



SPECIAL ARTICLE

Return of Individual Research Results



A Guide for Biomedical Researchers Utilizing Human Biospecimens

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The recent movement toward returning individual research results to study subjects/participants generates ethical and legal challenges for laboratories performing research on human biospecimens. The concept of an individual's interest in knowing the results of testing on their tissue is pitted against individual and systemic risks and an established legal framework regulating the performance of laboratory testing for medical care purposes. This article discusses the rationale for returning individual research results to subjects, the potential risks associated with returning these results, and the legal framework in the United States that governs testing of identifiable human biospecimens. On the basis of these considerations, this article provides recommendations for investigators to consider when planning and executing human biospecimen research, with the objective of appropriately balancing the interests of research subjects, the need for ensuring integrity of the research process, and compliance with US laws and regulations. (*Am J Pathol* 2020, 190: 918–933; <https://doi.org/10.1016/j.ajpath.2020.01.014>)

This article explores the issues pertaining to the return of individual research results, including raw data with or without interpretation, from the analysis of human biospecimens. The biomedical researcher engaged in research involving human subjects, especially through use of human biospecimens, will benefit from this article. This article may facilitate current research proposals by clearly distinguishing between existing regulations and proposed recommendations that would change the paradigm and may impact future research planning. Points for consideration and recommendations for returning results as a component of research activity are provided. The focus is limited to research as defined in the United States by the revised Common Rule of 2018 (Table 1): “systematic investigation, including research development, testing, and evaluation, that is designed to develop or contribute to generalizable

knowledge.”¹ State, local, and institutional regulations are not considered; therefore, the recommendations are not inclusive of all possible scenarios. Investigators should apply their own professional judgment in consultation with their institution's human subjects' protection infrastructure.

The authors have focused on the return of individual research results and have excluded discussion of the return of general research results—what the study found overall—to research subjects, as the issues involved in

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conveying general research findings are substantially different from those pertaining to returning individual research results. Neither recreational genomics results, such as geographic ancestry, because they are not research results, nor clinically meaningless data, such as raw data from single-cell RNA expression studies, are covered. Although the authors draw from a wide literature with diverse perspectives,^{4–29} some of which recommends statutory or regulatory changes, their perspective is grounded in current law, experience in research use of banked specimens and clinical laboratory operations, and positions previously espoused by the American Society for Investigative Pathology (http://asip.org/asip/assets/file/documents/asip_lettertonasaugust2017letteronly.pdf, last accessed March 2020; http://asip.org/asip/assets/file/documents/asipfollowup_lettertonas101817.pdf, last accessed March 2020). With these caveats, it is hoped through this document to clarify the practical, legal, and ethical landscape for researchers who derive data from individually identifiable biospecimens, drawing insight from the many authors who have previously explored the ethical and legal considerations surrounding research on human biospecimens.^{4–29}

In recent years, there has been significant advocacy for disclosing individual research results to research subjects. Far-reaching discussions regarding the practical, legal, and ethical issues governing such disclosure have been recorded by the Secretary's Advisory Committee for Human Research Protections^{30,31} (SACHRP) and the National Academies of Science, Engineering and Medicine³ (NASSEM). The ethical framework provided in the Belmont Report,¹ which provides much of the regulatory basis for research on humans and their biological material in the United States, emphasizes “respect for persons,” “beneficence,” and “justice” as criteria by which the ethical considerations regarding research may be understood. Respect for persons requires the recognition of an individual's autonomy (ie, their freedom of choice). For individuals capable of self-determination, respect for persons demands that individuals enter into research voluntarily after they are provided sufficient information to make an informed decision. The informed consent process requires the sharing of adequate information pertaining to the risks and benefits of participation in a manner that ensures both comprehension and that an individual's voluntary participation in research is not subject to undue influence or coercion. Beneficence is an obligation to ensure that the benefits of participation in research match the risks, a concept that is also known as clinical equipoise. Justice requires that groups who receive the benefits of research also bear its burdens, such that no group of individuals is unduly burdened or exclusively benefits from participation in research.

The recent movement toward the return of individual research results to participants is based on the belief that research subjects may potentially benefit from receiving their individual results, that this benefit may outweigh risks

associated with disclosure, and that the principles of respect for persons and beneficence favor providing individual research results. Nevertheless, the return of research results to subjects represents an “uncharted and untested” strategy for which risks and benefits are not yet fully understood.^{8,29} Certain harms resulting from return of false-negative and false-positive results are probably unavoidable, including anxiety, medical expense, delay in seeking treatment, or patient confusion.³² Furthermore, biosamples in most research laboratories do not undergo the rigorous chain of custody and quality assurance procedures typical of clinical laboratories and hence there is less certainty that biosamples are correctly identified.⁸ Several government agencies provide cautions about tests provided directly to consumers³³ by clinical laboratories regulated by the US Department of Health and Human Services under the Clinical Laboratory Improvement Amendments of 1988³⁴ (CLIA). The perceived need of subjects to follow up on misleading results may place demands on health care practitioners and systems, and may not be covered by insurance companies that could reasonably view counseling and confirmatory testing as not medically necessary.

The movement toward the return of individual results to research subjects introduces philosophical, practical, and legal challenges for investigators engaged in the analysis of individually identifiable biological specimens. Although the donation of a biospecimen for research has traditionally been considered an altruistic gift to the community at large, a commitment to return research results to individual tissue donors generates a reciprocal transaction, rather than a gift: “I am giving you my specimen with the expectation of receiving information about it.” To the extent that there is an expectation that this information will provide a potential medical benefit to the donor, it may also generate for nonclinical laboratories a conflict with CLIA, which states: “No person may solicit or accept materials derived from the human body for laboratory examination or other procedure unless there is in effect for the laboratory a certificate issued by the Secretary under this section applicable to the category of examinations or procedures which includes such examination or procedure.”³⁵ That is, only CLIA-certified laboratories can return results that will be used for clinical purposes.

