laboratories cannot return results unless they are CLIA-certified, so a research laboratory's return

C. Revised Access Rule

In 2014, following three years of deliberation, HHS announced its elimination of the laboratory exclusion from the HIPAA access rule and the CLIA prohibition on the return of laboratory test results to individuals.[100] HHS was motivated by concerns that these rules impeded individuals' access to their records, thereby preventing them from having a more active role in personal health care decisions.[101] HHS also stated that removing these impediments would support its commitments to personalized medicine and the widespread adoption of electronic health records.[102]

Focusing on HIPAA, the revisions eliminated the original HIPAA access rule's carve-out for laboratories.[103] In the Federal Register preamble, HHS explained that the purpose of this change was to require all HIPAA-covered laboratories to comply with the access rule regardless of their status under CLIA:

> Even if CLIA does not apply to the conduct of certain types of laboratory tests, HIPAA may still apply to require access to certain test reports to the extent the laboratory is a HIPAA covered entity and the information to which an individual is requesting access is protected health information under HIPAA.[104]

Elsewhere in the preamble, HHS further explained that under the proposed rule, which was adopted with only minor clarifications and conforming changes, "HIPAA covered entities that are laboratories subject to CLIA, as well as those that are exempt from CLIA, would have the same obligations as other types of covered health care providers" with respect to providing individuals access to their PHI.[105] That "exempt" in this context encompasses not only "CLIA-exempt" (i.e., New York and Washington) laboratories but also research laboratories is reinforced by the preamble's repeated reference to the expanded access obligations of all HIPAA-covered laboratories.[106]

Table C-3 compares the original and revised HIPAA access rules.

TABLE C-3 Original Versus Revised HIPAA Access Rule*

	Original Access Rule	Revised Access Rule
Who may request	Individuals who are the subject of PHI	Individuals who are the subject of PHI
Who may obtain	Individuals who are the subject of PHI and other persons as directed by individuals	Individuals who are the subject of PHI and other persons as directed by individuals

of results would trigger the need for CLIA certification, but at that time, CLIA prohibited certified laboratories from returning results.

[100] *See* CLIA Program and HIPAA Privacy Rule, 79 Fed. Reg. 7290 (Feb. 6, 2014).

[101] *See id*.

[102] *See id*.

[103] *See* 45 C.F.R. § 164.524(a)(1) (2018) (effective beginning April 7, 2014).

[104] CLIA Program and HIPAA Privacy Rule, 79 Fed. Reg. at 7296-97.

[105] *Id*. at 7292.

[106] This interpretation was also confirmed by OCR. Telephone communication with Deven McGraw, Deputy Director (former), Health Information Privacy, OCR (Jan. 5, 2018).

What may be	PHI about an individual maintained within a designated record set	PHI about an individual maintained within a designated record set
From whom may	HIPAA-covered entities, but not CLIA-regulated labs, "CLIA-exempt" labs, and research labs	HIPAA-covered entities

NOTE: * *Only the revised HIPAA access rule is legally in effect.*

In sum, the revised HIPAA access rule provides individuals with a broad right of access to their PHI contained within designated record sets maintained by HIPAA-covered laboratories.[107] A designated record set includes at least laboratory test reports, but as noted above, it also includes all other PHI maintained by a laboratory that is used to make any kind of decision about any person.[108]

In 2016, the Office for Civil Rights (OCR), the HHS office responsible for enforcing HIPAA, published guidance explaining the kinds of information that may fall within the designated record set maintained by laboratories.[109] The guidance states that in the context of a genetic test conducted by a clinical laboratory, the designated record set includes: the "completed test report"; the "full gene variant information generated by the test"; the "underlying data used to generate the report"; "as well as any other information in the designated record set concerning the test."[110]

There are two limits to the HIPAA access rule that are relevant to this analysis. First, the rule provides for a temporary suspension of access related to clinical research activities. Specifically, it provides that an individual's access to PHI created or obtained "in the course of research that includes treatment may be temporarily suspended for as long as the research is in progress" provided that the individual has consented to this temporary denial of access.[111] However, the right of access must be reinstated upon completion of the research.[112]

The second limit to the access rule is set forth in HIPAA's authorizing statute. It provides that HIPAA standards "shall not require disclosure of trade secrets or confidential commercial information" by covered entities.[113] Thus, a covered entity may legally refuse to provide

[107] Dr. Evans argues that, as applied to genetic information, the access rule is a federal civil rights regulation compelled by the understanding that "access to one's own genomic data is a foundational civil right that empowers people to protect all their other civil rights." Barbara J. Evans, *HIPAA's Individual Right of Access to Genomic Data: Reconciling Safety and Civil Rights*, 102 AM. J. HUM. GENETICS 5, 6-7 (2018).
[108] *See id.* at 7295; *see also* notes 94-95 and accompanying text.
[109] *See* HHS, *Individuals' Right Under HIPAA to Access Their Health Information 45 C.F.R. § 164.524*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/access/index.html (last visited Jan. 16, 2017) [hereinafter HHS, *Individuals' Right Under HIPAA*]. Relevant FAQs include "Does an Individual Have a Right Under HIPAA to Access from a Clinical Laboratory the Genomic Information the Laboratory Has Generated About the Individual?" and "Does an Individual Have a Right Under HIPAA to Access More Than Just Test Results from a Clinical Laboratory?" Both FAQs were last reviewed on June 24, 2016.
[110] *Id.* The guidance refers only to access to genomic information "maintained by or for a clinical laboratory that is a covered entity"; it does not address the access obligations of research laboratories. *Id.* However, earlier guidance states that research participants shall have access to "any research records or results that are actually maintained by the covered entity as part of a designated record set." *See* HHS, *What Does the HIPAA Privacy Rule Say About a Research Participant's Right of Access to Research Records or Results?*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/faq/311/what-does-hipaa-say-about-research-participants-right-of-access/index.html (last reviewed July 26, 2013). This earlier guidance was created in 2002 and last reviewed in 2013.
[111] 45 C.F.R. § 164.524(a)(2)(iii) (2018).
[112] *Id.*
[113] 42 U.S.C. § 1320d-1(e) (2018).

individuals any requested PHI contained within a designated record set that the entity views as a trade secret or confidential commercial information.[114] This limit on the HIPAA access rule may have special significance in the context of laboratories that maintain proprietary databases of test data and associated algorithms.[115]

If these limits do not apply, the covered entity must provide individuals "the access requested by the individuals," including inspection or obtaining a copy of the requested PHI, within 30 days of receipt of the request.[116] Alternatively, the covered entity may provide a summary or explanation of the PHI if agreed upon by the requesting individual.[117] The PHI must be provided in the form and format requested by the individual to the extent that it is readily producible in that form and format; otherwise, the PHI must be provided in "readable hard copy form" or any other agreed-upon form and format.[118] Finally, the covered entity may charge the requestor a reasonable, cost-based fee covering its labor, supplies, and postage expenses associated with responding to requests for copies.[119]

The 2016 guidance makes clear that an individual's reasons for requesting access to his or her PHI maintained in a designated record set are irrelevant to a covered entity's obligation to respond to that request:

> [A] covered entity may not require an individual to provide a reason for requesting access, and the individual's rationale for requesting access, if voluntarily offered or known by the covered entity or business associate, is not a permitted reason to deny access.[120]

Finally, the revised HIPAA access rule preempts any contrary provisions of state law.[121] Thus, state laws that prohibit an individual's direct access to test results are void to the extent they conflict with HIPAA.[122] However, states may provide greater rights of access than those set forth in HIPAA.[123]

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[114] In at least one instance, HHS has explicitly authorized a covered entity's refusal to disclose in these circumstances. *See* Robin Feldman & John Newman, *Copyright at the Bedside: Should We Stop the Spread?*, 16 STAN. TECH. L. REV. 623, 644 & n.105 (2013) (explaining that HHS informed a developer of proprietary cognitive test materials that it need not disclose any test results under HIPAA, even if the results include PHI, "to the extent that doing so would result in a disclosure of trade secrets").

[115] *See* Christi J. Guerrini, Amy L. McGuire & Mary A. Majumder, *Myriad Take Two: Can Genomic Databases Remain Secret?*, 356 SCIENCE 586 (2017) (describing the application of the HIPAA access rule to proprietary genomic databases). HIPAA's restriction on access to trade secret information is consistent with the trend in this country toward enhanced protection of trade secrets. *See, e.g.*, Defend Trade Secrets Act of 2016, Pub. L. No. 114-153 (May 11, 2016) (creating a federal civil cause of action for trade secret misappropriation).

[116] 45 C.F.R. §§ 164.524(b)(2)(i), 164.524(c)(1).

[117] *Id.* § 164.524(c)(2)(iii).

[118] *Id.* § 164.524(c)(2)(i).

[119] *Id.* § 164.524(c)(4).

[120] HHS, *Individuals' Right Under HIPAA*, *supra* note 109 (emphasis in original).

[121] 45 C.F.R. § 160.203.

[122] *See, e.g.*, CONN. AGENCIES REGS. § 19a-36-D32 (2018) (providing that laboratory findings on specimens may be reported to "lay persons" only upon the written request of their health care providers).

[123] 45 C.F.R. §§ 160.202, 160.203(b).

D. Enforcement

OCR enforces HIPAA by investigating complaints of HIPAA violations filed by individuals and conducting compliance reviews of covered entities.[124] Since April 2003, OCR has received over 169,000 HIPAA complaints and initiated over 860 compliance reviews.[125]

Following the filing of a complaint by an individual, OCR will investigate if the complaint is timely and alleges a violation against a HIPAA-covered entity.[126] If OCR concludes that a violation has occurred, it will attempt to resolve the case by obtaining voluntary compliance, corrective action, or a signed resolution agreement, and most investigations are concluded through these mechanisms.[127] However, if the covered entity does not take action to resolve the matter in a way that is satisfactory to OCR, OCR can impose civil money penalties upwards of $50,000 for each violation (but not more than $1,500,000 for identical violations per calendar year).[128]

Individuals' lack of access to their health information is among the top five issues that OCR investigates every year.[129] OCR's website identifies several examples of access-related complaints that it has investigated and resolved.[130] None of these appear to involve research laboratories.

An example of an ongoing OCR investigation alleging a clinical laboratory's denial of access was initiated against Myriad Genetics by four individuals for whom Myriad had performed genetic testing.[131] The individuals claim that HIPAA entitles them to four categories of information specific to those tests: (1) raw and assembled genetic sequence data; (2) a list of all variants identified, including benign variants; (3) results of large-scale analyses; and (4)

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[124] *See id*. §§ 160.306, 164.524(d)(2)(iii) (individual complaints); *id*. § 160.308 (compliance reviews).

[125] *See* OCR, *Enforcement Results as of November 30, 2017*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/data/enforcement-highlights/index.html (last reviewed Jan. 9, 2018) [hereinafter OCR, *Enforcement Results*].

[126] *See* OCR, *What OCR Considers During Intake & Review*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/examples/what-OCR-considers-during-intake-and-review/index.html?language=en (last reviewed June 7, 2017).

[127] *See* 45 C.F.R. § 160.312(a)(1) (authorizing resolution by informal means); OCR, *How OCR Enforces the HIPAA Privacy & Security Rules*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/examples/how-OCR-enforces-the-HIPAA-privacy-and-security-rules/index.html (last reviewed June 7, 2017). "A resolution agreement is a settlement agreement signed by HHS and a covered entity or business associate in which the covered entity or business associate agrees to perform certain obligations and make reports to HHS, generally for a period of three years," and may also agree to pay a resolution amount. OCR, *Resolution Agreements and Civil Money Penalties*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/agreements/index.html (last reviewed Dec. 28, 2017) [hereinafter, OCR, *Resolution Agreements*].

[128] *See* 45 C.F.R. §§ 160.312(a)(3)(ii), 160.402(a), 160.404(b)(2), 160.410(c); OCR, *Resolution Agreements*, *supra* note 127. In the case of a continuing violation, a separate violation occurs each day the covered entity or business associate is in violation. *Id*. § 160.406.

[129] *See* OCR, *Enforcement Results, supra* note 125; OCR, *Top Five Issues in Investigated Cases Closed with Corrective Action, by Calendar Year*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/data/top-five-issues-investigated-cases-closed-corrective-action-calendar-year/index.html?language=es (last reviewed June 7, 2017).

[130] *See* OCR, *All Case Examples*, HHS.GOV, https://www.hhs.gov/hipaa/for-professionals/compliance-enforcement/examples/all-cases/index.html#case6 (last reviewed June 7, 2017). Based on the website descriptions, it is unclear whether civil monetary penalties were imposed in any of these cases.

[131] *See* Health Information Privacy Complaint (filed with OCR on May 19, 2016), *available at* https://www.aclu.org/sites/default/files/field_document/2016.5.19_hipaa_complaint.pdf.

"records relating to clinical interpretation" of identified variants.[132] While Myriad initially refused to provide this information, it eventually disclosed to each complainant a list of identified variants and raw data from Myriad's large rearrangement test.[133] Myriad stated that it does not retain and so cannot disclose any other requested sequence information.[134] Nevertheless, OCR opened an investigation, which is ongoing.[135]

V. CLIA-HIPAA Interactions

A. Overview of Legal Obligations Related to Access

Table C-4 summarizes laboratories' current legal obligations regarding individual access under CLIA and HIPAA. Boxes A and C describe access obligations of HIPAA-covered laboratories with additional detail in Box C for laboratories not certified by CLIA before and after the 2014 regulatory changes. Boxes B and D describe access obligations of laboratories not covered by HIPAA.

TABLE C-4 Legal Obligations Related to Individual Access, by Type of Laboratory

	HIPAA-Covered Laboratory	Not HIPAA-Covered Laboratory
CLIA-certified laboratory	**A** Federal law (HIPAA): Mandatory access State law: Preempted unless provide greater access Example: Clinical laboratory	**B** Federal law (CLIA): Permissive access State law: Not preempted; can mandate, permit, or prohibit access Example: Independent clinical laboratory that does not seek third-party reimbursement
Not CLIA-laboratory	**C1 (pre-2014)** Federal law (CLIA): Prohibited access unless authorized by state law State law: Not preempted; could mandate, permit, or prohibit access **C2 (current)** Federal law (HIPAA): Mandatory access (but disclosure requires laboratory to become CLIA-certified according to CMS) State law: Preempted unless provide greater access Example: Research laboratory that is part of a covered entity	**D** Federal law: N/A State law: Not preempted; can mandate, permit, or prohibit access Example: Independent research laboratory

[132] *Id*. at Ex. 1.
[133] *See id*. at Exs. 2-3.
[134] *See id*.
[135] E-mail from Thomas Dresslar, Media Relations Associate, American Civil Liberties Union, to author (Dec. 1, 2017) (on file with author).

B. Potential Conflicts Between CLIA and HIPAA

As explained above, CMS has interpreted the CLIA exception for research laboratories to apply only where laboratories do not return individual-specific results or otherwise use those results to make clinical decisions. If laboratories return results to individuals or their clinicians for any reason, CMS's position is that they must become CLIA-certified.[136] Further, if laboratories return results to investigators and those results could be used in the treatment of research participants, they must become CLIA-certified.[137]

It is generally recognized that the 2014 changes to CLIA and HIPAA have created a dilemma for research laboratories that are not certified by CLIA but are covered by HIPAA because they conduct at least one electronic covered transaction or by virtue of their relationships with HIPAA-covered entities.[138] To comply with the expanded access rules, HIPAA-covered research laboratories must now return PHI contained within designated record sets (including but not limited to test results) when individuals request them to do so, but these laboratories cannot do so without becoming CLIA-certified (see Table C-4, Box C2).

Yet, the Secretary's Advisory Committee on Human Research Protections (SACHRP) has stated that it would be unrealistic to require all research laboratories to become CLIA-certified in order to comply with HIPAA.[139] That is because the process of CLIA certification is expensive and time consuming.[140] A National Heart, Lung, and Blood Institute Working Group has noted that many research laboratories are not CLIA-certified and many existing biobanks and current studies do not use CLIA-certified laboratories.[141]

Relying on principles of statutory interpretation, some scholars argue that, contrary to CMS's interpretation, the return of results by research laboratories should not trigger a requirement to obtain CLIA certification.[142] Focusing on the provision in CLIA that certification is not required if research laboratories do not return individual results "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of individual patients,"[143] they understand that the need for CLIA compliance is dependent on the purpose for which a laboratory reports results.[144] Although CLIA provides no guidance on how to assess the purpose of returning results, these scholars argue that returning results to an individual along with a suggestion that the individual seek confirmatory testing or consult a

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[136] *See supra* notes 42-45 and accompanying text.
[137] *See supra* note 46.
[138] *See, e.g.*, Evans et al., *supra* note 87, at 801; Mark Barnes, Susan Stayn, David Forster, Michele Russell-Einhorn, David Peloquin & Andres Medina-Jordan, *The CLIA-HIPAA Conundrum of Returning Test Results to Research Participants*, BNA MED. RES. L. & POL'Y REP. at 5 (July 15, 2015), *available at* https://www.ropesgray.com/~/media/Files/articles/2015/July/2015-07-15-Bloomberg-BNA.ashx. This dilemma has been considered by several national committees and working groups, but none has made recommendations regarding how to reconcile the regulations. *See* Gail P. Jarvik et al., *Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices in Between*, 94 AM. J. HUM. GENETICS 818, 819 (2014).
[139] *See* SACHRP, SEPT. 28, 2015 SACHRP LETTER TO THE HHS SECRETARY, ATTACHMENT C: RETURN OF INDIVIDUAL RESULTS AND SPECIAL CONSIDERATION OF ISSUES ARISING FROM AMENDMENTS OF HIPAA AND CLIA (passed July 22, 2015).
[140] Barnes et al., *supra* note 138, at 6.
[141] *See* Richard R. Fasbitz et al., *Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group*, 3 CIRCULATION: CARDIOVASCULAR GENETICS 574, 576-77 (2010).
[142] *See, e.g.*, Burke et al., *supra* note 23, at 107-08; Evans, *supra* note 28, at 562-63.
[143] 42 C.F.R. § 493.3(b)(2) (2018).
[144] Burke et al., *supra* note 23, at 107-08; Evans, *supra* note 28, at 562-65.

physician constitutes informational communication and does not amount to reporting for diagnostic, preventative, treatment, or health assessment purposes.[145] Thus, the return of results by research laboratories in such circumstances should not trigger the requirement to obtain CLIA certification.[146] Moreover, one of these scholars has separately argued that there may be a First Amendment right for a willing researcher to share results generated by a research laboratory with a willing participant.[147]