Review of Federal Oversight of Human Biospecimen Research

Background

The regulatory framework for return of research results is based on terminology that may not be part of everyday vocabulary. Many of these terms are described in a glossary found in [Table 1](#). For researchers working with samples that originated from a medical procedure, one key concept is the biospecimen, defined as any natural material from the human body, such as tissue, blood, and

Table 1 Glossary of Terms

Belmont Report	The Belmont Report ² was written in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and outlines the basic ethical principles in research involving human subjects. The current US system of protection for human research subjects (Common Rule) is heavily influenced by the Belmont Report.
Biobank	A biobank is a system (including facilities, personnel, and procedures) for storing and retrieving biological samples, including tissue, blood, and urine; derived materials, such as cells, proteins, and nucleic acids; and pertinent demographic and clinical data. Biobanks typically exist to support medical and environmental research.
Biospecimen (human)	A human biospecimen is any natural material from the human body, such as tissue, blood, and urine, as well as derived materials, such as cells and cellular analytes, including nucleic acids, proteins, carbohydrates, and lipids.
Biospecimen (identifiable)	An identifiable biospecimen is a biospecimen for which the identity of the donor is or may readily be ascertained by the investigator or is associated with the biospecimen. A subset of identifiable biospecimens includes coded biospecimens (indirectly identifiable biospecimens). Such biospecimens are samples with the individually identifiable information removed and replaced with a unique code. Identifiable information is retained separately such that the code can be used to link the biospecimen back to the donor. As long as a link exists that is accessible to the study investigators, these biospecimens are considered indirectly identifiable. Note: The terms code, link, and key are often used interchangeably.
Biospecimen (nonidentifiable)	A nonidentifiable biospecimen is a biospecimen for which the identity of the donor cannot be ascertained by the investigator. If the key is not available to anyone on the research team, these specimens are considered nonidentifiable even if the key is held in the biobank. The determining factor is whether the research team has the ability to re-identify a specimen. Analysis of these specimens may be conducted in a CLIA-certified laboratory, but such tests are not to be considered conducted under CLIA testing regulations, as the specimen has been de-identified and does not meet CLIA requirements for specimen identification.
Biospecimen (anonymized)	An anonymized biospecimen is a nonidentifiable biospecimen for which no identifiable information was collected or, if collected, was not maintained and cannot be retrieved, such that there is no way to identify the donor.
Biospecimen (de-identified)	A de-identified biospecimen is a biospecimen for which all of the 18 identifiers defined by the HIPAA Privacy Rule have been removed.
ClinGen	ClinGen is a resource funded by the NIH to define the clinical relevance of genes and gene variants for use in research and precision medicine.
Common Rule	The Federal Policy for the Protection of Human Subjects or the Common Rule ¹ is the standard of ethics by which government-funded research in the United States is held; nearly all US academic institutions hold their researchers to these statements of rights regardless of funding. It was first published in the Code of Federal Regulations in 1991 (45 CFR part 46) and codified in separate regulations by 15 federal departments and agencies. The Common Rule outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance. The Common Rule was revised in 2018; 20 agencies (including HHS) intend to follow the revised Common Rule.
Designated record set	A group of records maintained by or for a covered entity. It includes the medical records and billing records about individuals maintained by or for a covered health care provider, as defined by HIPAA.
Honest broker	An honest broker is a neutral person or system that gathers pertinent information regarding tissue and its associated data, removes identifiers or replaces them with codes, and releases only coded information to researchers.
Human subject/research subject/ research participant	Recently, it has been suggested ³ that the term research participants should replace research subjects. The authors have chosen to use the latter term because it is used in current regulations, such as the Common Rule. It is more precise because participants can include research investigators and health care providers who are also involved in the research study. Furthermore, for much biospecimen research, those donating specimens, although recognized for their important contribution, generally do not participate in the research process on an ongoing basis. These terms reference a living individual (see Common Rule) about whom an investigator (whether professional or student) is conducting research. Research is defined as obtaining information or biospecimens through intervention or interaction with the individual, and using, studying, or analyzing the information or biospecimens; or obtaining, using, studying, analyzing, or generating identifiable private information or identifiable biospecimens.

Incidental finding	An incidental finding (also referred to as a secondary finding) is a previously undiagnosed abnormality or medical condition that is discovered unintentionally and is unrelated to the issues addressed in a research study.
Investigational device exemption	An administration approval conducted under the authority of 21 CFR 812, which allows a medical device (eg, a laboratory test) that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.
Research	Research is a systematic investigation that is designed to develop or contribute to generalizable knowledge.
Secondary finding	A secondary finding (also referred to as an incidental finding) is a previously undiagnosed abnormality or medical condition that is discovered unintentionally and is unrelated to the medical issues addressed in a research study.
Secondary research	Secondary research is research that uses data and/or specimens that have been or will be collected for purposes unrelated to the (primary) study for which the specimen was collected.
Utility (clinical)	Clinical utility is the ability for a diagnostic procedure to provide information that can be used to guide medical or preventive care decisions.
Validity (analytic)	Analytic validity is a test's ability to accurately measure the analyte(s) of interest.
Validity (clinical)	Clinical validity is the ability of a test result to correlate with a clinical diagnosis or outcome, whether the information provides information useful for subsequent medical care or prevention measures.
Validity (test)	Test validity is the ability of a test to accurately measure what it is intended to measure (eg, the presence or absence of a mutation).
Vulnerable population	A vulnerable population consists of individuals who are potentially susceptible to coercion or undue influence. Children are included in this group. Other vulnerable populations include those who have limited decision-making capacity, such as individuals experiencing dementia or mental illness, with an impaired ability to act with autonomy (eg, prisoners), who are economically or educationally disadvantaged; and/or homebound or confined to nursing homes.

CLIA, Clinical Laboratory Improvement Amendments; HHS, US Department of Health and Human Services; HIPAA, Health Insurance Portability and Accountability Act; IRB, institutional review board.

urine, as well as derived materials, such as cells and cellular analytes, including nucleic acids, proteins, carbohydrates, and lipids. Biospecimens fall into two categories from a regulatory perspective: identifiable and nonidentifiable.

An identifiable biospecimen is a biospecimen for which the identity of the donor is or may readily be ascertained by the investigator or associated with the biospecimen. A coded biospecimen is an example of an indirectly identifiable biospecimen from which the individually identifiable information has been removed and replaced with a unique code. The identifiable information may be retained separately such that the code can be used to link the biospecimen back to the donor when appropriate. As long as a link exists and is available to the study investigators, these biospecimens are considered indirectly identifiable. The terms "code," "link," and "key" are often used interchangeably. Biobanks often serve as honest brokers for specimens identified by a code, enabling the biobank but not the investigator to trace the origins of the specimen and associated demographic and clinically relevant information. The biobank as honest broker may potentially update an investigator with new information, such as clinical outcomes, during the course of an investigation.

A nonidentifiable biospecimen is a biospecimen for which the identity of the donor cannot be ascertained by the

investigator. In its 2008 Guidance, the US Office of Human Research Protections clarified that, if the key is not available to anyone on the research team and there is no intent to identify the samples, such specimens are considered non-identifiable even if the key is held in the biobank.³⁶ The determining factor is whether the research team has the ability to re-identify a specimen. Although analysis of non-identifiable specimens may be conducted in a CLIA-certified laboratory, those tests are not subject to CLIA testing regulations because the specimen has been de-identified and does not meet CLIA requirements for specimen identification. There are two types of nonidentifiable biospecimens: anonymized and de-identified. An anonymized biospecimen is a biospecimen for which no identifiable information was collected or if collected was not maintained and cannot be retrieved, such that there is no way to identify the donor from whom the biospecimen was obtained. A de-identified biospecimen is a biospecimen for which all of the 18 identifiers defined by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule^{37,38} have been removed.³⁹

A biospecimen may contain germline cells (containing genes inherited from the parents and capable of being passed on to the next generation) as well as somatic cells; the latter contain genetic and epigenetic changes that have occurred during the life of the cells but are not generally heritable. When considering the return of individual research results, distinguishing between somatic cell and germline cell results

has important implications, especially when research subjects make reproductive decisions or consider informing family members about predispositions to disease.

In general, work performed in the United States by investigators who use anonymized, de-identified, or coded specimens does not meet the criteria of human subjects research and is exempt from compliance with most Common Rule requirements. The 2018 revised Common Rule¹ anticipates periodic rereview (at intervals of not more than 4 years) of the conditions under which a specimen may be considered nonidentifiable and thus not subject to regulations governing human subjects research. Investigators should consider the possibility that future regulations may require researchers to consider a subset of biospecimens as identifiable when certain technologies or techniques are used during research on what is currently considered a nonidentifiable biospecimen.^{40,41}

In the United States, the return of individual research results is governed by a complex assortment of federal, state, and local regulations. At this time, no federal law confers a fundamental right to access individual research results. However, recent changes to federal regulations^{2,39} are intended to promote transparency and to facilitate individual access to clinical and research test results. Together, these changes represent a paradigm shift in response to a growing advocacy community representing the interests of the patient, donor, and the general population. The movement is generally toward increased transparency and respect for the research subject community, encouraging information sharing with subjects. The interpretation of some federal regulations by various investigators, advisory committees, and regulatory agencies regarding the return of individual research results may appear to be discordant. These apparent disharmonies are discussed in detail below (*Laws and Regulations*).

The Belmont Report¹ cited earlier provides guidance on the social and ethical principles associated with research involving human subjects and forms the basis of protections that include informed consent, institutional review boards (IRBs), and the fundamental difference between research and clinical practice. The Common Rule,² HIPAA Privacy Rule,³⁷ CLIA,³⁴ and the Federal Food, Drug, and Cosmetic Act⁴² (and implementing regulations) all impact human subjects research and must be considered by investigators and the IRBs responsible for ensuring adherence to both equipoise in human subjects research and compliance with ethical and legal protections of human subjects.

Laws and Regulations

The Common Rule

The Common Rule² provides most of the regulatory framework governing human subjects research. Research on biospecimens and the data obtained from them are considered human subjects research unless the specimens are non-identifiable. In addition, research using human biospecimens

is not considered human subjects research if the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and the investigator(s) cannot readily ascertain the identity of the individual(s) because, for example, there are agreements, IRB-approved policies and procedures, or legal requirements in place that prohibit the release of the key to the code to the investigators under any circumstances until the individuals are deceased.³¹

Direct return of results from investigators to research subjects is not possible when specimens have been de-identified or coded. Indirect return of results through the honest broker providing the coded biospecimens may be possible; however, it is important that the research subject receiving these results is not able to identify the laboratory or communicate with the laboratory (which would result in re-identification of the specimen). Before designing research protocols, researchers should familiarize themselves with the obligations to return research results set forth in the agreement with the biobank. In general, most investigators use biospecimens obtained from biobanks through an honest broker and their investigations are not considered “human subjects research” under the Common Rule.³⁶

The revised Common Rule² allows for the use of broad consents under specific conditions. Although broad consent may facilitate access to biospecimens, it adds additional constraints when return of individual research results is contemplated. Under the revised Common Rule, individual consent must be obtained when there is a plan to return individual research results.² A broad consent is not sufficient to allow research subjects to receive results from a secondary research study.

The Common Rule specifically addresses the return of research results and requires an explicit statement in the informed consent if clinically relevant research results, including individual research results, will not be disclosed to research subjects. For example, if an investigator will not return so-called normal results and will return results only when abnormal findings are detected, this must be explicitly disclosed to the research subject.

The Common Rule does not explicitly define clinically relevant. However, results originating from CLIA-certified laboratories that meet the standards of analyte and test validity that are ordinarily provided as a part of medical care would clearly be considered clinically relevant. In the case of results obtained in research laboratories, the clinical relevance must be considered in light of the statutory language provided in CLIA (see below).

Clinical Laboratory Improvement Amendments of 1988 and Subsequent Updates

The CLIA statute is administered by the Centers for Medicare and Medicaid Services and regulates laboratories performing testing on human biospecimens.³⁴ The goal of CLIA is to ensure the accuracy and reliability of patient test results by establishing quality standards for laboratory testing performed

on human specimens, such as blood, other bodily fluids, and tissue, for the purposes of clinical care. CLIA requires the Secretary of the US Department of Health and Human Services to certify laboratories performing clinical testing. Defined by CLIA, a laboratory is “a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.”³⁵ Therefore, CLIA applies when patient-specific results are reported from the laboratory to another entity and the results are made available for the purposes of diagnosis, prevention, or treatment of disease, or assessment of health. Research laboratories are defined as laboratories “that test human specimens 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, individuals.”³⁵ As such, research laboratories that do not report individual patient-specific results are CLIA exempt. Careful consideration regarding the applicability of CLIA regulations must be given to the reporting of individual patient-specific research results that could be used for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.

HIPAA of 1996 and Subsequent Amendments

Under the purview of the US Office of Civil Rights, the HIPAA Privacy Rule gives patients the right to access health information maintained by HIPAA-covered entities (most health care providers and associated organizations) and held as part of a designated record set.^{37,38} Individual medical records are generally part of the designated record set. In many situations, an HIPAA-covered entity may include both clinical and research components. Results from the research component may not be part of the designated record set.³⁹ For those research studies conducted by HIPAA-covered entities, the HIPAA Privacy Rule allows a research subject to consent to suspension of his/her access rights during participation in a clinical trial; the right to access protected health information is reinstated at the conclusion of the clinical trial. HIPAA access requirements are generally limited to clinical results obtained in laboratories regulated under CLIA and when results become part of the individual’s medical record. The interpretation of what constitutes a designated record set is an area of open interpretation. Researchers are advised to follow their own institution’s guidance and seek additional clarity as needed.