Finally, some practitioners have noted that even if a conflict exists between CLIA and HIPAA, it is unclear whether OCR will require research laboratories to comply with the new access rule.[148] In this regard, it may be notable that OCR's 2016 guidance on access to genetic test information refers only to information maintained by or for clinical laboratories and does not also address the access obligations of research laboratories.[149]

C. Institutional Responses

Institutions have responded to the perceived CLIA-HIPAA conflict in different ways. Some institutions may be minimizing the conflict through policies that interpret the institution's designated record set to exclude some research-related information. For example, the policy of Johns Hopkins Medicine (JHM) is that researchers may not disclose results of research tests to subjects, patients, families, or caregivers "when such tests have been performed in laboratories that have not been CLIA-certified and do not have a state laboratory license."[150] More generally, JHM has taken the position that a "research record" is categorically not part of any designated record set and so is not subject to the HIPAA access rule.[151] Rather, "only information that is entered into an individual's medical record during the course of research would be part of the 'designated record set.'"[152] However, the policy recognizes that if the research involves treatment of a patient, and there is only one "record," the research and medical record could be the same.[153] The policy concludes: "[T]his is not a settled area of the law. Different experts have different opinions. But until there is further clarification, this is our position on this issue."[154]

Similarly, NYU Langone Health System's policy is that results of tests performed at laboratories not certified by CLIA to perform such tests are categorically not part of any designated record set and so are not subject to the HIPAA access rule.[155] The designated record

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[145] Burke et al., *supra* note 23, at 108.
[146] *Id*. However, these scholars note that where the research is a clinical trial occurring in a health care setting, the distinction between research and clinical care may be so fine that the "prudent course" is for investigators to presume that the requirements of clinical care will apply and return only those results generated or confirmed in CLIA-certified laboratories. *See id*. at 109.
[147] Evans, *supra* note 28.
[148] Barnes et al., *supra* note 138, at 3.
[149] *See* notes 109-110 and accompanying text; telephone communication with David Peloquin, *supra* note 91.
[150] Johns Hopkins Medicine, *Organization Policy 101.2: Research Laboratory Testing Results* (Aug. 2013), *available at* http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/101_2.html.
[151] Johns Hopkins Medicine, *HIPAA Questions and Answers Relating to Research*, http://www.hopkinsmedicine.org/institutional_review_board/hipaa_research/faq_research.html (Feb. 2015).
[152] *Id*.
[153] *Id*.
[154] *Id*.
[155] NYU Langone Health System, *Policy: Designated Record Set* (last rev. Nov. 1, 2017), *available at* https://nyulangone.org/files/policy-designated-record-set-nov-17.pdf.

set is further interpreted to exclude research records that are not used or available to treating providers to make health care decisions about patients.[156]

However, there is anecdotal evidence that institutional policies prohibiting the return of results generated by research laboratories are being overruled in some instances. For example, a qualitative interview study of 31 IRB professionals at six sites across the United States reported two cases in which research test results that could not be confirmed in CLIA-certified laboratories were nevertheless reported to individual research participants.[157] In one of these cases, the researcher had identified several genes associated with hyper-coagulability in a participant, and the IRB recommended returning this result after concluding that doing so posed a low risk of harm but high anticipated benefit to the participant.[158] Although additional instances have been noted in the literature,[159] the frequency with which these decisions are being made in practice is unclear.

VI. Federal Research Participant Protections

The return of results generated from biospecimens in research is relevant to federal regulations for the protection of research participants. These include the Common Rule[160] and regulations adopted by FDA.[161] Although this analysis is limited to federal protections, it is noted that several states also have adopted protections for research participants.[162]

A. Common Rule

1. Current The Common Rule applies to all "research" in which data or biospecimens are obtained through "intervention or interaction" with a "human subject," where the research is federally funded, federally supported, or conducted by institutions that have voluntarily agreed (through federal-wide assurances) to comply with the Common Rule for both covered and non-covered research.[163] However, several categories of research are excluded from the Common Rule's scope, including secondary studies involving only data or biospecimens that cannot be identified as originating from specific individuals.[164] For covered studies, the Common Rule requires IRBs to ensure that the risks of participation are minimized and reasonable in relation to

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[156] *Id*.
[157] Lynn G. Dressler et al., *IRB Perspectives on the Return of Individual Results from Genomic Research*, 14 GENETICS MED. 215, 216-17 (2012).
[158] *Id*. at 217.
[159] *See, e.g.*, Anya E.R. Prince, John M. Conley, Arlene M. Davis, Gabriel Lázaro-Muñoz & R. Jean Cadigan, *Automatic Placement of Genomic Research Results in Medical Records: Do Researchers Have a Duty? Should Participants Have a Choice?*, 43 J. L. MED. & ETHICS 827, 837 (2015) (describing the practice of the Familial Dilated Cardiomyopathy Research Project to notify participants of "suspected meaningful results" generated by a research laboratory).
[160] *See* 45 C.F.R. pt. 46 (2018).
[161] *See* 21 C.F.R. pts. 50, 56 (2018).
[162] *See* CAL. HEALTH & SAFETY CODE §§ 24170-24179.5 (West 2018); MD. CODE. ANN. HEALTH-GEN. § 13-2001 to -2004 (West 2018); N.Y. PUB. HEALTH LAW §§ 2440-2446 (McKinney 2018); VA. CODE ANN. § 32.1-162.16 to 162.20 (2017).
[163] *See* 45 C.F.R. §§ 46.101(a), 46.102(f). Research, in turn, is defined as "a systematic investigation . . . designed to develop or contribute to generalizable knowledge." *Id*. § 46.102(d).
[164] *See id*. § 46.102(f).

the anticipated benefits and also that participation is conditioned on informed consent.[165]

The Common Rule neither explicitly allows nor prohibits the return of results to study participants. Although it requires that potential participants be notified of certain study features for consent to be valid, these features do not include the study's plan (or not) to return results. Still, legal scholars have noted, the Common Rule requires that, when appropriate, a research participant be informed of "significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation."[166] They note that this requirement, at a minimum, may obligate investigators "to disclose the fact that significant findings might be discovered during the course of research and whether or not those will be offered to subjects and/or their physicians."[167]

In practice, when a study protocol includes a plan to return results, the IRB will review the plan to ensure its benefits outweigh its risks.[168] While IRBs can prohibit investigators from returning results, however, they cannot block access when study participants request results under HIPAA.[169]

2. Pending revisions In January 2017, following many years of deliberation, HHS announced its adoption of revisions to the Common Rule.[170] Most of the revisions, including all of those mentioned in this analysis, were scheduled to go into effect on January 19, 2018.[171] However, HHS postponed the effective date by six months to July 19, 2018.[172]

The revisions continue to exempt secondary studies involving only non-identifiable data or biospecimens. They also identify new categories of exempt studies, including secondary research involving only collection and analysis of identifiable health information originally collected for other purposes if that use already is regulated by HIPAA.[173] This exemption was adopted on grounds that HIPAA protections already in place for this kind of research are sufficiently "adequate" and it is "unduly burdensome and confusing" to require such research to also be subject to Common Rule protections.[174]

In addition to exempting new categories of research, the Common Rule revisions specify new categories of research eligible for limited IRB review. These include secondary studies of identifiable data and biospecimens where the investigator "does not include returning individual

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[165] *Id.* §§ 46.109, 46.111(a), 46.116.
[166] *Id.* § 46.116(b)(5).
[167] Amy L. McGuire, Bartha Maria Knoppers, Ma'n H. Zawati & Ellen Wright Clayton, *Can I Be Sued for That? Liability Risk and the Disclosure of Clinically Significant Genetic Research Findings*, 24 GENOME RES. 719, 720 (2014).
[168] *See* Stephanie A. Alessi, *The Return of Results in Genetic Testing: Who Owes What to Whom, When, and Why?*, 64 HASTINGS L. J. 1697, 1702-03 (2013).
[169] *See* Evans et al., *supra* note 87, at 800 ("Under the Privacy Rule, institutional review boards overseeing human-subjects research have no power to block § 164.524 access.").
[170] Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149 (Jan. 19, 2017).
[171] *Id.* at 7259 (revised § 101(l)). The requirement for one IRB to review cooperative research projects conducted in the U.S. will go into effect in January 2020. *Id*.
[172] *See* Federal Policy for the Protection of Human Subjects: Delay of the Revisions to the Federal Policy for the Protection of Human Subjects, 83 Fed. Reg. 2885 (Jan. 22, 2018).
[173] *See* Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. at 7262 (revised § 104(d)(4)(iii)); *see also id.* at 7191-92 (explaining that the information and biospecimens covered by this exclusion "would generally be found by the investigator in some type of records (in the case of information) or some type of tissue repository (such as a hospital's department for storing clinical pathology specimens)").
[174] *Id.* at 7194 (noting HIPAA's requirement that researchers obtain an individual's authorization for certain research uses of protected health information or a waiver of that authorization by an IRB or HIPAA privacy board).

research results to subjects as part of the study plan."[175] The regulations make clear, however, that an investigator of a study that falls within this category may still return results if required by law to do so.[176]

Otherwise, the changes require, for the first time, that investigators disclose their plans regarding return of results in some circumstances. Specifically, the revised Common Rule sets forth a new element of information that, when appropriate, must be provided to research participants.[177] That element is:

> A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.[178]

Furthermore, with respect to the storage, maintenance, and secondary research use of identifiable data and biospecimens, a research participant may provide "broad consent," which must be conditioned on disclosure of the following information:

> Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject.[179]

Under the new rules, it is therefore possible for a study investigator to have no plans to return research results, and to inform (and be required to inform) study participants that individual research results will not be returned, yet be required by HIPAA to return results to participants upon their request according to procedures outside of IRB review.

B. FDA Protections

FDA research participant protections apply to all "clinical investigations," regardless of funding source, that are regulated by FDA or that support applications for research or marketing permits for products regulated by FDA.[180] A clinical investigation is defined as an experiment involving a test article and one or more human participants.[181] Because the reach of FDA protections partially overlaps with the Common Rule, some research studies must comply only with FDA protections, some must comply only with the Common Rule, and some must comply with both.

FDA protections and the Common Rule have different regulatory purposes and so their substance is not identical. Still, many FDA protections are the same as or similar to provisions of the Common Rule.[182] Thus, for covered investigations, FDA regulations (like the Common Rule)

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[175] *Id*. at 7263 (revised § 104(d)(8)).
[176] *See id*. (revised § 104(d)(8)(iv)).
[177] *Id*. at 7266 (revised § 116(c)(8)).
[178] *Id*.
[179] *Id*. at 7266-67 (revised § 116(d)(6)).
[180] 21 C.F.R. §§ 50.1(a), 56.101(a) (2018).
[181] *Id*. §§ 50.3(c), 56.102(c).
[182] *See* Bonnie M. Lee, *Comparison of FDA and HHS Human Subject Protection Regulations*, FDA.GOV, https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm (last updated Mar. 10, 2009).

require IRBs to ensure that the risks of participation are minimized and reasonable in relation to the anticipated benefits and also that participation is conditioned on informed consent.[183] Also like the Common Rule, FDA regulations neither explicitly allow nor prohibit the return of results to study participants. Although they require that potential participants be notified of certain study features for consent to be valid, they do not include notification of the study's plan (or not) to return results.[184] However, FDA protections (like the Common Rule) include the requirement that, when appropriate, a research participant be informed of "significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation."[185] In practice, an IRB overseeing an FDA-regulated study will review the study's return-of-results plan to ensure that adequate protections accompany any return and prospective participants are informed through the consent process and provided an opportunity to opt-out of receiving results if not essential to the study.[186]

The pending revisions to the Common Rule have no effect on FDA research participant protections.[187] However, in the Federal Register preamble to the revisions, HHS stated its intention to "consider the need for updates to FDA regulations and other relevant federal departmental or agency regulations with overlapping scope."[188] Further, the 21st Century Cures Act, enacted in 2016, requires HHS to harmonize differences between the Common Rule and FDA research participant regulations "to the extent practicable."[189] Therefore, it should be expected that many Common Rule revisions will be incorporated into FDA regulations.

VII. FDA Regulations

A. Scope

Under the authority of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA is responsible for protecting and promoting public health by ensuring the safety and effectiveness of medical drugs and devices.[190] Devices regulated by FDA are defined broadly to include articles "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals."[191] So defined, FDA-regulated devices cover many laboratory tests, including *in vitro* diagnostic tests.

FDA classifies each device intended for human use on the basis of risk to consumers.[192] The greater the risk posed by a device, and the more control presumed necessary to ensure its safety and effectiveness, the higher will be its classification. Thus, Class I devices are subject only to general controls, including registration and labeling requirements, whereas most Class II devices require pre-market notification and "special controls," including stricter labeling

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[183] *See* 21 C.F.R. §§ 50.20, 50.25, 56.103, 56.109, 56.111.
[184] *See id*. § 50.25.
[185] *Id*. § 50.25(b)(5).
[186] Telephone communication with Abram Barth, Associate, Ropes & Gray LLP (Nov. 24, 2017).
[187] *See* James E. Valentine & David B. Clissold, *The Final Common Rule: Much Either Retained or Removed, But Not Much New Added*, FDA LAW BLOG (Feb. 17, 2017), http://www.fdalawblog.net/2017/02/the-final-common-rule-much-either-retained-or-removed-but-not-much-new-added.
[188] Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7151 (Jan. 19, 2017).
[189] 21st Century Cures Act, Pub. L. No. 114-255 § 3023(a)-(b) (2016).
[190] *See* 21 U.S.C. ch. 9 (2018).
[191] *Id*. § 321(h).
[192] *See id*. § 360c; 21 C.F.R. pt. 860.

requirements.[193] Class III devices are subject to the most stringent standards and require pre-market approval before marketing.[194] In determining the safety and effectiveness of a device for purposes of its classification, FDA considers four factors: (1) the individuals who are intended or represented as the users of the device; (2) conditions of use of the device; (3) the "probable benefit to health from the use of the device weighed against any probable injury or illness from such use"; and (4) the device's reliability.[195] FDA has classified over 1,700 distinct types of medical devices.[196]

B. Regulation of LDTs and DTC Genetic Tests

FDA has discretion in its enforcement of regulations, and historically the agency has followed a policy of enforcement discretion with respect to laboratory-developed tests (LDTs).[197] An LDT is an *in vitro* diagnostic device that is designed, manufactured, and used within a single laboratory.[198] In 2010, responding to concerns about the increasing complexity, reach, and risk of LDTs, as well as the use of results from faulty LDTs to direct major treatment decisions, FDA announced its intent to reconsider its policy of enforcement discretion with respect to LDTs.[199] Although some scholars questioned FDA's legal authority to regulate LDTs,[200] these concerns became moot in 2017 when FDA announced that it would not issue a final guidance to allow for further public discussion and to give Congress the opportunity to develop a legislative solution.[201]

Nevertheless, FDA generally does not exercise enforcement discretion against firms providing direct-to-consumer genetic tests, whether or not they constitute LDTs,[202] in part due to

[193] *See* 21 U.S.C. § 360c(a)(1)(A)-(B); 21 C.F.R. § 860.3(c)(1)-(2).
[194] *See* 21 U.S.C. § 360c(a)(1)(C); 21 C.F.R. § 860.3(c)(3).
[195] *See* 21 C.F.R. § 860.7(b).
[196] FDA, *Device Classification Panels*, FDA.GOV, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051530.htm (last updated June 26, 2014).
[197] *See* FDA, *Laboratory Developed Tests*, FDA.GOV, https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm (last updated Dec. 26, 2017).
[198] *See id*.
[199] *See id*.
[200] *See, e.g.*, Paul D. Clement & Laurence H. Tribe, *Laboratory Testing Services, as the Practice of Medicine, Cannot be Regulated as Medical Devices* (Jan. 6, 2015), http://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf. *Accord* Gail Javitt, *FDA's Legally-Suspect Shift of Clinical Lab Test Regulation Through Guidance Documents*, THE WLF LEGAL PULSE (Aug. 20, 2014), https://wlflegalpulse.com/2014/08/20/fdas-legally-suspect-shift-of-clinical-lab-test-regulation-through-guidance-documents (explaining that FDA's "legal authority to regulate LDTs, which are used to provide a medical service and are not distributed in interstate commerce as freestanding products, remains a subject of debate").
[201] FDA, *Discussion Paper on Laboratory Developed Tests (LDTs)*, at 1, FDA.GOV (Jan. 13, 2017), https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf.
[202] FDA, *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, at 5, n.4, FDA.GOV (Oct. 3, 2014), https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf (explaining that "FDA generally does not exercise enforcement discretion for direct-to-consumer (DTC) tests regardless of whether they meet the definition of an LDT").

concerns associated with returning results directly to customers.[203] In 2013, for example, FDA sent 23andMe a Warning Letter that its marketing of the Personal Genome Service (PGS) Test without FDA clearance or approval violated the FDCA, citing concerns that customers might self-manage their treatments based on false positive or false negative test outcomes.[204] In 2017, after 23andMe submitted a request for *de novo* classification of the PGS Test, FDA granted permission to market the test for certain genetic health risks as a Class II device.[205] However, based on concerns that included customers' potentially incorrect interpretation of results, FDA imposed special controls that include providing customers information to help them interpret results and requiring their opt-in to receive results related to risk of life-threatening but unpreventable or untreatable conditions.[206]

C. IDE Requirements

The FDCA and implementing regulations describe a path of regulatory exemption for the conduct of clinical investigations to determine the safety or effectiveness of "investigational devices."[207] Procedures for this exemption, known as an investigational device exemption (IDE), are detailed in Part 812 of FDA regulations and summarized in Figure C-1. Devices subject to an approved IDE are exempt from regulatory requirements related to, among other things, performance standards and premarket notification and approval.[208]

[203] Telephone communication with Alberto Gutierrez, Director (retired), Office of In Vitro Diagnostics and Radiological Health, FDA (Nov. 21, 2017).
[204] Warning Letter from Alberto Gutierrez, Director, Office of In Vitro Diagnostics and Radiological Health, FDA, to Ann Wojcicki, CEO, 23andMe, Inc. (Nov. 22, 2013).
[205] FDA, *Evaluation of Automatic Class III Designation for the 23andMe Personal Genome Service (PGS) Genetic Health Risk Test for Hereditary Thrombophilia, Alpha-1 Antitrypsin Deficiency, Alzheimer's Disease, Parkinson's Disease, Gaucher Disease Type 1, Factor XI Deficiency, Celiac Disease, G6PD Deficiency, Hereditary Hemochromatosis and Early-Onset Primary Dystonia, Decision Summary*, DEN160026 (correction date Nov. 2, 2017), *available at* https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf.
[206] *Id*. *Accord* Kayte Spector-Bagdady, *"The Google of Healthcare": Enabling the Privatization of Genetic Bio/Databanking*, 26 ANNALS EPIDEMIOLOGY 515, 518 (2016) (explaining that "FDA's current risk assessment of the 23andMe service is based entirely on the data and information that are *returned* to the customer" (emphasis in original)).
[207] *See* 21 U.S.C. § 360j(g) (2018); 21 C.F.R. pt. 812.
[208] 21 C.F.R. § 812.1(a). However, they may still be subject to requirements of IRB review. *See id*. §§ 50.1, 56.101, 812.62.