Interpretations of CLIA and HIPAA and Apparent Discordance

As noted above, CLIA states: “No person may solicit or accept materials derived from the human body for laboratory examination or other procedure unless there is in effect for the laboratory a certificate issued by the Secretary under this section applicable to the category of examinations or

procedures which includes such examination or procedure.”³⁵ Although this language might appear to refer to all laboratories, including research laboratories, the CLIA Regulations⁴³ exclude from applicability “Research laboratories that test human specimens but do not report *patient-specific* [italics added] results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, individual patients.”³⁵ The recent NASEM report, *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm*,³ contains an in-depth review of the apparent discordances between HIPAA and CLIA.

Interpretations of the HIPAA and CLIA regulations are still in flux, and the requirements under HIPAA and those under CLIA may on first glance seem to be contradictory in select situations. In contrast to HIPAA, for which the default is return of individual research results, CLIA prohibits not only the return of results from non-CLIA-certified laboratories, but also a request for additional samples from research subjects should corroboration be desired to verify the results from a non-CLIA-certified laboratory. The American Society for Investigative Pathology continues to advocate for resolutions to these discordances (<http://asip.org/asip/assets/file/documents/asiplettertonasaugust2017letteronly.pdf>, last accessed March 2020; <http://asip.org/asip/assets/file/documents/asipfollowuplettertonas101817.pdf>, last accessed March 2020). Researchers are advised to follow their institution’s guidance and seek additional clarity as needed.

Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act effectively prohibits the return of some individual research results.⁴² The law requires that persons who manufacture medical devices register with the Food and Drug Administration (FDA) and, in general, seek premarket approval for the manufacturing and distribution of these devices. The FDA asserts that laboratory-developed tests that report information used in patient care are regulated medical devices, although it has exercised enforcement discretion.⁴⁴ Laboratory testing that is not performed for patient care purposes is generally not regulated by the FDA or is regulated through the Investigational Device Exemption process. An Investigational Device Exemption is generally required for clinical investigations of device safety and effectiveness but is generally not required for noninvasive tests that are not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.³⁹ This has an impact on the return of individual research results similar to that of CLIA. That is, individual research results may not be returned unless they have been performed or confirmed using a validated method (either an *in vitro* diagnostic device used in conformance with its label and exempted, cleared, or approved by the FDA or a validated laboratory-developed test conducted in a CLIA-certified laboratory).

SACHRP Recommendations

SACHRP is an advisory body chartered by the US Department of Health and Human Services and prepares advisory documents and recommendations to the Secretary of US Department of Health and Human Services, the Assistant Secretary for Health, and the Director of the Office of Human Research Protections. SACHRP communications do not constitute regulations or requirements; instead, SACHRP recommendations demonstrate the possible trajectory of future requirements.

Although the Common Rule neither expressly encourages nor prohibits the return of individual research results, SACHRP has recommended a rebuttable presumption³¹ in favor of returning individual results. The underlying principle is one of recognition and appreciation for the contributions made by research subjects with the idea that the return of individual research results may lead to increased willingness to participate. SACHRP specifically notes that research findings do not need to have clinical value because “pure intellectual curiosity of the subjects is sufficient reason to return the results absent other reasons not to return them.”³¹ Nonetheless, SACHRP cites several reasons under which results need not be returned (ie, the presumption is rebutted):

- The identity of the research subject is not known.
- Returning the results in an ongoing study has the potential to cause bias and therefore invalidate the study.
- The clinical meaning and significance of the data are not known.
- The results are of low clinical significance.
- The validity of the results is questionable.
- The results are not actionable.
- The administrative and/or financial burden to the investigators, institutions, and/or other parties involved in the research is too high.

Because the investigator—research subject relationship is qualitatively different from that of the health care provider—patient relationship, it is difficult for an investigator to know what information would be of value for any particular individual. Some may advocate for relaying information through a physician or counselor who has a professional relationship with the individual. SACHRP, however, does not consider return of an individual’s research results solely to his/her health care provider to be “return of individual results to the subject.”²⁹

NASEM Recommendations

The recent NASEM report, *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm*,³ notes the importance of considering whether returning results would be of use or value to the research subject (assuming that it is feasible to return the research data). The report recommends considering the value of the

result to the participant, which takes into account not only the test validity and clinical relevance of the data but also whether the information is of significance to the individual (eg, for reproductive decision making, financial planning, or quality-of-life concerns). The report contains examples of ways in which participant understanding of research results can be supported and includes far-reaching recommendations for future changes in oversight of non—CLIA-certified laboratories concerning the issue of return of results. It appears, however, that the implementation of these proposals is not imminent.

Summary

Recent recommendations from SACHRP^{30,31} and NASEM³ reflect perspectives as well as the concerns of research subjects and advocacy organizations. These recommendations recognize research subjects as both important contributors to the research process and deserving of additional information as a result of their contributions to research.

The legal and regulatory background for the return of individual research results can be confusing. HIPAA seems to assume return of at least some types of research results; however, CLIA prohibits return of research laboratory results not performed by a CLIA-certified laboratory. The Federal Food, Drug, and Cosmetic Act provides regulatory authority to the FDA but that agency seems to be exercising enforcement discretion.⁴⁴

Research versus Clinical Laboratories - Pragmatic Considerations

In the United States, clinical laboratories are subject to stringent regulatory oversight under CLIA to ensure that tests informing medical decision making are accurate. CLIA certification is a key element of safe and effective patient care, supporting the return of the right information to the right patient. Under US law, CLIA certification must be obtained by laboratories accepting specimens that will generate information used in the care of patients or could affect medical decision making. Laboratory tests performed in CLIA-certified laboratories must meet analytic and test validity standards. In addition, CLIA-certified laboratories strive to meet clinical validity standards. Test results must be reported to the ordering physician(s) with sufficient information for proper interpretation, including false-positive and false-negative rates and levels of confidence as well as considerations of differential diagnosis. CLIA standards set a high bar for clinical care and support careful communication, allowing for appropriate incorporation of laboratory findings into the care and treatment of patients.