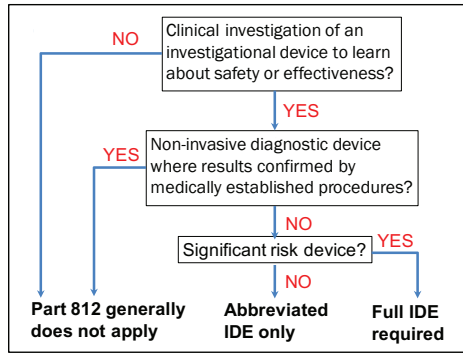

FIGURE C-1 Part 812 applicability.
NOTE: IDE = investigational device exemption.

Part 812 defines an "investigational device" as one "that is the object of an investigation," where an "investigation" is defined as "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device."[209] An approved or cleared device that is used in a study "in accordance with the approved or cleared labeling is not investigational and, therefore, is not subject to the IDE regulation."[210]

FDA has stressed that Part 812 is limited to investigations conducted for purposes of determining safety or effectiveness, and not for other purposes.[211] Nevertheless, FDA has viewed Part 812 as applying to all investigations involving devices where investigators expect to learn about the safety or effectiveness of the device, regardless of whether that is the primary research purpose.[212]

If investigators do expect to learn about the safety or effectiveness of an investigational device, the question becomes whether it poses a "significant risk," meaning it "presents a potential for serious risk to the health, safety, or welfare of a subject."[213] FDA has explained that risk depends not on the nature of the device, but rather on how the information that it generates will be used in a specific study, and also that risk is evaluated on a case-by-case basis according to the worst-case scenario.[214] Factors that FDA considers in determining whether an investigational device poses significant risk include the health status of the study population and

[209] 21 C.F.R. § 812.3(g)-(h); *see also id.* § 812.2(a) (providing that "[t]his part applies to all clinical investigations of devices to determine safety and effectiveness").
[210] FDA, *Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies-Frequently Asked Questions*, at 9, FDA.GOV (June 25, 2010) [hereinafter FDA, *IVD FAQs*]. A device may be an investigational device subject to Part 812 regardless of whether it is used in a clinical or research lab. Telephone communication with Alberto Gutierrez, *supra* note 203.
[211] *See* Procedures for Investigational Device Exemptions, 45 Fed. Reg. 3732, 3735 (Jan. 18, 1980).
[212] *See* NHGRI, *Investigational Device Exemptions (IDEs) and Genomics Workshop: Meeting Report*, GENOME.GOV (June 10, 2016), https://www.genome.gov/multimedia/slides/ideworkshop/ide_workshop_meeting_report.pdf [hereinafter NHGRI, *Meeting Report*].
[213] 21 C.F.R. § 812.3(m).
[214] *See* NHGRI, *Meeting Report*, *supra* note 212.

the manner in which results will be returned.[215] Factors that FDA does not consider in determining whether an investigational device poses significant risk include the size of the cohort and potential benefits to participants.[216]

Investigational devices that do not pose significant risk are subject only to abbreviated IDE requirements, including proper labeling and IRB approval.[217] When a device satisfies these abbreviated requirements, FDA considers it to have an approved IDE application.[218]

Further, Part 812 does not apply to a diagnostic device if it is properly labeled, "non-invasive," and not used for diagnostic purposes without confirmation of the diagnosis by a "medically established" diagnostic product or procedure.[219] The regulations define blood sampling that involves simple venipuncture, as well as the use of surplus body fluids and tissues originally taken for non-investigational purposes, as non-invasive.[220]

There is ambiguity, however, with respect to the kinds of devices that qualify as medically established. Devices that are used for purposes for which they already have been approved or cleared qualify as medically established.[221] But it is unclear whether unapproved or uncleared LDTs used in laboratories can qualify as medically established and whether and how CLIA certification of the laboratories might affect that determination.[222] In the context of genetic testing, FDA has stated that Sanger sequencing will sometimes constitute a medically established procedure.[223]

Recently, the IDE regulations were an issue for four studies funded by NIH as part of the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program.[224] In 2013, FDA asked the investigators of those studies, which include genetic testing of newborns, to participate in the IDE process.[225] FDA considered whether the genetic tests used in the studies were significant risk given that the results might be used to influence medical decision making for newborns.[226] FDA also expressed concern that results might not be confirmed in every case by medically established procedures before their return to participants.[227] Ultimately, all of the

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[215] Telephone communication with Alberto Gutierrez, *supra* note 203; *see also* NHGRI, *Points to Consider Regarding the Food and Drug Administration's Investigational Device Exemption Regulations in the Context of Genomics Research*, GENOME.GOV, https://www.genome.gov/27561291/points-to-consider-in-assessing-when-an-investigational-device-exemption-ide-might-be-needed (last updated July 27, 2017) [hereinafter, NHGRI, *Points to Consider*] (providing as an example of a significant risk study one that involves genome sequencing of healthy participants with an intent to return variants of unknown significance because the test results might lead healthy individuals to pursue unnecessary treatments that could expose them to harm).
[216] *See* NHGRI, *Points to Consider*, *supra* note 215.
[217] *See* 21 C.F.R. § 812.2(b)(1).
[218] *See id*.
[219] *See id*. §§ 812.2(a), 812.2(c)(3). However, it is still subject to regulations related to disqualification of investigators. *See id*. § 812.119.
[220] *Id*. § 812.3(k).
[221] *See* FDA, *IVD FAQs*, *supra* note 210, at 11.
[222] Telephone communication with Abram Barth, *supra* note 186.
[223] *See* NHGRI, *Meeting Report*, *supra* note 212 (noting that "although Sanger is analytically valid, it is not clinically valid," whereas "medically established" procedures are, by definition, clinically valid).
[224] *See* Julia Karow, *First Newborn Sequencing Study Gets FDA Green Light While Others Still Await Approval*, GENOMEWEB (Dec. 17, 2014), https://www.genomeweb.com/sequencing-technology/first-newborn-sequencing-study-gets-fda-green-light-while-others-still-await.
[225] *See id*.
[226] Personal communication with Amy McGuire, Leon Jaworski Professor of Biomedical Ethics, Baylor College of Medicine (Oct. 3, 2017).
[227] *See id*.

studies filed a "pre-IDE" to determine whether they needed to obtain an IDE, but only the North Carolina study was deemed to pose significant risk and required to submit a full IDE application.[228] Although FDA eventually approved the application, the process of obtaining approval set back the study at least a year.[229]

In 2016, the National Human Genome Research Institute (NHGRI) held a workshop to discuss the IDE regulations as they apply to clinical studies that use genomic technologies.[230] To develop the content of this event, NHGRI collaborated with FDA's Center for Devices and Radiological Health, which reviews IDE submissions and is responsible for FDA's medical device regulations.[231] Outstanding questions identified at the workshop's conclusion that are relevant to the return of results included whether FDA considers professional guidelines recommending the return of results to represent a standard of care, and if so, how those guidelines factor into FDA risk assessments.[232]

D. Unlawful Promotion

Although FDA regulates statements that device manufacturers can make about the clinical significance of test results, the agency's jurisdiction over the practice of medicine is limited.[233] According to its authorizing statute, FDA may not "limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."[234] However, the statute makes clear that the exclusion does "not change any existing prohibition on the promotion of unapproved uses of legally marketed devices."[235] Moreover, with respect to investigational devices, FDA regulations state that sponsors, investigators, and persons acting on their behalf may not promote or test market an investigational device before FDA has approved it for commercial distribution or "represent" that the device "is safe or effective for the purposes for which it is being investigated."[236]

According to legal scholars, these rules mean that FDA likely cannot prohibit statements that physicians make to patients about their laboratory test results, including explanations of the clinical significance of the results, if they are made during the course of medical practice.[237] However, it is unclear whether there are circumstances in which an investigator's communication to participants of interpreted results generated from an investigational device

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[228] *See* Karow, *supra* note 224. The "pre-IDE" process is briefly described in FDA, *IVD FAQs*, *supra* note 210, at 19-20.
[229] Telephone communication with Jonathan Berg, Assistant Professor, Department of Genetics, University of North Carolina at Chapel Hill (Dec. 20, 2017).
[230] *See* NHGRI, *Meeting Report*, *supra* note 212.
[231] *See id*.
[232] *See id*.
[233] *But see* Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 460-64 (2015) (identifying examples of indirect FDA regulation of the practice of medicine).
[234] 21 U.S.C. § 396 (2018).
[235] *Id*.
[236] 21 C.F.R. §§ 812.7(a), 812.7(d).
[237] *See* Evans at 273; Sarah Y. Kwon, *Regulating Personalized Medicin*e, 31 BERKELEY TECH. L. J. 931, 951 (2016); *see also* telephone communication with Alberto Gutierrez, *supra* note 203. However, if physicians' claims about test results violate the standard of care, they may be subject to tort lawsuits or disciplinary actions by state medical practice boards. *See* Evans at 272-73.

would constitute unauthorized activity, and where, precisely, the FDA draws the line between permissible communications and impermissible promotion.[238]

OTHER LEGAL ISSUES

VIII. Property Rights

The return of research results is also relevant to the issue of property rights, which is generally governed by the states. In general, state courts have not viewed research results, including data generated from genetic tests, as legal property belonging to research participants. This conclusion has been reached by several courts in lawsuits where individuals who provided biospecimens for research claimed an ownership interest in results of tests performed on those biospecimens or, more generally, information and discoveries obtained through analysis of the biospecimens.[239] In *Greenberg v. Miami Children's Hospital Research Institute*, for example, a federal district court in Florida held that donors' property rights in their biospecimens "evaporates once the sample is voluntarily given to a third party" and declined to recognize a "continuing right for donors to possess the results of any research."[240] Nevertheless, legal scholars describe a widespread belief that individuals "own" their personal data.[241]

Moreover, in the context of genetics, some state legislatures have explicitly recognized property rights of individuals in their test results.[242] A Colorado statute, for example, provides that "[g]enetic information is the unique property of the individual to whom the information pertains,"[243] although it permits the research use of information derived from genetic testing so long as the identity of any individual to whom the information pertains is not disclosed to third parties.[244] An Alaska statute similarly provides that "a DNA sample and the results of a DNA analysis performed on the sample are the exclusive property of the person sampled or analyzed."[245] The statute further authorizes civil and criminal liability against any person who

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[238] Telephone communication with Patricia Zettler, Associate Professor, Georgia State University College of Law (Nov. 2, 2017).

[239] *See, e.g.*, Moore v. Regents of the Univ. of Cal., 51 Cal. 3d 120, 136-41 (Cal. 1990), *cert. denied*, 111 S. Ct. 1388 (1991) (declining to find that a patient retained ownership rights in his excised cells); Ande v. Rock, 256 Wis. 2d 365, 382-83 (Wis. Ct. App. 2002) (rejecting plaintiffs' claim that, under Wisconsin law, they had a property interest in diagnostic results that had not been returned to them). *Accord* Washington Univ. v. Catalona, 490 F.3d 667, 675 (8th Cir. 2007), *cert. denied*, 128 S. Ct. 1122 (2008) (holding that, under Missouri law, individuals who donated their biological materials voluntarily to a research institution did not retain an ownership interest allowing them to direct the transfer of the materials to third parties).

[240] 264 F. Supp. 2d 1064, 1075-76 (S.D. Fl. 2003) (applying Florida law, dismissing a claim of conversion of body tissue and genetic information voluntarily given to researchers).

[241] *See, e.g.* Mark A. Rothstein, *Ethical Issues in Big Data Health Research*, 43 J. L. MED. & ETHICS 425, 427 (2015) (noting that "many individuals strongly believe that their biological specimens and health records 'belong to them'" so that they at least "ought to be consulted and asked for permission before their specimens and data are collected, analyzed, stored, and used for research"). Whether the propertization of data and biospecimens is socially desirable or not is the subject of ongoing academic debate. *See, e.g.,* Jorge L. Contreras, *Genetic Property*, 105 GEO. L. J. 1 (2016); Gail H. Javitt, *Take Another Little Piece of My Heart: Regulating the Research Use of Human Biospecimens*, 41 J. L. MED. & ETHICS 424 (2013).

[242] *See, e.g.*, ALASKA STAT. ANN. § 18.13.010(a)(2) (West 2017); COLO. REV. STAT. ANN. § 10-3-1104.7(1)(a) (West 2017); FLA. STAT. ANN. § 760.40(2)(a) (West 2017).

[243] COLO. REV. STAT. ANN. § 10-3-1104.7(1)(a).

[244] *See id*. § 10-3-1104.7(5).

[245] ALASKA STAT. ANN. § 18.13.010(a)(2).

retains a DNA sample or the results of a DNA analysis without informed consent.[246] A lawsuit alleging unlawful disclosure of test results in violation of these provisions is currently pending before the federal district court in Alaska.[247] The court has not yet interpreted the substantive provisions of the statute, although the test provider filed notice that it is challenging the statute as unconstitutionally vague because it does not allow reasonable people to understand what behavior would run afoul of it.[248]

Finally, parties can privately agree to allocate rights in test results that are different from default legal rules.[249] This is done, for example, by the Personal Genome Project (PGP),which conducts genetic sequencing on biospecimens donated by participants, collects results of health surveys and previous genetic tests, and publishes all individual-level data on the internet for use by researchers.[250] PGP's informed consent document provides that donors retain ownership of the data they provide, although by participating in PGP, they license it to use that data without restriction.[251] On the other hand, any information created or prepared by PGP from donated biospecimens and data, including the results of any research or analysis performed by or in collaboration with PGP, are "the property of and owned by the PGP and not by [participants]."[252] Although PGP will attempt to make this information available to participants and the public, it states that it "is unable to guarantee if, when or in what form [participants] will receive access to any information, data or materials as part of [their] participation."[253]

IX. Tort Liability

The return of research results may give rise to tort liability under state law for researchers and laboratories. A tort is a civil wrong (other than breach of contract) for which a remedy may be obtained, usually in the form of damages.[254] Tort liability associated with the return of research results can generally be categorized as non-disclosure liability or disclosure liability.

A. Non-Disclosure Liability

There are several legal theories under which a researcher can be sued for failure to return results, although negligence has been identified as the most probable cause of action.[255] An individual is liable for negligence where the individual owed a duty to another person, but breached that duty, and the person was harmed as a result.[256]

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[246] *Id.* §§ 18.13.020, 18.13.030.
[247] *See* Complaint, Cole v. Gene by Gene, Ltd., Case No. 1:14-cv-00004-SLG (D. Alaska) (filed May 13, 2014).
[248] *See* Jennifer K. Wagner, *A Constitutional Challenge to Alaska's Genetic Privacy Statute*, GENOMICS L. REP. (July 18, 2017), https://www.genomicslawreport.com/index.php/2017/07/18/a-constitutional-challenge-to-alaskas-genetic-privacy-statute.
[249] Individuals also can contractually agree to give broad rights to use their test results. Telephone communication with David Peloquin, *supra* note 91.
[250] HARVARD PERSONAL GENOME PROJECT, https://pgp.med.harvard.edu/about (last visited Jan. 29, 2018).
[251] *See* Personal Genome Project, Consent Form § 8.2 (rev. May 5, 2015), *available at* https://my.pgp-hms.org/static/PGP_Consent_2015-05-05_online_stamped.pdf (last visited Jan. 29, 2018).
[252] *Id.* § 8.3.
[253] *Id.*
[254] BLACK'S LAW DICTIONARY (10th ed. 2014) ("tort").
[255] *See* McGuire et al., *supra* note 167, at 720.
[256] *See id*.

Whether one owes a legal duty to another depends on the nature of their relationship and is highly context specific.[257] In general, individuals owe a duty of reasonable care under the circumstances, but tort law imposes no affirmative duties to act for another's benefit and individuals are not required to warn others of impending harm.[258] A number of factors can overcome this general tort law notion that individuals do not owe others affirmative duties, including the existence of a fiduciary relationship or other "special relationship," as well as contractual obligations.[259]

1. Fiduciary relationships Fiduciary relationships are two-way relationships based on trust: "[t]he principal must have placed trust in the fiduciary and the fiduciary must have accepted that trust."[260] The fiduciary duty has been described as "extremely high," where the fiduciary has "a duty to act with undivided loyalty in the best interests of the principal."[261] Physicians are held to be fiduciaries of their patients and are obligated to use their specialized knowledge and skill to act primarily in their patients' best interests.[262]

Researchers, on the other hand, are generally not viewed as fiduciaries because their obligation is to produce generalizable knowledge, which may require acting in ways that are not primarily for the benefit of research participants.[263] In several notable cases, courts have declined to view researchers as fiduciaries of participants in their studies where the researchers were not also the participants' treating physicians.[264]

There is a question, however, whether a researcher's act of returning clinically relevant results to a research participant, including interpretation of the clinical relevance of those results, by itself constitutes the practice of medicine that transforms their relationship into one of physician and patient. If so, the researcher assumes the fiduciary duties of a physician. No court apparently has addressed this issue in a precedential opinion, although legal scholars have argued that communication of the need to seek care is not necessarily the practice of medicine:

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[257] *See* Elizabeth R. Pike, Karen H. Rothenberg & Benjamin E. Berkman, *Finding Fault? Exploring Legal Duties to Return Incidental Findings in Genomic Research*, 102 GEO. L. J. 795, 816-17 (2014); Prince et al., *supra* note 159, at 835.

[258] *See* Pike et al., *supra* note 257, at 816; Stacey A. Tovino, *Incidental Findings: A Common Law Approach*, 15 ACCOUNTABILITY RES. 242, 248 (2008) ("Under general principles of tort law, individuals do not have a duty to warn of risks they did not create absent a special relationship or other exceptional circumstances.")

[259] *See* Pike et al., *supra* note 257, at 816-17.

[260] Tovino, *supra* note 258, at 250-51.

[261] *Id*. at 251.

[262] *See* McGuire et al., *supra* note 167, at 720.

[263] *See id.* at 720-21; *see also* Pike et al., *supra* note 257, at 820 (explaining that, "[a]s a general rule, researchers are not fiduciaries of participants, so they do not owe fiduciary duties to act in a participant's best interest"); Leslie A. Meltzer, *Undesirable Implications of Disclosing Individual Genetic Results to Research Participants*, 6 AM. J. BIOETHICS 28, 29 (2006) (stating that, in contrast to the clinical care setting, "in the research setting, investigators are not fiduciaries of participants" because their primary goal "is not, and indeed cannot be, to benefit any one participant").

[264] *See* Moore v. Regents of the Univ. of Cal., 51 Cal. 3d 120, 133 (Cal. 1990) (rejecting the claim that a researcher who was not a physician had a fiduciary relationship with the complainant); Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1070-72 (S.D. Fl. 2003) (explaining that there is "no automatic fiduciary relationship that attaches when a researcher accepts medical donations" and finding that the plaintiffs' failure to sufficiently allege that the defendant researchers had accepted the plaintiffs' trust was fatal to their claim of breach of fiduciary duty); Ande v. Rock, 256 Wis. 2d 365, 377-79 (Wis. Ct. App. 2002) (finding no legally cognizable allegations in the complaint that there existed a physician-patient relationship between tested children and non-treating researchers).

> Law recognizes a distinction between informing a person of the need to seek medical care and actually rendering medical care. . . . Return of research results lacks the treatment step that is necessary to create a [physician-patient relationship] and transform research into medical practice.[265]

Another question is whether a laboratory is a health care provider, which is presented in a pending federal lawsuit in South Carolina. The *Williams v. Quest Diagnostics* lawsuit is based on allegations that a clinical laboratory returned erroneous genetic test results and did not provide corrected test results until almost eight years later.[266] Bringing suit on behalf of her son, who died as a result of receiving the wrong treatment, the plaintiff alleges negligence and other claims based on the laboratory's failure to correctly classify her son's genetic variant consistent with then-known scientific information.[267] However, the laboratory seeks to reframe the case as a medical malpractice suit, which would be barred under the state's statutes of limitations and repose.[268] To resolve this issue, the trial judge asked the South Carolina Supreme Court to determine ("certify" the question) whether a clinical laboratory is a licensed healthcare provider under South Carolina law.[269] Although the federal court's decision in this case will not be binding on subsequent cases except in limited circumstances,[270] it nevertheless may have practical significance to the extent that judges presiding over similar cases choose to follow its reasoning.[271]

2. Special relationships In addition to fiduciary relationships, "special relationships" between researchers and research participants can give rise to affirmative duties to disclose certain findings.[272] Two courts have recognized the potential existence of such a relationship in the research context in the absence of any physician-patient relationship. First, in *Blaz v. Michael Reese Hospital Foundation*, a federal court in Illinois found a special relationship existed

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[265] Burke et al., *supra* note 23, at 107. However, where the testing is conducted at the request of a physician, some scholars have argued that the "tests are merely an extension of the *doctor's* favored methods for evaluating a patient and diagnosing the problem" and so the testing service is "part and parcel of the doctor's practice of medicine." Clement & Tribe, *supra* note 200, at 12 (emphasis in original) (arguing that FDA cannot regulate LDTs because doing so would constitute unlawful interference with the practice of medicine).

[266] Complaint, Williams v. Quest Diagnostics, Inc., Case No. 2016-CP-40-01166 (S.C. Ct. Com. Pl.) (filed Feb. 24, 2016).

[267] *Id*.

[268] *See* Laurel Coons, *Williams v. Athena Motion to Dismiss Hearing—SC Supreme Court May Be Asked to Decide Whether a Diagnostic Laboratory Qualifies as a Healthcare Provider*, GENOMICS L. REP. (Jan. 26, 2017), https://www.genomicslawreport.com/index.php/2017/01/26/williams-v-athena-motion-to-dismiss-hearing-sc-supreme-court-may-be-asked-to-decide-whether-a-diagnostic-laboratory-qualifies-as-a-healthcare-provider.

[269] *See* Turna Ray, *Wrongful Death Suit Awaits Input from South Carolina Supreme Court*, GENOMEWEB (Apr. 4, 2017), https://www.genomeweb.com/molecular-diagnostics/wrongful-death-suit-awaits-input-south-carolina-supreme-court.

[270] Deborah Levenson, *Lawsuit Raises Questions about Variant Interpretation and Communication*, 173 AM. J. MED. GENETICS SEQUENCE 838, 839 (2017) (summarizing commentary by John Conley, William Rand Kenan Jr. Professor of Law, UNC School of Law). Specifically, if the decision is appealed to the U.S. Court of Appeals for the Fourth Circuit, that appellate court's decision would be binding on federal courts within the Fourth Circuit applying the same South Carolina laws. *See id*.

[271] *See* Coons, *supra* note 268 (afterword by John Conley). Moreover, the South Carolina Supreme Court's ruling on the narrow question whether clinical laboratories are licensed healthcare providers in South Carolina, which it has certified, will be binding on all courts applying South Carolina law. *See id*.

[272] *See* McGuire et al., *supra* note 167, at 721.

between research participants and a physician in charge of follow-up to the research program by virtue of his specialized knowledge and communication with participants.[273] Even though the participants were not the physician's patients, the court held that the special relationship created a duty on the part of the physician to warn of risks.[274]

Two years later, in *Grimes v. Kennedy Krieger Institute*, Maryland's highest court took a more expansive view and suggested that a special relationship between researchers and participants can exist by virtue of the "very nature of nontherapeutic scientific research" and also that informed consent documents can give rise to duties to warn.[275] At issue in *Grimes* was a nontherapeutic study led by Kennedy Krieger Institute (KKI) to investigate the effectiveness of lead-based paint abatement strategies on local housing rented to families with small children. The study included treatment groups of homes that received varying levels of less-than-comprehensive lead abatement and control groups of homes that received comprehensive lead abatement or were recently constructed and presumed not to have lead-based paint.[276] Effectiveness of the abatement strategies was determined by comparing lead levels in the blood of the children with lead samples taken from the homes, exterior soil, and drinking water.[277]

The *Grimes* opinion is directed to the research experiences of two participants who were children. Participant Ericka Grimes lived with her family in a home where initial lead dust testing revealed "hot spots" of lead, although her mother was not informed of these results until nine months after sample collection.[278] In the meantime, Miss Grimes was tested three times for lead in her blood; the second and third tests detected elevated lead levels.[279] Her family sued for failure to timely disclose the property's elevated lead dust levels.[280] Participant Myron Higgins lived with his mother in a home that tested positive for lead but had received partial abatement.[281] After they moved in, lead dust samples were taken using two different methods; his mother was not informed of the elevated lead dust levels detected by one of the methods.[282] Mr. Higgins was tested three times for lead in his blood and all tests detected elevated lead levels.[283] His family sued for failure to timely disclose the property's original lead test results and failure to ever disclose the elevated lead dust levels detected after they moved in.[284]

The lower court granted summary judgment for KKI in both cases on grounds that KKI had no legal duty to warn the research participants of potential harms, and the rulings were appealed to the Court of Special Appeals.[285] The Court of Appeals of Maryland then granted certiorari to consider the relevant issues and concluded that summary judgment was incorrectly granted because such a duty to warn may exist as a matter of law.[286]

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[273] 74 F. Supp. 2d 803, 806-807 (N.D. Ill. 1999).
[274] *See id*.
[275] Grimes v. Kennedy Krieger Inst., Inc., 782 A.2d 807, 834-35, 843-46 (Md. 2001).
[276] *See id*. at 820-23.
[277] *See id*. at 822.
[278] *See id*. at 824-25.
[279] *See id*. at 825.
[280] *See id*. at 825-26, 844-45.
[281] *See id*. at 826.
[282] *See id*. at 827-28, 845.
[283] *See id*. at 828-29.
[284] *See id*. at 829-31, 845.
[285] *See id*. at 818.
[286] *See id*. at 818-19.

The court held that "the very nature of nontherapeutic research on human subjects can, and normally will, create special relationships out of which duties arise."[287] The creation of such a relationship is especially likely where researchers "recruit people, especially children, whose consent is furnished indirectly," to participate in potentially dangerous research.[288] Alternatively, the court held that the informed consent documents signed by the participants' family members created bilateral contracts that obliged KKI to provide "full, detailed, prompt, and continuing warnings as to all the potential risks and hazards inherent in the research or that [arose] during the research."[289] In its subsequent denial of a motion for reconsideration, however, the court clarified that its opinion was limited to the finding that summary judgment was improperly granted and that "[e]very issue bearing on liability or damages remains open for further factual development."[290] Further, the opinion has been widely criticized and generally not followed.[291]

3. Scope of duties If researchers owe legal duties to participants with whom they interact, the scope of that duty and whether it includes an obligation to return certain results depends on the prevailing standard of care. The standard of care can be established by guidance and recommendations to return results, recognition by scholars and the research community of an ethical obligation to return results, and a common practice of returning results.[292] Legal scholars have explained that the "more encompassing guidelines and practices are with regard to return of results, the more sweeping the potential ethical and legal obligation" to do so will be.[293] Furthermore, if the practice of returning results becomes routine, researchers "*will* be legally required" to do so because "[t]his is the way tort law has worked for decades."[294] Finally, in the case of physician-investigators, legal scholars have suggested that if the research itself generates individualized and identifiable data, medical obligations may trump research obligations and support a "higher duty to disclose relevant and significant findings."[295]

B. Disclosure Liability

Many kinds of actions associated with the return of research results may give rise to tort liability. These include: (1) disclosure of correct results to the wrong individual as a result of, e.g., improper labeling; (2) disclosure of incorrect results to the right individual as a result of, e.g., improper test administration; (3) disclosure of results to individuals who are not authorized

[287] *Id*. at 834-35.
[288] *Id*. at 845-46.
[289] *Id*. at 843-44.
[290] Grimes v. Kennedy Krieger Inst., No. 128 Sept. Term 2000 (Md. 2001) (per curiam) (denying motion for reconsideration).
[291] *See, e.g.*, Pike et al., *supra* note 257, at 820 n.132 (noting that "courts that have considered similar fact patterns have generally refused to extend the holding of *Grimes*, and *Grimes* has been the subject of significant scholarly criticism"); Diane E. Hoffmann & Karen H. Rothenberg, *Whose Duty is it Anyway? The Kennedy Krieger Opinions and its Implications for Public Health Research*, 6 J. HEALTH CARE L. & POL'Y 109 (2002) (criticizing the duty implied by the court as unclear and potentially overbroad).
[292] *See* Pike et al., *supra* note 257, at 798, 822-23; Tovino, *supra* note 258, at 255. *But see* Wolf, *supra* note 22, at 440-41 (2012) (describing numerous ethics recommendations on return of results that have been promulgated over the years, none of which apparently has been cited in support of legal liability).
[293] Ellen Wright Clayton & Amy L. McGuire, *The Legal Risks of Returning Results of Genomics Research*, 14 GENETICS MED. 473, 475 (2012).
[294] *Id*. (emphasis in original).
[295] McGuire et al., *supra* note 167, at 721.

to receive them; and (4) failure to update previously disclosed results and return the updated results.

Researchers who return results must do so consistent with the standard of care and regulatory requirements.[296] Thus, laboratories that deviate from good laboratory practices and standards regarding interpretation may be exposed to tort liability if they return erroneous results to individuals who are harmed as a result.[297] In fields like genomics, however, the standard of care regarding interpretation is rapidly evolving.[298] "[G]iven that there is still fervent debate about how to interpret variants," legal scholars have argued, "it will be extremely difficult to prove what the standard of care is or that it has clearly been breached by a researcher acting in good faith" who provides interpreted genetic results.[299]

Nevertheless, researchers are generally required to comply with standards that seek to maximize the analytic and clinical validity of findings.[300] Legal scholars have concluded that if researchers return erroneous results generated by a research laboratory and not validated in a CLIA-certified lab, and they do not make clear that the results need to be repeated before any clinical interventions are undertaken, the researchers may be liable in tort.[301] However, the legal effect of such disclaimers, and whether they will absolve researchers of tort liability, remains unclear.

Meanwhile, disclosure of results to individuals who are not authorized to receive them may give rise to negligence claims where, among other things, the tested individual suffered discrimination as a result. These negligence claims would be in addition to any privacy claims that might be available to the tested individual. On the other hand, a laboratory's obligation to update previously returned results in response to, for example, new scientific evidence or consensus, or following the laboratory's adoption of a different classification scheme, remains unsettled. This question is raised in *Williams v. Quest Diagnostics* but has not yet been resolved.[302]

X. Anti-Discrimination Statutes

There is a complex web of federal and state laws that address unwanted access to and discriminatory use of health information. Whereas unwanted access is the domain of privacy laws, which are based on ethical principles of autonomy, discriminatory use is the domain of

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[296] *See id*. at 721-22.
[297] *See id*. at 722.
[298] *See id*.
[299] *Id*.
[300] *Id.* at 721.
[301] *See id*. at 722.
[302] *See* Complaint, Williams v. Quest Diagnostics, Case No. 2016-CP-40-01166 (S.C. Ct. Com. Pl.) (filed Feb. 24, 2016). In *Williams*, the clinical laboratory allegedly made an error in the original variant classification, which did not reflect the then-existing literature, and it did not correct this classification in a revised report until almost eight years later. *See id*. The plaintiff's position is that the revised report "corrected an *error* in the original classification rather than provid[ed] an *update* or reinterpretation." Jennifer K. Wagner, *Litigating the Accountability of Clinical Genomics Laboratories*, GENOMICS L. REP. (May 31, 2016), https://www.genomicslawreport.com/index.php/2016/05/31/litigating-the-accountability-of-genomics-laboratories (emphasis in original). The analogous question regarding the potential duty of physicians to provide patients new information that might be relevant to their ongoing medical care is addressed in Mark A. Rothstein & Gil Siegal, *Health Information Technology and Physicians' Duty to Notify Patients of New Medical Developments*, 12 HOU. J. HEALTH L. & POL'Y 93 (2012).

anti-discrimination laws, which are animated by concerns with equality and fairness.[303] As noted by legal scholars, however, privacy laws can "do the work" of preventing discrimination by blocking access to information that might be the basis for discriminatory conduct.[304] Therefore, provisions relevant to both types of activities are sometimes included in the same statute.

A. Federal Statutes

The major federal statutes that address problematic downstream uses of health information, whether generated in research or clinical contexts, are the Genetic Information Nondiscrimination Act (GINA), which is focused on genetic information, and the Americans with Disabilities Act (ADA), which is directed toward actual and perceived disabilities.

1. Genetic Information Nondiscrimination Act Passed in 2008, GINA limits access to and use of genetic information in health insurance and employment contexts, where an individual's genetic information is generally defined to encompass information about his or her genetic tests, the genetic tests of family members, the manifestation of a disease or disorder in family members, the request or receipt of genetic services by the individual or family members, and participation in clinical research by the individual or family members that includes genetic services.[305] The legislative purpose of GINA is to promote genetic testing for personal health and research purposes by allaying concerns with the potential misuse of information learned from genetic tests.[306]

Focusing on its application to health insurance, prior to GINA, HIPAA prohibited group health insurers from using genetic information to determine eligibility or set premiums for individuals or from treating genetic information as the basis of any pre-existing condition exclusion.[307] GINA extended these protections to individual health insurers and further prohibits group health insurers from using genetic information about an individual to determine coverage or set premiums for a group.[308] Moreover, under GINA, health insurers cannot request or require genetic testing prior to an individual's enrollment and cannot request, require, or purchase genetic information for underwriting purposes.[309] While health insurers cannot deny coverage on the basis of genetic information, however, GINA permits them to do so based on already expressed genetic conditions.[310] This loophole was closed in 2011 by the Patient Protection and Affordable Care Act (ACA), which prohibits health insurers from denying coverage based on any pre-existing condition.[311]

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[303] *See* Jessica L. Roberts, *Protecting Privacy to Prevent Discrimination*, 56 WM. & MARY L. REV. 2097, 2105-07, 2109-12 (2015).
[304] *See id*. at 2121-22 (describing a privacy-nondiscrimination "symbiosis").
[305] Genetic Information Nondiscrimination Act (GINA) of 2008, Pub. L. No. 110-233 (2008) (codified as amended in scattered sections of 26, 29, and 42 U.S.C.).
[306] *See id*. § 2.
[307] *See* 29 U.S.C. § 1181 (effective to Feb.16, 2009); 29 U.S.C. § 1182 (effective to May 20, 2008).
[308] *See* Amanda K. Sarata & Jody Feder, *The Genetic Information Nondiscrimination Act of 2008 (GINA)*, Cong. Res. Serv. Report No. RL34584, at 5, 10 (Aug. 6, 2015) (explaining the legal effect of GINA).
[309] *See* 42 U.S.C. §§ 300gg-4(c)(1), 300gg-4(d)(1) (2018).
[310] *See* Robert C. Green, Denise Lautenbach & Amy L. McGuire, *GINA, Genetic Discrimination, and Genomic Medicine*, 372 N. ENGL. J. MED. 397, 397-98 (2015).
[311] *See* Patient Protection and Affordable Care Act (ACA), Pub. L. No. 111-148 § 1201 (2010) (codified at 42 U.S.C. § 300gg-3(a)).