The maintenance of CLIA certification requires substantial ongoing investment in training, professional expertise, and administrative oversight. CLIA certification requires a substantial institutional commitment to procedures and the

infrastructure necessary to meet CLIA standards, as well as staffing and resources to meet quality control and administrative requirements.

Requirements for research laboratories differ from those of clinical laboratories. The goal of research laboratory testing is to expand the generalizable knowledge base. Research sample testing procedures are designed to accurately capture data from specimens in aggregate and may change substantially over the course of a research investigation. In many circumstances, there is no need to correlate results directly with an individual. Furthermore, the research itself may be focused on developing an improved laboratory test that must be validated in controlled clinical investigations before use in patient care; sharing nonvalidated results could lead to inappropriate treatment. The ability to conduct research on biospecimens in the aggregate is a cost-effective means of gaining knowledge. Recently, both the NIH and the National Science Foundation expressed concern about the lack of research reproducibility in preclinical research, and there are reports in the literature^{45–47} estimating that more than half of preclinical research studies cannot be reproduced. Furthermore, procedures and personnel training in research laboratories are not set up to ensure the unbroken fidelity in provenance for biospecimens that are required in CLIA-certified laboratories.⁸ For example, biosamples and their derivatives undergo many container transfers, often manually labeled, with few or no cross-checks to ensure identity fidelity. Proficiency training of CLIA-certified laboratory personnel to ensure identity fidelity is not normally practiced in research laboratories. Also, de-identification procedures are not necessarily stringently applied in research laboratories. The rate of attribution error will be unknown in most circumstances and likely will be higher than results generated in a CLIA-certified laboratory. These findings and observations further call into question the advisability of returning individual research results generated in non-CLIA-certified laboratories. Moreover, research laboratory testing is often performed on nonidentifiable biospecimens under blinded conditions so as not to bias results. Taken together, these aspects of research laboratory testing often preclude the return of individual results to research subjects.

Determining if Returning Individual Research Results Is Feasible/Required

As discussed above, current SACHRP recommendations support a rebuttable presumption³¹ favoring the return of individual research results in many situations. Much of SACHRP's discussion concerns the clinical actionability of test results; however, there is no specific regulatory framework for defining actionability. Significant discussion continues around whether actionability should be limited to clinical actionability (ie, those situations where medical

intervention can support prognosis, treatment, or quality-of-life interventions). For genetic results, the ClinGen working groups funded by the NIH have made slightly different recommendations, employing the criteria of well-established clinical interventions that are specific to the genetic disorder under consideration and that prevent or delay clinical disease, lower clinical burden, or improve clinical outcomes (including outcomes for at-risk family members).⁴⁸ Similar criteria have been used by the American College of Medical Genetics (ACMG).^{49,50} Ideally, clinical interventions would be based on high-quality evidence of efficacy, such as randomized blinded clinical trials, and in which effectiveness has been demonstrated in subsequent clinical practice. Such a high standard is seldom achieved, and it is generally necessary to make decisions based on evidence of lower quality. The recommendations made by the working groups are made in the context of returning incidental (secondary) findings from testing done in CLIA-certified laboratories, not findings from non-CLIA-certified laboratories. Researchers may also determine that a broader definition of actionability is desirable—one in which additional considerations important to research subjects are included (eg, reproductive decision making, financial planning, or quality-of-life concerns). For specific research projects, incorporating this broader definition of actionability may encourage the disclosure of additional information to research subjects.

Identifiable Biospecimens Analyzed in Clinical Laboratories

In general, clinical laboratory results provided by CLIA-certified laboratories should be considered validated, particularly if FDA-cleared or approved medical devices are used and the specific tests are those for which the laboratory has received CLIA approval. Given adequate resources, these results should be returned unless doing so jeopardizes the validity of the research, such as for some blinded clinical trials or observational studies in which receiving results could potentially modify participant behavior. This is further supported when the CLIA-certified laboratory includes the laboratory test as part of the designated record set and therefore individuals may request these results under HIPAA provisions. HIPAA requirements to make information available on request do not generate an obligation for either the laboratories or the investigators to proactively provide these results unless promised in the informed consent process.

Situations may arise in which a result is produced by a CLIA-certified laboratory but is not currently clinically actionable (eg, genetic data placing the subject or his/her offspring in a high-risk category for a particular disease for which there is no current prevention or treatment). It might be appropriate to return such data in the hope that they become clinically actionable in the future.

Recommendation: Investigators should return results from tests performed under a laboratory's CLIA certification provided that doing so does not undermine the integrity

of the underlying investigation and return of individual results is feasible given the resources available.

Recommendation: Investigators should not return results that are neither actionable nor validated.

Recommendation: Investigators should consider returning results that are validated but currently not clinically actionable.

Identifiable Biospecimens Analyzed in Research (Nonclinical) Laboratories

In contrast to CLIA-certified laboratories, most research laboratories that perform testing on human specimens do not report patient-specific results for the purposes of diagnosis, prevention, or treatment of disease. As such, research laboratories are not required to establish and document results to the standards of CLIA. The calibration and measurement units reported by CLIA-certified laboratories are strictly standardized; however, research laboratories are free to express results in units that support the specific investigation underway. Results of the same test on the same specimen from a non-CLIA-certified laboratory and a CLIA-certified laboratory may not be comparable solely because of differences in the way the results are reported. Therefore, research results generated in a laboratory that is not CLIA certified should not be used for the purposes of patient care nor reported in the patient's health record. Although the Office of Civil Rights interprets the HIPAA Privacy Law as permitting disclosure of individual research results from non-CLIA-certified laboratories (giving the research participant the option to seek confirmatory testing by a CLIA-certified laboratory and/or seek medical advice), the Centers for Medicare and Medicaid Services interprets the CLIA statute as prohibiting non-CLIA-certified laboratories from accepting specimens for testing if these results will be reported in a manner that can influence medical care. The apparent discordance between HIPAA and CLIA has led to considerable discussion about harmonizing terminology and shifting the current paradigm toward the return of individual research results in situations currently not legally permissible. From a legal perspective, however, the CLIA and HIPAA regulations are not contradictory; the HIPAA Privacy Law is not written in a way that invalidates or supersedes CLIA. In fact, the CLIA statute has the effect of making the HIPAA regulatory interpretation (to return individual research results) moot because the investigator in a non-CLIA-certified laboratory cannot release a result that was not legally obtained in the first place.

Recommendation: Only results from CLIA-certified laboratories should be reported to individual research subjects.

Nonidentifiable Biospecimens

Often, human biospecimens used for research purposes are anonymized or de-identified to protect the privacy and

confidentiality of research subjects. As such, investigators utilizing these biospecimens for research purposes do not know the identity of the donor, making it impossible to interpret and return individual research results.

Recommendation: Research results that cannot be interpreted at the individual level, such as results derived from anonymized or de-identified biospecimens, cannot practically be returned by the research team.

Planning for Return of Research Results

General Parameters

It is generally the decision of the investigator and the sponsor to return results to research subjects. Consideration of which results may be returned need not be limited to, or even include, the actual results of the study; study participants may find it valuable to have results from tests performed to establish eligibility as part of the research protocol. For example, if the research is on the metabolism of a new drug, a research subject may also want to receive the results of the liver function tests performed before the study to classify the subject to a study arm. Investigators should think broadly about what constitutes a result when evaluating which results to potentially return.

In deciding whether to return research results to subjects, investigators should consider the potential value to the subject, together with the potential effects on subject behavior (eg, unblinding of a clinical study). Investigators should also consider the potential costs and benefits associated with testing in a CLIA-certified laboratory, as well as the costs associated with returning the results to subjects and safeguarding them against unintentional disclosure to unauthorized recipients. In many cases, investigators will determine that only some of the research data should be shared with subjects.

Research subjects may be interested in receiving raw data, especially when the data approximates whole-genome or whole-exome sequencing. Increasingly, there are third-party applications that take raw genetic data and provide interpretations to individuals; some research subjects are interested in paying for this interpretation. However, raw data provided by different laboratories may not be reported in an equivalent manner, often making it difficult for a third party to provide an accurate interpretation. Investigators should determine whether raw genetic data will be released and determine what caveats should accompany the provision of these data, with or without interpretation.

When extensive genomic testing is a component of the research, researchers should familiarize themselves with the ACMG minimum list of medically actionable genes in clinical genomic sequencing to be reported as incidental (secondary) findings (ie, unanticipated but clinically important findings).^{48,50–53} Investigators using specimens from registries or biobanks should familiarize themselves with policies required and permitted by those entities. When

research is being performed on specimens from a biobank, the investigator should understand the consent process used and any obligations placed on the researcher for return of results. Policies promulgated by registries and biobanks vary widely. Consent documents may clearly exclude return of results or, alternatively, provide detailed mechanisms for reporting research results to participants. Investigators using registries or other biobanks that have a policy to return results should determine if their institution permits forwarding of results to the honest broker and should be careful to avoid conflicts with the revised Common Rule.² In such situations, researchers may want to seek advice from legal counsel or institutional resources to clearly understand the interface between the revised Common Rule and biobank policies.

Recommendation: Investigators and their associated institutions should determine which, if any, individual research results may be returned to subjects. When considering what constitutes a result, investigators may consider various testing performed during the research protocol and not solely the research data generated at the completion of the study.

Recommendation: Investigators should take into account the ACMG incidental findings list of possible genes with significant clinical impact when determining what results will be provided to individuals.

Recommendation: When using specimens from a registry or biobank, the investigator should understand and comply with the requirements of the entity as well as applicable laws and regulations.

Informed Consent - Honoring Research Subjects' Preferences

Research subjects should have the option not to receive results, and researchers should honor such opt-out decisions. As part of the consent and opt-out process, care should be taken to consider both expected research data and results that may indicate a medical emergency. Planning ahead and ensuring these issues are dealt with during the informed consent process greatly simplifies decision making for investigators once studies are underway. The Common Rule² prohibits investigators from returning individual research results to subjects without the consent of the participant; it also requires the consent of the participant if medically important research results are to be withheld. The informed consent process is the optimal opportunity for the research subject to be offered choices regarding the return of individual research results. In most basic research studies, there is no ongoing contact between the research subject and the research team. This differs substantially from clinical research, in which there are often ongoing interactions between the two parties and thus opportunities to modify the informed consent over time. In addition, the ongoing interactions that are often part of clinical research may increase the likelihood that research subjects may change their

mind about receiving results and accommodations should be made to allow such changes.

Research subjects should be informed if research results and tests conducted by the investigator during the course of research are part of the HIPAA designated record set. In addition, subjects should consent to adding research results to their formal medical record, as well as communicating research results to medical professionals involved in their medical care.

The Common Rule prohibition on returning individual research results to subjects without their consent extends to secondary research. Researchers conducting secondary research must obtain the subject's specific consent to receive the secondary research results, as a broad consent used when gathering the specimen is insufficient in accordance with the revised Common Rule.²

The informed consent process should not overstate to research subjects the potential value of receiving their research results. Even screening tests and treatments validated in large randomized controlled clinical trials benefit at most only a small minority of patients and have modest impact on overall mortality.

Recommendation: Research subjects must consent to the return of individual research results; investigators conducting secondary research on biospecimens must obtain the participant's consent for the return of the specific secondary research results before returning any information.

Recommendation: Research subjects should be informed if the research results will be included in their medical record.

Designing a Communications Plan

An IRB-approved communications plan is a critical design element for studies returning individual research results to subjects. A good communications plan need not be lengthy but should focus on establishing clear take-away messages for research subjects, including the level of uncertainty about findings and possible follow-up actions.

A well-crafted communications plan establishes limits to the investigator's obligations, which should be consistent with the available research funds to support the proposed plan. The communications plan further defines the level of organizational commitment that will support the initiative. The written plan for returning individual results is critical for organizational oversight and should be reviewed and approved by the IRB.

A protocol for returning research results to participants should specifically address the following issues:

- Content of the results to be returned.
- Timing and method for communicating results.
- Obligations of the participant to maintain updated contact information.
- Option to receive or not receive results in the informed consent process.

- Who will communicate results and to whom.
- What will constitute a good faith effort to communicate research results?
- Any obligations (or lack thereof) for investigators to report specific findings with medical implications, including clinically relevant reportable findings as per the ACMG list of genes for which incidental findings should be considered, as well as any obligations to search for subsequent advances in scientific knowledge.
- When obligations to recontact or re-interpret research findings cease.
- Which results, if any, will become part of a designated record set (and therefore part of the medical record)?
- The level of uncertainty or caveats around the results to be provided.
- The mechanism for asking questions and receiving additional information if feasible and appropriate.

The informed consent process establishes expectations for the research subject, the investigator, and their institution. As such, it should outline roles and responsibilities for each party. A well-crafted informed consent outlines many of the protocol elements listed above, which are addressed in more detail in the remainder of this article.