GINA similarly limits both access to and use of genetic information by employers. Thus, employers are prohibited from requesting, requiring, or purchasing genetic information about employees or their family members.[312] Employers also may not use genetic information to make employment decisions related to, e.g., hiring, firing, promotion, and compensation, or to deprive employees of employment opportunities.[313] Finally, employers must treat the genetic information of their employees as confidential medical records that generally may not be disclosed.[314]

Yet GINA, even as amended by the ACA, has important limits. First, GINA applies only to health insurers and employers; it does not apply to life, disability, or long-term care insurers or to other contexts in which discrimination may occur, such as housing and education.[315] Further, with respect to its prohibitions on employers, GINA does not protect against discrimination based on non-genetic health information or manifested disease.[316] For these and other reasons, GINA has been widely criticized.[317]

From fiscal years 2010 to 2017, the Equal Employment Opportunity Commission (EEOC), which is responsible for enforcing GINA, received between 201 and 333 GINA-related complaints each year.[318]

2. Americans with Disabilities Act While GINA prohibits discrimination on the basis of genetic information, the ADA prohibits discrimination against individuals with disabilities in employment, public services, and public accommodations contexts.[319] The threshold issue in every ADA case is whether the individual alleging discrimination has a disability. The ADA, as amended by the ADA Amendments Act of 2008, defines a disability as: (1) a physical or mental impairment that substantially limits one or more "major life activities" of an individual; (2) a record of such an impairment; or (3) being regarded as having such an impairment.[320] A major life activity is defined to include activities such as concentrating, communicating, caring for oneself, and performing manual tasks, as well as the operation of major bodily functions.[321]

Although the ADA instructs that the definition of disability should "be construed in favor of broad coverage of individuals . . . to the maximum extent permitted,"[322] it is unclear whether an asymptomatic individual, such as an individual who has a genetic predisposition for a not-yet-manifested condition, can have a disability recognized by the ADA.[323] This question is presented

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[312] *See* 42 U.S.C. § 2000ff-1(b).
[313] *See id*. § 2000ff-1(a).
[314] *See id*. § 2000ff-5(a)-(b).
[315] *See* Mark A. Rothstein, *GINA, the ADA, and Genetic Discrimination in Employment*, 36 J. L. MED. & ETHICS 837, 837 (2008).
[316] *See id*.
[317] *See, e.g.*, Mark A. Rothstein, *Putting the Genetic Information Nondiscrimination Act in Context*, 10 GENETICS MED. 655 (2008).
[318] *See* EEOC, *Genetic Information Non-Discrimination Act Charges*, EEOC.GOV, https://www.eeoc.gov/eeoc/statistics/enforcement/genetic.cfm (last visited Feb. 2, 2018).
[319] Americans with Disabilities Act of 1990 (ADA), Pub. L. No. 101-336 (1990) (codified at 42 U.S.C. ch. 126 and amended by the ADA Amendments Act of 2008, Pub. L. No. 110-325 (2008)).
[320] 42 U.S.C. § 12102(1).
[321] *See id*. § 12102(2).
[322] *Id*. § 12102(4)(A).
[323] *Compare* 1 DISABILITY DISCRIMINATION IN THE WORKPLACE § 13:8 (last updated Oct. 2017) (stating that asymptomatic individuals might be covered if they are "regarded as" or perceived to be disabled), *with* Rothstein, *supra* note 315, at 839 (stating that, "[i]n the context of genetic discrimination in employment, asymptomatic individuals are unlikely to be covered by the ADA"), and Anya E.R. Prince & Benjamin E. Berkman, *When Does an Illness Begin: Genetic Discrimination and Disease Manifestation*, 40 J. L. MED. & ETHICS 655, 657 (2012) (stating

in *Chadam v. Palo Alto Unified School District*, a lawsuit filed on behalf of a California student who was asked to transfer middle schools on the basis of his genetic status as a carrier of a variant associated with cystic fibrosis.[324] The student, who has not exhibited symptoms of the disease, alleged that the school district's actions violated the ADA, and in 2016, the U.S. Court of Appeals for the Ninth Circuit upheld his claim on appeal of its dismissal.[325] The case remains pending.[326]

In employment contexts, the ADA prohibits employers from discriminating against individuals who, with or without reasonable accommodation, can perform the essential functions of employment positions.[327] Employers are further prohibited from conducting medical examinations or making inquiries of job applicants and employees as to whether they have a disability or the nature or severity of such disability unless the examinations or inquiries are job-related.[328] However, employers may conduct examinations and make inquiries after a job offer has been made (but before employment has begun) for any reason, and they may condition the offer on the results so long as any exclusionary criteria that are applied are job-related and consistent with business necessity.[329]

From fiscal years 2010 to 2017, the EEOC, which also is responsible for enforcing alleged violations of the employment discrimination provisions of the ADA, received approximately 25,000 ADA-related complaints each year.[330]

B. State Statutes

GINA and the ADA establish a floor of minimum protection against health-related discrimination and do not preempt state laws that provide equal or greater protection.[331] Over the years, many state anti-discrimination statutes have been enacted that vary widely in scope and applicability.

Focusing on genetic discrimination, some states have enacted anti-discrimination statutes limited to specific genetic conditions. For example, in 1975, North Carolina became the first state to prohibit employment discrimination against individuals with sickle cell trait or

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that "[t]here is arguably no protection for individuals who have manifested some symptoms, but whose symptoms have not risen to the level of substantial limitations").

[324] *See* Second Amended Complaint for Damages, Case No. 4:13-cv-04129-CW (N.D. Cal.) (filed Feb. 28, 2014).

[325] *See* Memorandum, Chadam v. Palo Alto Unified School District, No. 14-17349, D.C. No. 4:13-cv-04129-CW (9th Cir. 2016).

[326] A 5-day jury trial has been scheduled for September 2018. *See* Jennifer K. Wagner, *Keeping an Eye on "Perceived Disability" Litigation in California: Chadam v. Palo Alto Unified School District*, GENOMICS L. REPORT (May 2, 2017), https://www.genomicslawreport.com/index.php/2017/05/02/keeping-an-eye-on-perceived-disability-litigation-in-california-chadam-v-palo-alto-unified-school-district.

[327] *See* 42 U.S.C. §§ 12111(8), 12112(a)-(b).

[328] *See id*. §§ 12112(d)(1)-(2), 12112(d)(4).

[329] *See id*. § 12112(d)(3). The ADA's regulation of employer medical examinations and inquiries based on stage of employment are described in Mark. A. Rothstein, *Innovations of the Americans with Disabilities Act: Confronting Disability Discrimination in Employment*, 313 J. AM. MED. ASS'N 2221 (2015).

[330] *See* EEOC, *Americans with Disabilities Act of 1990 (ADA) Charges*, EEOC.GOV, https://www.eeoc.gov/eeoc/statistics/enforcement/ada-charges.cfm (last visited Feb. 2, 2018).

[331] *See* 42 U.S.C. § 2000ff-8(a)(1) (GINA employment provisions); 42 U.S.C. § 12201(b) (ADA).

hemoglobin C trait.[332] States like New Jersey have expanded this list to also include thalassemia trait, Tay-Sachs trait, and cystic fibrosis trait.[333]

Most states, however, have enacted general laws that prohibit employment and/or insurance discrimination based upon genetic test results or "genetic status."[334] According to NHGRI, 35 states and the District of Columbia have enacted statutes that limit unwanted access to and/or discriminatory use of genetic information in employment contexts, and 48 states and the District of Columbia have enacted similar statutes limiting these activities in health insurance contexts.[335] Moreover, 24 states have passed laws regulating genetic discrimination by life, disability, or long-term care insurers.[336] In 2011, California passed the most comprehensive anti-discrimination statute to date, the California Genetic Information Nondiscrimination Act (CalGINA), which prohibits genetic discrimination in emergency medical services, housing, mortgage lending, and state-funded programs, including public education.[337]

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[332] *See* Karen Rothenberg et al., *Genetic Information and the Workplace: Legislative Approaches and Policy Challenges*, 275 SCIENCE 1755, 1755 (1997) (citing N.C. GEN. STAT. ANN. § 95-28.1 (West 2018)).
[333] *See* N.J. STAT. ANN. §§ 10:5-5(x), 10:5-12(a) (2017).
[334] *See, e.g.*, ARIZ. REV. STAT. ANN. § 41-1463(B)(3) (2017) (prohibiting employment discrimination against individuals based on the results of genetic tests received by employers); FL. STAT. ANN. § 627.4301(2)(a) (West 2017) (prohibiting health insurers from canceling, limiting, or denying coverage, or establishing differentials in premium rates, based solely on genetic information).
[335] *See* NHGRI, *Table of State Statutes Related to Genomics*. GENOME.GOV, https://www.genome.gov/27552194/table-of-state-statutes-related-to-genomics (last updated Oct. 11, 2017).
[336] *See id*.
[337] *See* California Genetic Information Nondiscrimination Act, 2011 Cal. Legis. Serv. ch. 261 (West 2011) (Senate Bill No. 559); *see also* Jennifer K. Wagner, *Genetic Discrimination Case Against School District is Appealed to Ninth Circuit*, GENOMICS L. REPORT (Feb. 2, 2016), https://www.genomicslawreport.com/index.php/2016/02/02/genetic-discrimination-case-against-school-district-is-appealed-to-ninth-circuit (explaining CalGINA's applicability to educational contexts).

D

The Return of Individual-Specific Research Results from Laboratories: Perspectives and Ethical Underpinnings[1]

INTRODUCTION

Over the past two decades one of the more challenging ethical questions in research has concerned what obligations investigators have, if any, to share information with those who serve as research subjects. Should they share aggregate results once the study is complete? If so, should this occur pre- or post-publication? Should they share incidental findings that, while not part of the study's objectives, could carry important health implications for an individual subject? If so, how important, how well verified, and how actionable must such incidental findings be to warrant the extra effort of (re)contacting that particular subject? And what about individual-specific results? If those should be shared, are there limits, or must all person-specific data be individually shared? And should it be shared incrementally as it is gathered, or only upon completion of the study?

In addressing such questions, a critical issue concerns the theoretical ethical basis on which the answers are determined. An assertion that "Of course we must (or must not) share X" is vacuous if not supported by a persuasive "because." In recognition of that, a variety of theories have emerged. As briefly described below, some are grounded in the relationship between investigators and their research subjects and propose varying obligations on that basis. Others look to more basic concepts such as the rule of rescue, the duty to warn, or a "common humanity" duty to be helpful.

[1] A white paper commissioned by the National Academies of Sciences, Engineering, and Medicine's Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories, written by Haavi Morreim, J.D., Ph.D., University of Tennessee.

Unfortunately, as this paper will argue, these theories largely turn out to be little more than collections of intuitions, flat assertions, and thinly supported inferences. Nevertheless, that does not mean that we can only shrug helplessly. As explained by Jonsen and Toulmin (1988) many years ago, we need not always agree on our theories in order to reach reasonable consensus regarding what to do in a given situation.

As we proceed, a few caveats can be noted. First, a definition or two. An *incidental finding* (IF) is commonly defined as a "finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" (Wolf et al., 2012, p. 364). An *individual research result* (IRR) is a "finding concerning an individual contributor that has potential health or reproductive importance and is discovered in the course of conducting research and is not beyond the aims of the study" (Wolf et al., 2012, p. 364). Although the current NAS project focuses mainly on the return of individual results, this paper encompasses the entire range because theories about ethical underpinnings are essentially the same across the board. That is, the focus here is on return of results (RoR) generally.

A second caveat is that for any proposed theory to tell us how we should manage the returns of research results, numerous practical questions then arise concerning how best to craft an adequate consent process up front, how much funding should be built into research projects to cover the costs of (re)identifying and (re)contacting subjects, whether and in what ways an apparently important finding should be verified before sharing, how best to share news that the person may find difficult to hear, etc. These issues, though important, are not the focus of this paper.

Third, although this paper refers to research subjects and questions about whether and when their individual research results or incidental findings should be returned to them, technically such persons may not be research subjects at all. Once one's information—e.g., genetic information stored in a biobank—has been de-identified, the use to which that information is put is no longer defined as research, and the person who contributed it is no longer deemed by the Common Rule to be a research subject (Richardson and Cho, 2012; Wolf, 2013; Wolf et al., 2012). Nevertheless, economy of language suggests that we refer here to "investigators" and research "subjects" or "participants."

Fourth, the focus here is limited to a narrow, fundamental question: When, if ever, is returning results, whether IFs or IRRs, morally imperative for all human subjects research, solely by virtue of the fact that it is research and it involves human beings—and if so, why would such returns be morally required?

Note that discussing whether RoR is morally imperative is not equivalent to asking whether it is ever permissible, perhaps even desirable, to share results. Surely there are very good reasons to support sharing. Many projects move forward far better when participants are active as partners. For some particularly

devastating diseases, people banding together in a mode of "entrepreneurial philanthropy" may require that, as a condition of receiving funding and other assistance from the group, researchers must agree to share whatever they learn with the scientific community as a whole and individually with participants as well. Building on each other's work can then promote progress more quickly than if investigators operate in secretive separate silos, desperately competing to see who publishes first. Similar utilitarian considerations support building RoR into other kinds of research. It may, for instance, be difficult to recruit enough people to participate in a research effort unless they are promised that they will learn what the scientists ultimately learn, perhaps including their own personal results. In such cases RoR happens not because of any global moral imperative, but via express decisions to incorporate RoR into the protocol. In essence, returning results becomes a kind of contractual right. That said, this paper explores only the narrower questions whether and why RoR might be imperative in any human subjects research.

Finally, an important regulatory issue could upend even the most thoughtful discussion. Its resolution must be regulatory, not philosophical, hence the issue will be only briefly noted here. According to the Secretary's Advisory Committee on Human Research Protections (SACHRP, a unit of the Department of Health and Human Services), a conflict has emerged between regulations pursuant to the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and mandates rooted in the Clinical Laboratory Improvement Amendments (CLIA) of 1988 mandates (OHRP, 2015). On one hand, HIPAA can effectively preempt questions about whether to return individual research results because it requires that individuals gain access, upon request, to any records generated by a HIPAA-covered laboratory. The adverse implications for single- or double-blinded research are obvious. At the same time, CLIA prohibits returning results from non-CLIA-certified laboratories—which are used in many research projects. Thus, a non-CLIA lab existing within a HIPAA-covered entity is in an impossible predicament: it both must return, and must not return, individual results. Thus noting this potential regulatory snag, we turn to various proposed ethical underpinnings that would require RoR.

EVOLVING CONSENSUS PERSPECTIVES

We begin by recalling that sometimes it is possible to reach a consensus even without agreeing on its moral basis. A number of working groups have produced powerful consensus documents over the years. Among the first was the National Bioethics Advisory Commission (NBAC) in 1999 (NBAC, 1999; see also Wolf et al., 2012). NBAC recommended returning only those genetic or genomic research findings (whether IFs or IRRs) that are scientifically valid and confirmed and which have significant health implications and a readily available treatment. Similarly, a 2001 paper sponsored by the Centers for Disease Control and Prevention

proposed that IRRs in population-based research should only be returned when they are valid and when a proven intervention is available for reducing risk (Beskow et al., 2001; see also Wolf et al., 2012).

In 2006 a working group for the National Heart, Lung, and Blood Institute (NHLBI) produced a position paper holding that genetic results should be returned "when the associated risk for the disease is significant; the disease has important health implications such as premature death or substantial morbidity or has significant reproductive implications; and proven therapeutic or preventive interventions are available" (Bookman et al., 2006, p. 1033; also see discussion in Jarvik et al., 2014). And in 2008 a symposium sponsored by the National Institutes of Health (NIH)/National Human Genome Research Institute published a recommendations regarding IFs, distinguishing between "should return" (strong net benefit), "may return" (possible net benefit), and "should not return" (unlikely net benefit), with recommendations in each category that were dependent on the degree of analytic and clinical validity and on the likelihood that reporting could actually make an important health difference in the person's life (Wolf et al., 2008).

In 2010 a follow-up NHLBI group offered updated guidelines, suggesting that genetic research should be returned to study participants if the information has important health implications that are valid, actionable (with established therapeutic or preventive interventions available), and consented to by the participant. This group likewise distinguished among "should return," "may return," and "should not return" (Fabsitz et al., 2010; see also Wolf et al., 2012).

A 2-year NIH project focused on biobanks and archived datasets, evaluating responsibilities to return results, whether they were IFs or IRRs. In 2012 the members of that project offered the CARR approach: "(1) clarify the criteria for evaluating findings and the roster of returnable findings, (2) analyze a particular finding in relation to this, (3) reidentify the individual contributor, and (4) recontact the contributor to offer the finding" (Wolf et al., 2012).

A year later the American College of Medical Genetics and Genomics (ACMG) recommended that all clinical laboratories that conduct genetic sequencing should seek out and report pathogenic mutations for 56 specified genes (Green et al., 2013; Jarvik et al., 2014; McGuire et al., 2013). Importantly, the group believed that this information should be provided regardless of the patient's preferences. "[I]n selecting a minimal list that is weighted toward conditions where prevalence may be high and intervention may be possible, we felt that clinicians and laboratory personnel have a fiduciary duty to prevent harm by warning patients and their families about certain incidental findings and that this principle supersedes concerns about autonomy" (Green et al., 2013, p. 6).[2]

[2] With this recommendation in mind the Working Group emphasized the importance of talking with patients in advance about the possibility of uncovering certain kinds of important genetic findings.

Meanwhile, in 2014 the Clinical Sequencing Exploratory Research Consortium and the Electronic Medical Records and Genomics Network—multisite research programs—offered a consensus statement regarding practical strategies for when to return genomic results to research participants (Jarvik et al., 2014). Their principles included

- research differs significantly from clinical care, hence standards of disclosure differ;
- researchers have no duty to use limited funds affirmatively to hunt for actionable genomic findings;
- analytically and clinically valid information should, if actionable and important, be returned to research participants; and
- participants have a right to refuse such information.

Across the board, certain themes are common. The finding, whether an IF or IRR, must be analytically and clinically valid. Speculative possibilities do not warrant return. The finding must be important to the person's health, although there is not universal agreement about whether results implicating reproductive decisions should be returned (Fabsitz et al., 2010; see also Wolf, 2013). And the results should be actionable, meaning that there must be some sort of meaningful intervention that can prevent or at least ameliorate the course that would likely occur without the information and intervention.

Fairly broad agreement about what to do, then, appears possible. The reasons why we might embrace such conclusions, however, are open to far greater dispute.

PROFFERED BASES OF INVESTIGATORS' OBLIGATIONS

A. Bases with Little Support

Two potential justifications for requiring researchers to share IFs and IRRs have little support. First, although empirically it seems fairly well established that many people would like to receive such results, the bare fact that that desire exists does not, of itself, mean that investigators must *ipso facto* comply. The reasons are numerous. Returning results can be costly, from the process to verify whether an apparent result is clinically valid to the challenges in re-identifying someone whose data has been anonymized and the difficulties of locating someone whose contact information may have changed. Moreover, even if someone has said "I want all the information," such a broad statement does not necessarily tell us what the person's more nuanced preferences would be, under more specific circumstances (Beskow and Burke, 2010).

Second, the goals of research are very different from those of clinical medicine. Although investigators have obligations to protect research subjects from harm, those obligations stem from a very different relationship. Unlike the case

for a clinical physician–patient relationship, there is very little enthusiasm for the notion that investigators could be deemed fiduciaries of subjects (Clayton and McGuire, 2012; Miller et al., 2008; Morreim, 2005; Richardson and Belsky, 2004; Wolf, 2012). Whereas a physician's loyalty and primary obligation are to promote the patient's best interests, as in classic fiduciary relationships, the investigator's primary allegiance is necessarily pinned on something else—namely, on the science: high-quality methods, data and inferences.

> [T]he physician owes the patient a robust duty of clinical care. The physician's goal is to serve the patient's interests. A great deal follows from this, including informational obligations to disclose to the patient the diagnosis, treatment options, and other information material to treatment decisions. However, on the research side, the researcher's core goal is to seek generalizable knowledge for the benefit of the many. The researcher owes a much thinner duty of clinical care, focused on averting and addressing research-caused harm. (Wolf, 2013, p. 561)

B. Investigator–Subject Relationship

More commonly, ethical analyses of investigators' obligations to return IFs and IRRs have relied on particular conceptions of the investigator–subject relationship, from which specific ethical obligations are then said to flow. Several such theories have emerged, and we begin with the one most commonly described: partial entrustment. Critical evaluation of this and the other theories is reserved for Part IV.

1. Partial Entrustment

The theory of "partial entrustment," articulated by Richardson and colleagues (Richardson, 2008; Richardson and Belsky, 2004; Richardson and Cho, 2012; Richardson et al., 2017), proposes that "participants permit researchers access to their private data, specimens, and bodies, access that researchers otherwise would not have. This grant of access represents an act of partial entrustment ('partial' because participants are not fully entrusting their medical welfare to the researcher, as they would to a clinician)" (Wolf, 2013, p. 561). Investigators therefore shoulder certain duties of ancillary care—not clinicians' full duties of care, but not the "no duty of care" that we attribute to pure scientists (Wolf, 2013, p. 561).

"The model's core argument is this: Having gotten the participants to waive their rights against such access to private aspects of their bodies, the researchers obtain special responsibilities to look after the fundamental values that those rights normally protect" (Richardson and Cho, 2012, p. 470). That core argument stems from two basic realities: participants' vulnerability and investigators' discretion (Richardson and Belsky, 2004). Participants authorize the researcher to

> employ significant personal judgment in deciding how to act on the behalf of something the beneficiary cares about," so that "how the entrusted person chooses to exercise this discretion may considerably affect the beneficiary's well-being. . . . They allow researchers "to collect confidential medical information about them; to touch, poke, or cut them; to collect bodily samples from them; or to undertake medical procedures on them. In addition, they may agree to give up some of their normal control over their own health, as happens if they agree to participate in blinded studies or in psychiatric drug trials involving washout phases. (Richardson and Belsky, 2004, pp. 27–28)

Such "broad discretionary control over someone's wellbeing" also means the investigator is forbidden conflicting loyalties, hence "will count as trustees and take on a trustee's fiduciary obligation to decide matters solely on the basis of the beneficiary's best interests" (Richardson and Belsky, 2004, p. 28). The situation is analogous to the old legal concept of a bailment: someone who has accepted custody of another's property (or here, specified areas of one's body and privacy) has accepted an accompanying responsibility to take due care to protect that property, and must use one's superior position to discern how best to protect the vulnerable one (Richardon and Belsky, 2004).

The moral obligations arising from such entrustment are compassion, engagement, and gratitude. Compassion requires being attentive and responsive to the person's needs; engagement means engaging with research participants as whole people and not limiting the relationship just to the research interaction; and gratitude can require recognizing participants' other health needs (Richardson and Belsky, 2004). The resulting duties include returning any IFs or IRRs that could make a difference to the participant (Richardson and Cho, 2012)—so long as those results fall within the range of entrustment—and, beyond this, providing medical care for any health conditions that are discovered within the range of entrustment. All such duties, however, are said to be constrained by various factors that affect the strength of the participant's claim: the degree of the participant's vulnerability, dependence on the research team for receiving care, the intensity of the engagement between investigator and participant, the level of gratitude the investigators owe participants, and the costs to the research enterprise that would arise as investigators try to honor their obligations (Richardson and Cho, 2012).

2. Professional Relationship

Miller, Mello, and Joffe (2008) also offer a relationship-based rationale for investigators' obligations to return findings, but with broader roots and narrower obligations than the partial entrustment model. Rather than focusing only on the investigator–participant relationship, they reflect on professional relationships generally. A professional is

> a person who possesses specialized knowledge, whose work involves the frequent exercise of discretion, and who can claim membership in a learned profession with a regulatory structure and ethical code of conduct. The hallmarks of a professional relationship are that the professional is entrusted by another with access to private information and/or other domains of individual privacy, such as the home or the body. Professional relationships are often, though not always, characterized by a service role, and may, but do not necessarily, involve a fiduciary relationship. (Miller et al., 2008, p. 274)

Research subjects entrust their bodies and private information to investigators who are professionals with enhanced capacities to recognize the significance of such things as incidental findings, which in turn shapes the obligation to respond to them. Miller et al. (2008) provide the example of a plumber who enters someone's basement and sees signs of termites. His professional relationship with the homeowner and his superior ability to recognize this problem, it is suggested, create an obligation to disclose this finding. Similarly, a company physician performing a work physical on a prospective employee is not the fiduciary of that person. And neither is an insurance physician examining an injured person to determine how large the insurance payment should be. But in those cases, too, the professional's greater capacity to recognize a problem—e.g., an aortic aneurysm—combined with a privacy that has given the professional a privileged access to information, create an obligation for that professional to share important findings with the vulnerable person.[3]

Miller et al. (2008) distinguish their approach from Richardson's partial entrustment. Whereas Richardson focuses solely on the investigator–subject relationship, Miller et al. derive obligations for any professional relationship in which privileged access to private matters has been conveyed. More narrowly, however, Miller et al. do not demand that the investigator actually care for the health of the research participant (within the domain of entrustment). Conveying one's findings is one thing; taking on clinical care responsibilities is quite another. This is because clinical research does not aim to promote participants' health, hence participants are not entrusting their *health* to the investigator. Nevertheless, a professional relationship plus privileged access to private information provides sufficient basis, they argue, to warrant an obligation to return IFs. Although their writing does not specifically address IRRs, it is reasonable to suppose the same rationale would warrant returning IRRs, or at least those are valid, important, and

[3] "We argue that if (but not only if) A is in a professional relationship with B, such that A has consensual access to private information bearing on the welfare of B, then A has a limited obligation to intervene to help B based on incidental findings outside the scope of the contractual professional relationship. In contrast, when A and B are strangers, unless the conditions that trigger the rescue principle apply, the fact that A detects a potential problem pertaining to B does not give rise to an obligation to help" (Miller et al., 2008, p. 276).

actionable. Additionally, the distinction between whether the result was within the research aims or incidental to them would seem superfluous for Miller et al.

3. Additional Relationship-Focused Theories

Several other approaches are somewhat less far-reaching than the ones discussed so far, but nevertheless base an obligation to return IFs and IRRs on some aspect of the investigator–subject relationship. One such view deems the investigatory and the subject to be partners working toward a common goal. In this view, research participants are not simply disenfranchised providers of material; they are in some sense actively collaborating on the project and should be treated as such (Kohane et al., 2007; Partridge and Winer, 2002).

Another perspective suggests that the fundamental bioethical principle of "respect for persons" requires that investigators bear special obligations to treat their subjects in certain ways—for instance, to exhibit gratitude for the subjects' contributions. Shalowitz and Miller, for instance, maintain that respect for research participants requires, at minimum, that investigators should not coerce or deceive the participants and that they must obtain informed consent to honor participants' self-determination (Shalowitz and Miller, 2005). Accordingly, with respect to IFs and IRRs, "[i]t would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information about themselves derived from their participation in research" (Shalowitz and Miller, 2005, p. 738). Sharing IRRs respects self-determination, permitting subjects to use such information for their health care and lending special consideration for the information those subjects helped to generate. Indeed, investigators should not merely respond to requests for information sharing; with IRB oversight they should affirmatively invite such requests (Shalowitz and Miller, 2005). The obligation is not absolute, however, as IRRs could appropriately be withheld if their disclosure might compromise someone's safety (for instance, in cases of misattributed paternity).

Finally, Illes et al. (2006) extend the theme of respect for participants' autonomy and interests to encompass the need to recognize participants' generosity with appropriate reciprocity. Investigators can only proceed with their scientific mission if they receive subjects' contributions, and it is only right to recognize that in some concrete way. Here, reciprocity is said to require communicating those findings that may affect participants' health or, at the very least, to share aggregate findings (Clayton and McGuire, 2012; Ossorio, 2012).

C. Obligations Not Based on the Investigator–Subject Relationship

Several commentators suggest that we need not refer at all to the investigator–subject relationship in order to find an obligation to return certain IFs or IRRs. The duty to warn, for instance, comes from the age-old principle that if one

person sees that another is unwittingly about to enter a high danger that quite likely he or she would not voluntarily embrace, then the person seeing the danger has an obligation to warn the other. John Stuart Mill, in *On Liberty*, gives the famous bridge example: If a person sees that someone is unwittingly about to cross a bridge that is terribly unsafe, it may even be acceptable to "seize him and turn him back, without any real infringement of his liberty; for liberty consists in doing what one desires, and he does not desire to fall into the river" (Mill, 1859, p. 57).

In the research setting no "seizing" is contemplated, but only a duty to inform someone of a serious, validated, actionable hazard.[4] Indeed, as noted above, the ACMG concluded that investigators need not even obtain subjects' prior consent to be warned about serious incidental findings. Rather, subjects should be counseled, in advance, that if such IFs are found, they will be relayed.[5]

The rule of rescue is a somewhat broader, also very basic moral precept. Beskow and Burke (2010) emphasize that the "duty to rescue is based on the premise that, when confronted with a clear and immediate need, an individual who is in a position to help must take action to try to prevent serious harm when the cost or risk to self is minimal" (Beskow and Burke, 2010, p. 1). It applies mainly if not exclusively to rather dire situations (Miller et al., 2008). If an investigator discovers, e.g., that a research participant has a gene that carries a high risk of early-onset colorectal cancer in the absence of any family history for that disease, then conveying that information to that patient could be life-saving.

Rescuing is typically a more involved process than merely warning. The rescuer could incur cost or risk, himself, if the rescue is to be successful. Hence, ordinarily the rule of rescue is said to apply only when the burden on the rescuer is minimal (Beskow and Burke, 2010). "Although the duty to rescue is a legal concept, our intent is to propose an ethical underpinning for what participants have called basic 'human decency' when discussing researchers' obligations concerning genetic information" (Beskow and Burke, 2010, p. 2). These cases, it is suggested, will be "exceptionally rare" (Beskow and Burke, 2010, p. 2).

The duty to help, or to be helpful, is a still broader concept implying an obligation to produce positive benefit, not just to avoid a clear and imminent harm. The principle applies when we can be of great benefit to someone else, without significant sacrifice to ourselves (Miller et al., 2007). Ossorio, for instance,

[4] In the *Tarasoff* case, somewhat similarly, the California Supreme Court found that a mental health professional had a duty to warn a family about an imminent threat of grave danger posed by a patient. *Tarasoff v. Regents of the University of California*, 17 Cal. 3d 425, 551 P.2d 334, 131 Cal. Rptr. 14 (Cal. 1976).

[5] See Green et al. (2013): "The Working Group therefore recommended that whenever clinical sequencing is ordered, the ordering clinician should discuss with the patient the possibility of incidental findings, and that laboratories seek and report findings from the list described in the Table without reference to patient preferences. Patients have the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing." See also Wolf et al. (2008, p. 229), discussing duty to warn of foreseeable harm.

examines the duty to help as grounding a duty even for secondary researchers (those working with tissues or data gathered by others) to return certain kinds of findings, so long as doing so poses little or no risk or burden to the helper, and does not interfere with that person's legitimate aims (Ossorio, 2012). Ossorio cites philosophers Frances Kamm and Thomas Scanlon: "[I]f a person can be of great help to somebody else (i.e., save her a great deal of time, money, irritation) in pursuing an important life project, at essentially no cost/burden to the helper, it would be wrong not to help absent a compelling reason not to help" (p. 462).

Across the duty to warn, the rule of rescue, and the duty to help, the unifying theme seems to be common decency, or a shared sense of common humanity. There are some things we do for each other, simply because we are moral beings who can, do, and in some sense must think beyond our own selfish interests.

A related but somewhat distinctive approach, stemming partly from contractual elements of the investigator–subject relationship, is the concept of stewardship (Ossorio, 2012; Richardson and Cho, 2012). Someone who shares his time and information and even permits bodily invasion should legitimately be able to expect at the least that the terms on which he shared will be honored with due care: that a tissue specimen will not be wasted or lost; a biobank will store samples at proper temperatures; the analysis will not be so poorly done that it is useless; and in general, the promises made by those who asked for subjects' participation will be kept, and a fruitful research effort will be pursued.

CRITICAL ANALYSIS

If we are to conclude that investigators are morally required to return IFs or IRRs under certain circumstances, then we should be able to adduce fairly forceful reasoning to support that supposed obligation. "Well, isn't it just obvious?!" is not good enough. A flat assertion—a "Hey, presto!" move, as one of my professors in graduate school used to call it—is insufficient. Unfortunately, many of the theories discussed in Part III rely heavily on "Hey, presto."

Let us begin with Richardson et al.'s theory of partial entrustment. As noted above, it embraces several core moves:

(1) participants waive certain rights to privacy and bodily integrity, rendering themselves vulnerable;
(2) such waivers are defined and circumscribed by the informed consent;
(3) these waivers grant investigators discretion over the health of participants, within the identified range;
(4) hence, such waivers count as partially entrusting one's health to the researchers, within the identified range of waiver;
(5) therefore, investigators have obligations to care for participants' health, within the waiver and discretion; and

(6) the strength of those obligations can be adjusted by such factors as cost, degree of vulnerability, etc.

Virtually all of these moves are open to challenge, once we get past (1) and (2). Although research participants do waive certain rights and grant certain permissions as specified in the consent form, by no means does this grant researchers vast discretion over their health. In reality, most research protocols afford investigators very little discretion, because high-quality medical science commonly involves tight controls. Protocols are designed to control as many variables as possible, so that the results in the end can be attributed specifically to the factors under study. Thus, for instance, subjects in a Phase III trial of a new hypertension drug will commonly be limited to people who have only hypertension—not also diabetes, heart failure, cirrhosis, and cancer. The more variables are at play—the more complex the enrolled subjects' health—the less it will be possible to pin the results just on the new drug. So the protocol keeps the variables to a minimum.

In this sense, the more scientifically pristine (well controlled) the study, the less discretion the investigator actually has. He or she might perhaps have discretion to decide which laboratory personnel to hire, or perhaps which shipping company will carry specimens to an out-of-state laboratory. The investigator may or may not have the discretion to decide which laboratory equipment to use. After all, where the choice of laboratory equipment could affect results, especially in a multisite study, individual investigators may have no discretion at all to deviate from the protocol-specified laboratory equipment. As another example, a genetic study that simply seeks to list associations between certain genotypes and certain phenotypes may grant the investigator no discretion whatever over participants' health. It is one thing to have discretion over certain processes in the research, and another thing entirely to have discretion over someone's health. To move from the former to the latter is simply a non sequitur.

Even where investigators do have some discretion that can affect participants' health, that leeway will ordinarily be closely limited. For instance, an investigator may need to make a judgment call when it is not clear whether someone is eligible to enter a study. Perhaps the blood pressure fluctuates between being "high enough" and "not quite high enough." This, however, hardly amounts to direct discretion over that person's *health*. It simply addresses the question whether the person can enter this particular study and incur whatever potential risks or benefits the study carries. At a later stage, if an enrolled participant experiences problems related to the study, investigators typically have only two sorts of health-affecting discretion: whether to remove the person from the study entirely, or whether to avail oneself of protocol-permitted ancillary care. A drug study might, e.g., permit symptom-relieving medications for a cold, even while forbidding other medications during the course of the trial.

These limited forms of discretion hardly amount to vast control over someone's health, or even over the person's health within the scope of the trial. After

all, research avowedly does not seek to benefit any particular person. Rather, it seeks generalizable knowledge that is hoped to benefit future persons, even if by fortunate happenstance it also might benefit some of the current study subjects. And the investigator may have little control even over the aspects of health under study. A study that simply, e.g., adds a new seizure medication to one's usual regimen may leave ordinary care up to the participant's usual clinical physician, leaving the investigator with little if any discretion over the person's health, or even his seizure-related health.

In sum, the leap from "I let you look at my genes" to "You looked at my genes, so now you must take care of all my genetic illnesses" or even "Now you must tell me everything my genes say about my health—give me a freebie *23 & Me*!" simply does not logically follow. Hey presto.

The gap becomes even clearer when we look at other arenas of information sharing. Many people share remarkable amounts of highly private information to friends and to "friends" on social media or even to a stranger-seatmate on a subway. Such waivers of privacy convey no discretion to the other person, other than presumably the right to tell my friends all about "that crazy person I sat next to on the subway this morning." Moreover, my sharing intimate, excruciating details of my noxious, oozing skin disease hardly makes you responsible to care for my health. Even if we are friends. Or "friends."

Richardson and Belsky (2004) actually come close to acknowledging that their schema is built on little more than intuition. As they reject the polar opposites between "Investigators are responsible for every health need of their subjects" at one end and "Investigators are mere scientists with no obligations whatever" at the other, they recognize that these are "intuitive grounds for rejecting polar positions" (p. 26). In the end we are left with intuition posing as some sort of elaborate inference. Richardson and colleagues provide no particular reason for rejecting, as an alternative, Clayton and McGuire's option of simply stating, in the informed consent, "We will tell you nothing about what we find," perhaps reserving the option to share an IF or IRR under the most extraordinary circumstances (Clayton and McGuire, 2012).[6]

[6] As a side note it should be observed that Richardson and Belsky err when they claim that the investigator's relationship with the subject is essentially parallel to a bailment. First, there are many types of bailment relationships (gratuitous bailment, bailment for hire, bailment for mutual benefit, involuntary bailment, etc.; see *Black's Law Dictionary*: "bailment"). "A bailment relationship can be implied by law whenever the personal property of one person is acquired by another and held under circumstances in which principles of justice require the recipient to keep the property safely and return it to the owner." *Black's Law Dictionary*, citing 8A Am. Jur. 2d Bailment § 1 (1997). In the research setting, virtually never is it contemplated to return the original property, intact, to the owner. At most, some down-the-road product might, or might not, be returned. Importantly, as we consider what sort of "property" might be returned to a research participant, we need to recognize that bailments are ordinarily defined by contract, and that the specific type of bailment circumscribes the bailee's duties and discretion. A bailment in which I have entrusted/loaned my car to you for the evening would generally mean you must take reasonable care of it and return it to me at the end of the evening. You

We turn next to the "professional relationship" approach proposed by Miller et al. (2008). As we recall, their theory focuses on professional relationships and privileged access to private information.

> We argue that if (but not only if) A is in a professional relationship with B, such that A has consensual access to private information bearing on the welfare of B, then A has a limited obligation to intervene to help B based on incidental findings outside the scope of the contractual professional relationship. In contrast, when A and B are strangers, unless the conditions that trigger the rescue principle apply, the fact that A detects a potential problem pertaining to B does not give rise to an obligation to help. (p. 276)

Thus, if the plumber I hired to work on a problem down in my basement sees termites there, he is obligated to tell me.