Recommendation: Investigators should develop a communications plan that outlines the issues involved in returning individual results to research subjects. This plan should be approved by the IRB.

Recommendation: The return of individual research results should be discussed as part of the informed consent process and executed in a manner that supports participant understanding of the meaning, usefulness, and limitations of the results, as well as what follow-up (eg, further medical evaluation or counseling) may be required.

Recommendation: The informed consent document should establish clear expectations for the investigator, their institution, and the research subject.

Determining Who Receives the Results

Researchers should establish systems for returning individual research results only to those who indicated during the informed consent process their desire to receive results. The informed consent should clearly indicate who will receive the results and how the results will be communicated. When investigators return results directly to research subjects, the latter become responsible for communicating that information to health care providers, family members, and others as they deem appropriate. Reasons for returning results directly to the research subject and not the subject's health care provider include the following: research subjects are generally best positioned to determine which health care provider should receive the information; health care providers may be unclear on their obligation to follow up on research results; and some results may be seen as confidential by the research subject, especially in sensitive

situations, such as mental health concerns, and other socially sensitive conditions, such as sexually transmitted diseases.

In most cases involving research laboratories, an investigator will not have the understanding of personal circumstances that might influence a subject's preference and may be concerned that, by providing results to a research subject, the researcher is engaging in the practice of medicine or establishing a health care provider–patient relationship when none was intended.³ In this case, if an appropriate clinician with an established relationship with the research subject can be identified and with the research subject's consent, the identified provider may be an appropriate channel for return of research results. Research results should not be dumped on unsuspecting health care providers, particularly if they are not familiar with the types of results provided.

In rare situations, it may be appropriate to include a clause in the informed consent document, allowing research results to be returned to family members in case of the participant's death or incapacitation. This situation may occur especially in genetic research using germline biospecimens in which the research results may have implications for surviving family members.

The investigator considering the return of genetic results may want to incorporate genetic counseling into the return protocol. In such situations, the informed consent and HIPAA authorization should include the research subject's consent to disclose research results to the genetic counselor. This may involve additional expense, and adequate funding should be obtained before offering genetic counseling services.

Others to whom research results potentially could be returned include family members, guardians, and legally authorized representatives for special populations and incapacitated participants (*Considerations for Special Populations*).

Recommendation: Given that the specifications of prior Recommendations are met for return of individual research results, individual research results should be provided directly to the research subject. Results may be provided directly to health care providers, including genetic counselors, only with the participant's consent. Investigators should ensure that adequate funding supports the chosen communications plan.

Determining Who Communicates Research Results

The primary concern in choosing the means of communication is to ensure that research subjects understand the information being conveyed, any uncertainty or caveats, and appropriate next steps, if any, to be taken by the research subjects.

Failure to clearly communicate results to research subjects may result in misinterpretations, causing harm, such as personal distress and/or inappropriate courses of action. Communication should take into account the health literacy

of the research subject population. Once agreeing to provide individual research results, the investigator is under an obligation that may be expensive in terms of time and resources. For example, investigators may consider whether it would be helpful to use graphs, tables, reference ranges, or other tools to put the research results into context for research subjects. Such clear communication should ideally indicate both what the results mean and, just as important, what they do not mean. Clear communication regarding appropriate confirmatory testing is warranted, as is specifying the investigator's obligation, if any, to perform confirmatory testing and the research subject's next steps to obtain confirmatory testing. The recent NASEM report³ contains some excellent suggestions for supporting participant understanding of the research results being communicated.

Investigators have a variety of means available to communicate with research subjects, including in-person discussions, telephone calls, e-mail, web portals, and the postal service. Communication costs may be significant and depend on both the method of communication and who is doing the communicating. When using data from registries or similar organizations, a method of established communication may already be in place and familiar to participants, and such established vehicles for the return of individual research results are often an excellent choice. Considerations that may influence the selection of a communication method are as follows:

- Nature of the results being returned, including whether the results are covered under HIPAA privacy regulations.
- Whether return is a one-time event at the conclusion of the study or an ongoing process during the course of the research study.
- Whether the research subject may want or need to reference the data in the future.
- The size of the data file, especially in the case of raw data.
- The sensitivity of the information being returned.
- The need for interpretation of the results by clinicians and/or investigators.
- The need for follow-up counseling.
- The ease in which the communication vehicle will support clear portrayal of the results.
- The nature of the community to which results are returned and the resources available (eg, internet accessibility, comfort with technology, level of education).
- Potential language comprehension considerations.

The informed consent should address research subject responsibilities related to the return of individual research results (eg, updating contact information). Furthermore, the consent may specify what will be considered reasonable good faith efforts to communicate results and under what circumstances communication efforts will be discontinued.

The communicator should have the expertise to answer questions likely to be posed by the research subject and should operate within the scope of their professional

practice or license. Factors that may influence selection of the appropriate communicator include potential clinical actionability of the results being communicated and appropriate next clinical steps; scope of professional practice/license and expertise and ability to effectively communicate; and prior experience with communicating research results.

Recommendation: Investigators should select communication methods and resources designed to support research subjects' understanding of the results, address any uncertainty or caveats concerning the results, and outline any appropriate next steps to be taken by the research subjects. Consideration should be given to the health literacy of the subject as well as the ability of the communicator to provide the results. Furthermore, the cost of the communications plan should be consistent with available funding.

Recommendation: The informed consent process should establish the good faith efforts that will be made by the research team to communicate with the subjects and the responsibilities of all participants.

Timing the Return of Results

Decisions regarding the timing of the return of individual results are integral to the design of most interventional clinical trials and must thus be factored into planning of the trial, generation of the protocol, and construction of study operations manuals. Care must be taken to ensure that results are not returned in a manner that would undermine the integrity of the clinical trial by changing the behavior of the research subjects. There are many ways in which knowledge of clinical laboratory results can undermine the blinding of a clinical trial. For this reason, many trials will opt not to provide trial data to either research subjects or site investigators, except in rare circumstances, such as abnormal laboratory values pointing to a medical emergency. Plans for dealing with such results should be incorporated into study materials.

Studies on banked or registry biospecimens are generally performed well after the samples were originally obtained; it is therefore difficult in many cases to specify when data may become available to research subjects. It is important not to rush the return of results, especially if there is potential for increased uncertainty of meaning and significance with early data return. Research subjects who have provided a biospecimen may have an unrealistic expectation that data will be conveyed soon after specimen donation; the informed consent process should clarify how long the biospecimen may be held before it is considered for inclusion in a research study so that appropriate expectations are established.