The thesis seems to be overkill in several respects, as evidenced by the plumber example. The fact that the person has some sort of expertise does not imply that he or she is a "professional." And it is not clear on what basis a plumber would have any particular expertise regarding termites. Yet Miller et al. have placed a firm moral duty of disclosure on the poor plumber. Perhaps we can appreciate this overkill better by exploring a series of hypotheticals.

- An employee at a quickie oil change shop may know barely more than the customer, if that, about changing oil. And yet, because my car is on the hoist, he may see something (let's say, a worn brake line about to rupture) that I am unlikely to see, simply because I don't spend much time underneath my car. Actually none, if I can help it. Is the oil change guy suddenly to be deemed a professional? And is his look at the underside of my car somehow a "privileged" access? Likely not. It's just that not many people are likely to spend time underneath my car. That peek at the underbelly is not some sort of sacred conveyance or privilege. Rather, it's simply a matter of (un)likelihood: so few people are under my car that, if I'm to get any early warning at all about the leak or the worn hose, then the oil change guy pretty much has to be the source. The same goes for my dark, dank, dungeony, now also termite-infested basement—very few people (including me) will spend time there. So if the plumber says nothing about my termites, or if the oil guy doesn't comment on my about-to-rupture brake line, the consequences could be disastrous.
- Suppose a woman visits a luxury lingerie boutique, staffed by people who are trained to help customers find the best fit for their undergarments.

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do not become responsible for all its mechanical defects—or even the defects that crop up while you are driving it. And yet this is precisely what Richardson and Belsky seem to want: the entrustment to you somehow makes you responsible for the problems that emerge while you use it, at least if you're using my car for the agreed-on purpose. The analogy quickly falls apart and should best be abandoned.

The woman consults with a bra-fitter who sees a mole on the woman's skin, in a place usually covered by a bra. Because her aunt recently died of melanoma, the bra-fitter knows all too well that this mole is quite possibly a melanoma. Is "bra-fitter" a profession? The two women are not strangers (the woman shops here several times per year), and the bra-fitter has some specialized knowledge, so are they somehow in a "professional relationship"? Hardly. This is quite an ordinary relationship between a customer and a service person. The bra-fitter has "privileged access" only because the woman in this story is modest enough that she does not wear clothing that reveals cleavage. Otherwise the mole would be quite public. But in this case, if the bra-fitter does not say something, it is quite possible the melanoma may remain unrecognized for quite some time. As above, the reality seems to be more that, by happenstance, not many people are likely to see the problem and, equally by happenstance, the bra-fitter recognizes the mole's foreboding significance. One would hope that the fitter would mention something to the woman. If so, we need not resort to elaborate theories of professions and privilege. It just seems like common human decency.

- Now suppose the woman's likely-melanoma mole is located instead on her forearm. She is on a plane sitting next to someone who happens to be a dermatologist. They exchange the usual seatmate pleasantries. As the woman settles in and pushes her sweater sleeves up toward her elbows, the mole is revealed. It is unmistakable to any dermatologist even though, to the less-trained eye, it probably just looks unattractive. As luck would have it, her seatmate is a dermatologist from Florida, where melanoma is quite common. Here, simply being seatmates is hardly a "professional relationship" even though the dermatologist is a professional. And there is no "privileged access" because the mole is exposed for anyone to see. And yet we may well wish the dermatologist would suggest that she have it checked out.

Once again, it is not highly likely that anyone else will notice the problem in a timely way, especially if it is winter and the woman normally wears her sleeves at full length. But again, circumstances that actually are just a matter of happenstance could create something of an obligation. If they do, that obligation stems from the fact that the situation could be serious and, for various reasons, no one else is likely to warn in time. We need not strain to posit a "professional relationship"—an oil change guy, a bra-fitter, or even a plumber—and we need not insist on "privileged access" to recognize that any of these people might be in a situation where (1) they happen to recognize something serious and (2) it is not likely anyone else will see the problem in time to avoid an adverse outcome. Conversely, if a problem is highly visible and widely recognizable as being serious,

then any responsibility to warn becomes more widely diffused. In that setting we are hard-pressed to insist that any specific person bears the moral obligation.

In sum, in the research setting the main reason the investigator may have a specific, personal duty to return an IF or IRR need not rely on any sort of professional relationship or privileged access. It is enough that (1) the investigator is among the few who will actually see the relevant data and (2) the investigator may be the only one who will recognize the significance of such data for the individual research subject. These two factors are sufficient to trigger a duty to convey the information. Occam's razor: there is no need for high-flying philosophical pirouettes to accomplish something very basic.

We turn next to Shalowitz and Miller (2005), who focus on respect for participants. Since "[i]t would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information about themselves derived from their participation in research" they wrote (p. 738), investigators must return IFs and IRRs.

The problem with this approach is that it begs the question. Logically, a question is begged when the arguer presupposes as true the very thing he or she is trying to prove. Here, the authors build their conclusion—"Investigators should share IFs and IRRs"—into the very definition of "respect." However, it is not clear why respect must necessarily be exhibited in this particularly rich way. One could alternatively respect subjects and their autonomy by informing them, up front: "If you sign up for this trial we will not return any results to you [barring exceptional circumstances]." Or one could say "We will only share aggregate results at the conclusion of the trial." In that way, those who wanted IRRs could simply decline to participate. Or one could pay subjects financially for their time and trouble, as is often done for normal volunteers in Phase I trials of new pharmaceuticals.

In some cases, subjects enroll in research for purely altruistic reasons. Jesse Gelsinger, for instance, was said to have enrolled in a gene transfer study solely to help infants who had far more devastating cases of ornithene transcarbamylase deficiency than his own (Wilson, 2009). Similarly, those who supplied tissue for research on Canavan disease (a fatal, incurable genetic disorder most commonly seen in Ashkenazi Jewish families) had hoped that their donations would be used to further scientific understanding of the disease and to develop ways of testing for it prenatally.[7] They had expected that

> any carrier and prenatal testing developed in connection with the research for which they were providing essential support would be provided on an affordable and accessible basis, and that [the investigator's] research would remain in the public domain to promote the discovery of more effective prevention techniques and treatments and, eventually, to effectuate a cure for Canavan disease.

[7] *Greenberg v. Miami Children's Hosp Research Institute, Inc.*, 208 F.Supp.2d 918 (2002).

Their expectation was based on similar efforts to address Tay-Sachs disease.[8] Participants were bitterly disappointed when the investigators later applied for a patent on the gene and its application, which would mean significantly restricting access to the fruits of their contributions. In this instance "respect" for participants meant not that they would receive any sort of individual-specific return of information, but rather that their efforts would help scientists detect and treat this deadly disease in a way that would make breakthroughs widely accessible to everyone who was suffering.

More broadly, good stewardship of resources may be an important way to exhibit respect for those who provide the resources (Ossorio, 2012, p. 465). If I donate money to the Humane Society my expectation is not that they will show gratitude by spending lots of my money thanking me, but rather by helping as many animals as possible. A thank-you note, or even an automatic email thanks, may be appropriate and wise. But exercising good stewardship may be the best way to respect my donation.

All this is not to say that any of these alternatives is *the* "correct" way to exhibit respect. To the contrary, the upshot is simply that one cannot credibly insist that returning IRRs and IFs is the one and only, or even a required, way of exhibiting respect (see also Clayton and McGuire, 2012, p. 475).

Our response must be the same regarding appeals to reciprocity as the justification for a mandate to return IFs and IRRs (Illes et al., 2006, p. 783). Reciprocity is essentially an expression of gratitude and respect. Even if gratitude is appropriate in return for someone's contribution to research, that gratitude might have many different forms. In reality, the contribution of any one individual is often miniscule relative to the broader research project (Ossorio, 2012, p. 465), even if in some other studies the contribution is substantial and ongoing. And even if the person is making a significant sacrifice, there are other ways to recognize it, from paying money, to returning aggregate results, to exercising the utmost good stewardship. To assert that the reason we must return IRRs and IFs is because we must exhibit gratitude, and then to define gratitude exclusively as requiring return of IRRs and IFs begs the question.

CONCLUSION

As noted at the outset, and as explained by Jonsen and Toulmin (1988) many years ago, we need not always agree on our theories, to reach reasonable consensus regarding what to do in a given situation. Here, quite a broad consensus has emerged suggesting that investigators should return IFs and IRRs when they are valid, clinically important, and actionable. Perhaps one day we might identify a clear moral underpinning—a universally agreed-on, clear and helpful moral keystone—that can tell us, in more controversial situations, just what to do.

[8] *Greenberg v. Miami Children's Hosp Research Institute, Inc.*, 208 F.Supp.2d 918, 921 (2002).

Unfortunately, that appears unlikely. The more detailed and prescriptive the theories we have seen, the more they seem to rely on leaps of faith, non sequiturs and question-begging. Essentially they each are products of diverging moral intuitions. Even the ostensibly simple Rule of Rescue can easily take us beyond a supportable consensus. Active rescue, after all, does not merely warn someone of a danger. It involves actively delivering help—here, presumably some form of clinical care to address the medical peril uncovered in the IF or IRR. Admittedly, the rule of rescue requires such assistance only if the risk and burden to oneself is minimal. But once that threshold into active assistance is crossed, we must then consider how great that "minimal" burden is, ushering us into controversies analogous to those discussed above.

Accordingly, it appears that once we venture beyond a duty to warn and the "common human decency" concept on which it is based, we risk several problems. We can end up reinforcing the therapeutic misconception (Clayton and McGuire, 2012); burdening researchers with heavy costs (Illes et al., 2006; Ossorio, 2012; Partridge and Winer, 2002; Shalowitz and Miller, 2005; Wolf et al., 2006), potentially in the form of asking researchers to make up for lack of access to health care elsewhere in the system; and potentially diverting legitimate research into some sort of chimeric entity that does not distinguish well between research and clinical care (Clayton and McGuire, 2012; Miller et al., 2008). The upshot is not hopeless, it is simply a recognition that the more complex the situation, the less likely we will achieve any solid theoretical basis on which to base a strong consensus. And that should come as no surprise.

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E

Biographical Sketches of Committee Members, Consultants, and Staff

COMMITTEE

Jeffrey R. Botkin, M.D., M.P.H. (*Chair*) is a professor of pediatrics at The University of Utah and an adjunct professor of human genetics. He is the chief of the Division of Medical Ethics and Humanities in the Department of Internal Medicine. He obtained his B.A. from Princeton University, M.D. from the University of Pittsburgh, and M.P.H. from the Johns Hopkins Bloomberg School of Public Health. Dr. Botkin is the associate vice president for research integrity at The University of Utah with oversight responsibilities for the institutional review board, conflict of interest, responsible conduct of research, biosafety, and research ethics education. His research and publications are focused on the ethical, legal, and social implications of genetic technology, with a particular emphasis on research ethics, newborn screening, and prenatal diagnosis. Dr. Botkin was formerly the chair of the Secretary's Advisory Committee on Human Research Protections at the Department of Health and Human Services and also of the Committee on Bioethics for the American Academy of Pediatrics. He served on the National Academies' Committee on Ethical and Social Policy Aspects of Mitochondrial Replacement Therapy and is a member of the National Advisory Council for the National Human Genome Research Institute. Dr. Botkin chairs the National Institutes of Health's Embryonic Stem Cell Working Group and is a member of the Food and Drug Administration's Pediatric Ethics Advisory Committee. Dr. Botkin is an elected fellow of the Hastings Center.

Paul S. Appelbaum, M.D., is the Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law and the director of the Center for Law, Ethics, and Psychiatry

in the Department of Psychiatry, College of Physicians and Surgeons of Columbia University; he is also a research psychiatrist at the New York State Psychiatric Institute; and an affiliated faculty member at Columbia Law School. He directs Columbia's Center for Research on Ethical, Legal, and Social Implications of Psychiatric, Neurologic, and Behavioral Genetics, and heads the Clinical Research Ethics Core for Columbia's Clinical and Translational Science Award program. Dr. Appelbaum is the author of many articles and books on law and ethics in clinical practice. His current research focuses on the implications of new genetic technologies. Dr. Appelbaum is past president of the American Psychiatric Association (APA) and of the American Academy of Psychiatry and the Law and has twice served as the chair of the Council on Psychiatry and Law and of the Committee on Judicial Action for APA. Dr. Appelbaum is currently the chair of the *Diagnostic and Statistical Manual of Mental Disorders* Steering Committee for APA, and immediate past chair of the Standing Committee on Ethics of the World Psychiatric Association. He has received the Isaac Ray Award of the American Psychiatric Association for "outstanding contributions to forensic psychiatry and the psychiatric aspects of jurisprudence," was the Fritz Redlich Fellow at the Center for Advanced Study in the Behavioral Sciences, and has been elected to the National Academy of Medicine.

Suzanne Bakken, R.N., Ph.D., FAAN, FACMI, is the Alumni Professor of Nursing and a professor of biomedical informatics at Columbia University, and she is the co-chair of the health analytics center of the Data Science Institute. Following doctoral study in nursing at the University of California, San Francisco, she completed a National Library of Medicine postdoctoral fellowship in medical informatics at Stanford University. The goal of Dr. Bakken's program of research is to promote health and reduce health disparities in underserved populations through the application of innovative informatics and data science methods. A major focus of her current grant portfolio is the visualization of health care data for community members, patients, clinicians, and community-based organizations. Dr. Bakken currently directs the Precision in Symptom Self-Management Center and the Reducing Health Disparities Through Informatics pre-doctoral and postdoctoral training program, both funded by the National Institute of Nursing Research. She also served as the principal investigator of the Agency for Healthcare Research and Quality–funded Washington Heights Inwood Informatics Infrastructure for Comparative Effectiveness Research (WICER) and its follow-up study, WICER 4 U, which is focused on promoting the use of WICER infrastructure through stakeholder engagement, including the return of individual research results. She has also received funding from the National Cancer Institute, National Library of Medicine, National Institute of Mental Health, and the Health Resources and Services Administration. Dr. Bakken has published more than 250 peer-reviewed papers and in January 2019 she will assume the role of the editor-in-chief of the *Journal of the American Medical Informatics Association*. In 2010

she received the Pathfinder Award from the Friends of the National Institute of Nursing Research and she was inducted into the International Nurse Researcher Hall of Fame in 2018. In 2015–2016 Dr. Bakken served as the American Academy of Nursing, the American Nurses Association, and the American Nurses Foundation Distinguished Nurse Scholar-in-Residence at the National Academy of Medicine and is a member of the National Academies' Roundtable on Health Literacy. She is a fellow of the New York Academy of Medicine, American Academy of Nursing, American College of Medical Informatics, International Academy of Health Sciences Informatics, and a member of the National Academy of Medicine.

Chester Brown, M.D., Ph.D., is the St. Jude Chair of Excellence in Genetics and a professor in and the division chief of genetics at the University of Tennessee Health Science Center, Le Bonheur Children's Hospital and St. Jude Children's Research Hospital. He was recruited to his current position to help develop precision medicine initiatives in Memphis, Tennessee, including the development of DNA and tissue repositories and large-scale omics technologies to aid in population-based genomic research, considering also the ethical, legal, and social implications of such efforts in underserved communities. His clinical interests include a variety of rare genetic syndromes in children and adults with a research emphasis on rare genetic disorders that have severe, early-onset obesity as a feature. He completed his undergraduate degree at Howard University, followed by M.D./Ph.D. training at the University of Cincinnati College of Medicine. His postdoctoral and subsequent faculty roles were in pediatrics and medical genetics at Baylor College of Medicine. He has more than 20 years of clinical experience with medical genetics patients representing a broad spectrum of conditions. He is an active member of the Society for Pediatric Research and a member of a National Institutes of Health (NIH) study section, and he recently completed service as a committee member for the National Academies of Sciences, Engineering, and Medicine to develop a framework to inform decision making related to genetic testing. He also directs a basic science research laboratory supported by grants from the National Institute of Child Health and Human Development, the National Institute of Diabetes and Digestive and Kidney Diseases, industry, and a variety of foundations. He works collaboratively to better understand the host genomic factors that contribute to HIV and tuberculosis progression in African children, funded by the NIH/National Institute of Allergy and Infectious Diseases H3Africa initiative. He has continued clinical practice throughout his career and has never lost sight of the fundamental importance of careful observation and listening carefully to patients.

Wylie Burke, M.D., Ph.D., is a professor emeritus and former chair of the Department of Bioethics and Humanities at the University of Washington. Her work focuses on the ethical and policy implications of genetic information in research, public health, and clinical care. She founded the University of Washington Center for Genomics and Healthcare Equality, a National Human Genome Research

Institute–funded center of excellence in ethical, legal, and social implications research addressing the implications of genomic research for underserved communities, and she co-directs the Northwest Alaska Pharmacogenomics Research Network, a research partnership involving universities and tribal communities in Alaska, Montana, and Washington State. Dr. Burke received a Ph.D. in genetics and an M.D. from the University of Washington and she completed internal medicine residency training at the University of Washington, where she was also a medical genetics fellow. She is a member of the National Academy of Medicine and past president of the American Society of Human Genetics.

Richard Fabsitz, Ph.D., joined the Department of Global and Community Health as adjunct faculty after a long-term career with NIH. His NIH career began with the National Institute of Mental Health but was primarily spent at the National Heart, Lung, and Blood Institute where he last served in the position of deputy chief of the Epidemiology Branch. His professional experience is primarily in research team management, program administration, and the conduct of cardiovascular epidemiology research in large population-based studies focused on longitudinal cohort studies, Native Americans, families, twins, and genetics. Additional research interests include the use of metrics in the management of scientific research, methods to promote collaboration and innovation in research projects, research translation, and the ethical and practical issues surrounding the return of genetic research results to study participants. He has authored or co-authored a wide range of journal articles related to cardiovascular epidemiology and the above research interests.

Vanessa Northington Gamble, M.D., Ph.D., a physician and medical historian, is the University Professor of Medical Humanities and a professor of health policy and American studies at The George Washington University (GWU). Before coming to GWU, she was the director of Tuskegee University's National Center for Bioethics and Health Care. She is an internationally recognized expert on the history of race and American medicine, racial and ethnic inequities in health and health care, and bioethics. Dr. Gamble chaired the committee that took the lead role in the successful campaign to obtain an apology in 1997 from President Clinton for the infamous United States Public Health Syphilis Study at Tuskegee. She has been appointed to numerous boards and committees including the National Advisory Council of the Agency for Healthcare Research and Quality, the ethics subcommittee of the Advisory Committee to the director of the Centers for Disease Control and Prevention, the National Advisory Council for Human Genome Research, Ibis Reproductive Health, National Caucus and Center on Black Aged, Inc., and Hampshire College. Dr. Gamble is a member of the National Academy of Medicine and a fellow of the Hastings Center.

Gregg Gonsalves, Ph.D., is an assistant professor of epidemiology of microbial diseases at the Yale School of Public Health. His research focuses on the use of quantitative models for improving the response to epidemic diseases. Dr. Gonsalves is also an associate professor (adjunct) and research scholar in law at Yale Law School, a co-director of the Yale Collaboration for Research Integrity and Transparency, and a leading HIV/AIDS activist. For more than 20 years, he worked on HIV/AIDS and other global health issues with several organizations, including the AIDS Coalition to Unleash Power, the Treatment Action Group, Gay Men's Health Crisis, and the AIDS and Rights Alliance for Southern Africa. He was also a fellow at the Open Society Foundations and in the Department of Global Health and Social Medicine at Harvard Medical School from 2011 to 2012. He is a 2011 graduate of Yale College and received his Ph.D. from the Yale Graduate School of Arts and Sciences/School of Public Health in 2017.

Rhonda Kost, M.D., is the director of the Clinical Research Support Office, co-director of the Community Engaged Research Core, and an associate professor of clinical investigation in The Rockefeller University Center for Clinical Translational Science. She is interested in developing models and evidence-based measures of the research process that reflect the values of the stakeholders. Her research has included the areas of informed consent, participant experience, and the development of a academia–community research partnership. She led a multicenter team that developed a suite of validated participant-centered research participant perception surveys now adopted by academic centers to drive improvements in the participant experience. She recently co-authored a guide for investigators along with participant materials to help the parties align their informed consent discussion of research involving next-generation sequencing with a potential return of results. She also developed a collaborative Community-Engaged Research Navigation model to foster sustainable research partnerships between basic scientists and affected communities. She is the Rockefeller principal investigator on several federally funded collaborative projects to study innovations in participant recruitment. Dr. Kost has served on numerous NIH/Clinical and Translational Science Awards Program national committees, chairing the Regulatory Support Key Function Committee as well as its recruitment and research advocacy taskforces. At Rockefeller, she chairs the Action Committee for Community Engaged Research and is vice-chair of the institutional review board. Dr. Kost received her M.D. from Harvard, completed internal medicine residency training at Yale and an infectious diseases subspecialty training at Case Western Reserve, and served as a medical staff fellow at NIH's National Institute of Allergy and Infectious Diseases. Prior to joining Rockefeller, she designed and conducted clinical trials at the Aaron Diamond AIDS Research Center.

Debra G. B. Leonard, M.D., Ph.D., received her M.D. and Ph.D. from the New York University School of Medicine and is currently a professor in and the chair

of the Department of Pathology and Laboratory Medicine at the Robert Larner, M.D. College of Medicine at the University of Vermont and at the University of Vermont Health Network. She was previously the vice chair for laboratory medicine in the Department of Pathology and Laboratory Medicine at Weill Cornell Medical College and the director of the clinical laboratories for New York-Presbyterian Hospital-Weill Cornell, where she also served as the director of the Pathology Residency Training Program. Dr. Leonard is a nationally recognized expert in molecular pathology. She has served on several national committees that develop policy for the use of genetic and genomic technologies and information, including the Secretary's Advisory Committee on Genetics, Health and Society that advised the Secretary of Health and Human Services, and the Roundtable on Genomics and Precision Health of the National Academies of Sciences, Engineering, and Medicine. Dr. Leonard is the editor of two molecular pathology textbooks and has spoken widely on various molecular pathology test services, the future of molecular pathology, the impact of gene patents on molecular pathology practice, and the transition to genomics as a tool for population health management.

Amy McGuire, J.D., Ph.D., is the Leon Jaworski Professor of Biomedical Ethics and the director of the Center for Medical Ethics and Health Policy at Baylor College of Medicine. Dr. McGuire's research focuses on the clinical integration of emerging technologies, with a particular focus on ethical and policy issues in human genetics and genomic research. Her research is funded by the National Institutes of Health. Dr. McGuire served as a member of the National Advisory Council for Human Genome Research from 2011 to 2015. Currently she is on the program committee for the Greenwall Foundation Faculty Scholars Program in Bioethics and is the president of the Association of Bioethics Program Directors.

James H. Nichols, Ph.D., D.A.B.C.C., F.A.C.B., is a professor of pathology, microbiology, and immunology and the medical director of clinical chemistry and point-of-care testing at Vanderbilt University School of Medicine in Nashville, Tennessee. Dr. Nichols received his B.A. in general biology/premedicine from Revelle College, University of California, San Diego. He went on to complete an M.S. and a Ph.D. in biochemistry from the University of Illinois, Urbana-Champaign. Dr. Nichols was a fellow in the postdoctoral training program in clinical chemistry at the Mayo Clinic in Rochester, Minnesota. He is board certified in both clinical chemistry and toxicological chemistry by the American Board of Clinical Chemistry. Dr. Nichols spent several years as the associate director of clinical chemistry, the director of point-of-care testing, and an associate professor of pathology at Johns Hopkins Medical Institutions. He later served as the medical director of clinical chemistry for Baystate Health in Springfield, Massachusetts, and was a professor of pathology at Tufts University School of Medicine. Dr. Nichols' research interests span evidence-based medicine, information management, laboratory automation, point-of-care testing, and toxicology. Dr. Nichols

has served on the Clinical Laboratory Improvement Amendments Advisory Committee and has been involved with the Clinical and Laboratory Standards Institute (CLSI) in a number of roles including the CLSI board of directors. He was a member of the CLSI Subcommittee on Point-of-Care Testing as well as the vice-chairholder and chairholder of the CLSI Consensus Committee on Point-of-Care Testing, the CLSI Consensus Council and chairholder of the Evaluations Protocols Expert Panel. Dr. Nichols has also served in several leadership positions with the American Association for Clinical Chemistry (AACC), the AACC Academy, and Laboratory Medicine Best Practices committees with the Centers for Disease Control and Prevention.

Bray Patrick-Lake, M.F.S., as the director of stakeholder engagement for Duke Clinical Research Institute, supports efforts to actively engage patients, health advocacy organizations, and other stakeholders in local and national research programs. She has led extensive efforts through the Clinical Trials Transformation Initiative to incorporate patient voices into clinical trial design, conduct, oversight, and regulatory frameworks as well as in improvement of the clinical trial enterprise. She co-chaired the advisory committee for the NIH director's working group responsible for authoring the vision and roadmap to launch the Precision Medicine Initiative Cohort Program. She served as the interim director of engagement for several months after the program launched and became the All of Research Program, for which she currently serves on the national advisory panel. She also leads engagement work at Duke's Coordinating Center for the NIH Environmental Influences on Child Health Outcomes (ECHO) program and serves on the National Academies of Sciences, Engineering, and Medicine Health Sciences Policy Board. Ms. Patrick-Lake founded a nonprofit disease advocacy organization for cardiac patients and served as a patient representative at the Food and Drug Administation on a variety of advisory committees and panels; in workgroups for the European Medicines Agency, the Innovative Medicines Initiative, NIH, and the National Academy of Medicine; and as a patient stakeholder or co-investigator for Agency for Healthcare Research and Quality and Patient-Centered Outcomes Research Institute (PCORI). She has been a member of the PCORnet Coordinating Center's executive leadership committee, where she developed patient engagement strategies. She is member of the American Cancer Society's clinical trials steering committee and has served on the MDEpiNet's National Medical Device Registry Task Force, the Medical Device Innovation Consortium's Patient-Centered Benefit–Risk Steering Committee, the American College of Cardiology (ACC) Foundation's patient-centered care shared decision making and patient-generated health data working groups, and the ACC Transcatheter Valve Therapy Registry Stakeholder Advisory Committee. She currently also serves as a PCORI reviewer and ambassador.

Consuelo H. Wilkins, M.D., M.S.C.I., is the executive director of the Meharry-Vanderbilt Alliance and an associate professor of medicine at both Vanderbilt University Medical Center and Meharry Medical College. As the associate director of the Vanderbilt Institute for Clinical and Translational Science, she oversees programs in team science and community engagement. Dr. Wilkins is currently a principal investigator of the Vanderbilt-Miami-Meharry Center of Excellence in Precision Medicine and Population Health, which focuses on decreasing disparities among African Americans and Latinos using precision medicine, and the Vanderbilt Recruitment Innovation Center, a national center dedicated to enhancing recruitment and retention in clinical trials. She has pioneered methods of stakeholder engagement that involve community members and patients in research across the translational spectrum. One approach, the Community Engagement Studio, was recently scaled to engage more than 650 community members across 12 states in 77 face-to-face consultations for the Precision Medicine Initiative Pilot. This work included eliciting perspectives from diverse communities on returning individual research results. With colleagues at Vanderbilt, Dr. Wilkins has developed a framework that extends the concept of return of results to "return of value," which integrates influencers of participants' perspectives of value and considers clinical and personal utility. Prior to joining the faculty at Vanderbilt University Medical Center in 2012, Dr. Wilkins was an associate professor in the Department of Medicine, Division of Geriatrics, with secondary appointments in psychiatry and surgery (public health sciences) at Washington University School of Medicine in St. Louis. She served as the founding director of the Center for Community Health and Partnerships in the Institute for Public Health, the co-director of the Center for Community Engaged Research in the Clinical and Translational Science Awards Program, and the director of "Our Community, Our Health," a collaborative program with Saint Louis University to disseminate culturally relevant health information and facilitate community–academic partnerships to address health disparities.

Brian J. Zikmund-Fisher, Ph.D., is an associate professor in the Department of Health Behavior and Health Education, University of Michigan (UM) School of Public Health, as well as a research associate professor in the Division of General Internal Medicine, University of Michigan Medical School, and an associate director of the UM Center for Bioethics and Social Sciences in Medicine. Dr. Zikmund-Fisher uses his interdisciplinary background in decision psychology and behavioral economics to study factors that affect individual decision making about a variety of health and medical issues. His research in health communications focuses on making risk statistics, test results, and other types of quantitative health information intuitively meaningful and useful for decision making by patients and the public. Dr. Zikmund-Fisher also studies the effects of poor numeracy on people's ability to use numbers to inform their health decisions and the role of narratives in health communications. He serves as an associate editor

for the journals *Medical Decision Making* and *Medical Decision Making: Policy and Practice*.

CONSULTANTS

Rebecca L. Davies, Ph.D., is the director of Quality Central at the University of Minnesota College of Veterinary Medicine. Dr. Davies received her Ph.D. in comparative animal physiology from the University of Minnesota and is an associate professor in the Department of Veterinary Population Medicine. From 2003 to 2016, Dr. Davies was the faculty advisor for the Veterinary Diagnostic Laboratory Comparative Endocrinology and Immunology Laboratory. From 2009 to 2012, Dr. Davies also served as the quality assurance manager for the Veterinary Diagnostic Laboratory. In 2012 Dr. Davies founded the Quality Central program to provide support for the integration of quality assurance (QA) best practices into service and research programs. In 2016 she began to focus on the integration of QA best practices into research and training programs in order to support the intent of research scientists to conduct rigorous and reproducible research. Quality Central provides the expertise needed to execute a sustainable and risk-based plan that will generate evidence that research data meet quality, integrity, and stewardship requirements throughout the research life cycle. Dr. Davies serves on the American Association of Veterinary Laboratory Diagnosticians laboratory accreditation committee and is an active member of the Society for Quality Assurance and the Research Quality Association. She is a member of the Committee for Core Rigor and Reproducibility within the Association of Biomolecular Resource Facilities, and a member of the education and training working group within the Asian and Pacific Rim Research Integrity Network. Dr. Davies' current interests include the adoption of voluntary QA practices within non-regulated research programs, sustainable models for incorporating research QA into basic research environments, research on research, and the use of laboratory error data and QA metrics to drive continuous improvement in laboratory and research settings.

Christi Guerrini, J.D., M.P.H., is an assistant professor in the Center for Medical Ethics and Health Policy at Baylor College of Medicine (BCM), where she conducts research at the intersection of innovation, health, policy, and ethics. In 2016 Ms. Guerrini was awarded a 4-year K01 award from the National Human Genome Research Institute to study ownership interests in citizen science. She also currently serves as an affiliated researcher at the University of Houston Law Center's Institute for Intellectual Property & Information Law. Ms. Guerrini received her J.D. from Harvard Law School and M.P.H. from The University of Texas School of Public Health. She graduated Phi Beta Kappa with highest honors from the University of Virginia, where she received her B.A. Prior to joining BCM, Ms. Guerrini served as the intellectual property fellow at Chicago-Kent College of Law and taught patent law and legal writing courses at Brooklyn Law School. Ms. Guerrini also litigated patent, trademark, contract, and class action disputes

across a spectrum of industries in private practice. She is admitted to practice in Texas and Illinois and before the U.S. Patent and Trademark Office.

E. Haavi Morreim, J.D., Ph.D., is a professor in the College of Medicine at the University of Tennessee Health Science Center. She does clinical teaching, consulting, and writing, with special interests in health care's changing economics, conflict resolution, and the litigation issues surrounding clinical medical research. She has been on the editorial board of several journals, including *IRB: Ethics and Human Research*, *The Journal of Law, Medicine & Ethics*, and *Accountability in Research*. She also chaired the Independent Patient Advocacy Council created to serve patients enrolled in the AbioCor artificial heart trial in the early 2000s. Dr. Morreim is an active Tennessee Supreme Court–listed mediator for disputes in both civil and family matters. She is also a licensed attorney, assisting clients pro bono in selected cases and representing clients successfully before the Tennessee Court of Appeals. Dr. Morreim has authored two books and more than 160 articles in journals of law, medicine, and bioethics, including *California Law Review*, *Vanderbilt Law Review*, *Journal of the American Medical Association*, *Archives of Internal Medicine*, and *The Wall Street Journal*. She has presented hundreds of invited lectures nationally and internationally to such groups as the American Medical Association and the American Bar Association.

STAFF

Michelle Mancher, M.P.H., is a program officer on the Board on Health Sciences Policy and study director for this study. She served as a staff co-director for the *Integrating Clinical Research into Epidemic Response: The Ebola Experience* report and as a liaison for the Sharing Clinical Trial Data Action Collaborative. Ms. Mancher joined the National Academies of Sciences, Engineering, and Medicine in 2009 and has since worked on many consensus studies and workshops related to health care services delivery, clinical trial data sharing, and medical product research and development, including *Initial National Priorities for Comparative Effectiveness Research*; *Clinical Practice Guidelines We Can Trust*; *Variation in Health Care Spending: Target Decision Making Not Geography; Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk;* and *Global Health Risk Framework: Research and Development of Medical Products: Workshop Summary.* Prior to joining the National Academies, Ms. Mancher held positions at the Arthritis Foundation: Metro DC Chapter, Clinton Foundation's Alliance for a Healthier Generation, and the New York City Health and Hospital Corporation's office of managed care. Ms. Mancher holds a master's degree in public health in health care management and policy from Columbia University and a bachelor of arts in international relations from The George Washington University.

Autumn S. Downey, Ph.D., joined the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine as a program officer in 2012. She is currently co-directing a consensus study on evidence-based practices for public health emergency preparedness and response as well as a standing committee on the health risks of air pollution exposure for Department of State employees and their families stationed overseas. Other National Academies studies she has worked on include *Preventing Cognitive Decline and Dementia*; *A National Trauma Care System*; *Healthy, Resilient, and Sustainable Communities After Disasters*; *BioWatch PCR Assays*; and *Advancing Workforce Health at the Department of Homeland Security*. Dr. Downey received her Ph.D. in molecular microbiology and immunology from the Johns Hopkins Bloomberg School of Public Health, where she also completed a postdoctoral fellowship at the school's National Center for the Study of Preparedness and Catastrophic Event Response. Prior to joining the National Academies, she was a National Research Council postdoctoral fellow at the National Institute of Standards and Technology, where she worked on environmental sampling for biothreat agents and the indoor microbiome.

Emily R. Busta, M.S., is an associate program officer on the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine. Ms. Busta joined the National Academies in October 2014 as a member of the staff of the Forum on Drug Discovery, Development, and Translation. She worked on the consensus report *Integrating Clinical Research into Epidemic Response: The Ebola Experience*. Prior to joining the National Academies, she held positions as a research assistant in a laboratory studying placentology at the University of Colorado Denver–Anschutz Medical Campus (CU Anschutz) and as a toxicology review fellow at the Center for Food Safety and Applied Nutrition of the Food and Drug Administration, where she developed and tested computational toxicology models and performed safety reviews of new food contacts. Ms. Busta holds an M.S. in biomedical basic sciences from CU Anschutz and a B.S. in molecular toxicology from the University of California, Berkeley.

Olivia C. Yost, M.S., is a research associate on the Board on Health Sciences Policy. She currently provides research support to several consensus and standing committees, including the Committee on the Use of Elastomeric Respirators in Health Care. Prior to joining the National Academies in 2015, Ms. Yost worked as a research officer for ARCHIVE Global, where she managed field studies focused on evaluating the impact of malaria, tuberculosis, and gastrointestinal infection control strategies in Bangladesh, Cameroon, and Haiti. Ms. Yost received her M.S. in the control of infectious diseases from the London School of Hygiene & Tropical Medicine in 2012. Her graduate research focused on developing rapid testing methodologies for assessing soil contamination from decaying, small-scale wastewater infrastructure in rural Alabama. She received her B.A. in history and communications from Franklin University Switzerland in 2011.

Caroline M. Cilio, M.B.E., is a senior program assistant on the Board of Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine. Ms. Cilio joined the National Academies in 2016 and works on the Forum on Aging, Disability, and Independence and on Physician-Assisted Death: Scanning the Landscape and Potential Approaches—A Workshop. Ms. Cilio holds a master of bioethics and a B.A. in health and societies, an interdisciplinary study focused on medical sociology and health policy, from the University of Pennsylvania.

Andrew M. Pope, Ph.D., is the director of the Board on Health Sciences Policy. He has a Ph.D. in physiology and biochemistry from the University of Maryland and has been a member of the National Academies of Sciences, Engineering, and Medicine staff since 1982 and of the Health and Medicine Division staff since 1989. His primary interests are science policy, biomedical ethics, and environmental and occupational influences on human health. During his tenure at the National Academies, Dr. Pope has directed numerous studies on topics that range from injury control, disability prevention, and biologic markers to the protection of human subjects of research, National Institutes of Health priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism. Since 1998, Dr. Pope has served as the director of the Board on Health Sciences Policy, which oversees and guides a program of activities that is intended to encourage and sustain the continuous vigor of the basic biomedical and clinical research enterprises needed to ensure and improve the health and resilience of the public. Ongoing activities include forums on neuroscience, genomics, drug discovery and development, and medical and public health preparedness for disasters and emergencies. Dr. Pope is the recipient of the Health and Medicine Division's Cecil Award and the National Academy of Sciences President's Special Achievement Award.