With the passage of time, interpretations of data, particularly genetic data, may change.^{54–56} As a part of informed consent, investigators should make it clear to research subjects whether and when such changes in understanding will trigger additional disclosures to subjects, and when obligations to recontact will cease (eg, when funding ends).

As described above, the informed consent process should also establish research subject obligations, such as maintaining updated contact information to facilitate communication with the research team.

Recommendation: Investigators should clearly communicate when research subjects might expect return of their individual results and when obligations to recontact will cease. Such timing should ensure that the study itself will not be compromised.

Adequate Funding and Organizational Commitment

It is critical to ensure that the research protocol includes adequate funding to execute the communications plan. Organizational commitment, training resources, and logistical support are also vital elements. Researchers are not obligated to take on routine return of individual results when suitable funding has not been obtained.

Recommendation: Adequate funding, training, and organizational support must be available to meet obligations to research subjects. Investigators should carefully consider and obtain needed financial and logistical support to successfully implement the proposed return of individual results plan.

Considerations for Special Populations

For purposes of this article, special populations include study participants representing two distinct categories—vulnerable populations (Table 1) and culturally or geographically distinct populations.

The Common Rule requires that research studies include additional safeguards to protect the rights and welfare of vulnerable populations,⁵⁷ and it may be useful to include individuals with special expertise associated with these individuals in both the study team and IRB.

Culturally or geographically distinct populations are those groups whose ordinary cultural milieu differs from that of the general population (and typically that of the investigator). This designation may be applicable to members of indigenous populations, such as Native American, Amish, or other religious communities, or to those living in geographic isolation, such as members of highly rural communities. Vulnerable populations and those seen as culturally or geographically distinct may overlap. The safeguards required for the protection of these populations are as varied as the populations themselves.

Large-scale research projects involving biospecimens may also warrant special consideration. This may include community participation on an advisory board⁵⁸ or other methods of ensuring that the interests of the research subject population are heard and appropriately accommodated.

Recommendation: When working with vulnerable or culturally distinct populations, investigators should

consider unique aspects that may impact the return of individual research results.

Recommendation: For large-scale research projects, investigators may consider ways to seek input from the research subject population.

Summary of Recommendations

These Recommendations are designed primarily as an educational resource for biomedical researchers to assist in navigating issues pertaining to the return of individual research results. Adherence to these Recommendations is voluntary and does not necessarily ensure compliance with all applicable regulations or a successful research or clinical outcome. These Recommendations are focused on US federal regulations; state, local, and institutional regulations have not been considered. Therefore, these Recommendations are not inclusive of all possible scenarios. Investigators should apply their own professional judgment in consultation with their institution's human subjects protection infrastructure.

Planning the Study and the Informed Consent Process

1. *Investigators and their associated institutions should determine which, if any, individual research results may be returned to subjects. When considering what constitutes a result, investigators may consider various testing performed during the research protocol and not solely the research data generated at the completion of the study.*
2. *Investigators should develop a communications plan that outlines the issues involved in returning individual results to research subjects. This plan should be approved by the IRB.*
3. *The return of individual research results should be discussed as part of the informed consent process and executed in a manner that supports participant understanding of the meaning, usefulness, and limitations of the results, as well as what follow-up (eg, further medical evaluation or counseling) may be required.*
4. *The informed consent document should establish clear expectations for the investigator, their institution, and the research subject.*
5. *When using specimens from a registry or biobank, the investigator should understand and comply with the requirements of the entity as well as applicable laws and regulations.*
6. *Research subjects must consent to the return of individual research results; investigators conducting secondary research on biospecimens must obtain the participant's consent for the return of the specific secondary research results before returning any information.*
7. *Research subjects should be informed if the research results will be included in their medical record.*

8. *The informed consent process should establish the good faith efforts that will be made by the research team to communicate with the subjects and the responsibilities of all participants.*
9. *Investigators should clearly communicate when research subjects might expect return of their individual results and when obligations to recontact will cease. Such timing should ensure that the study itself will not be compromised.*
10. *Adequate funding, training, and organizational support must be available to meet obligations to research subjects. Investigators should carefully consider and obtain needed financial and logistical support to successfully implement the proposed return of individual results plan.*
11. *When working with vulnerable or culturally distinct populations, investigators should consider unique aspects that may impact the return of individual research results.*
12. *For large-scale research projects, investigators may consider ways to seek input from the research subject population.*

Communicating Results

13. *Investigators should select communication methods and resources designed to support research subjects understanding of the results, address any uncertainty or caveats concerning the results, and outline any appropriate next steps to be taken by the research subjects. Consideration should be given to the health literacy of the subjects as well as the ability of the communicator to provide the results. Furthermore, the cost of the communications plan should be consistent with available funding.*
14. *Only results from CLIA-certified laboratories should be reported to individual research subjects.*
15. *Investigators should return results from tests performed under a laboratory's CLIA certification provided that doing so does not undermine the integrity of the underlying investigation and return of individual results is feasible given the resources available.*
16. *Investigators should not return results that are neither actionable nor validated.*
17. *Investigators should consider returning results that are validated but not currently clinically actionable.*
18. *Investigators should take into account the ACMG incidental findings list of possible genes with significant clinical impact when determining what results will be provided to individuals.*
19. *Research results that cannot be interpreted at the individual level, such as results derived from anonymized or de-identified biospecimens, cannot practicably be returned by the research team.*
20. *Given that the specifications of prior Recommendations are met for return of individual research results,*

individual research results should be provided directly to the research subject. Results may be provided directly to health care providers, including genetic counselors, only with the participant's consent. Investigators should ensure that adequate funding supports the chosen communication plan.

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References

1. Code of Federal Regulations: Protection of Human Subjects, title 45 CFR 46 (2018). Available at <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html> (accessed December 2019)
2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: The Belmont Report: Office of the Secretary Ethical Principles and Guidelines for the Protection of Human Subjects of Research. April 18, 1979. Available at <http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html> (accessed December 2019)
3. National Academies of Sciences, Engineering, and Medicine: Returning Individual Research Results to Participants: Guidance for a New Research Paradigm. Washington, DC: The National Academies Press, 2018. Available at <https://doi.org/10.17226/25094> (accessed December 2019)
4. Clayton EW, Steinberg KK, Khoury MJ, Thomson E, Andrews L, Kahn MJ, Kopelman LM, Weiss JO: Informed consent for genetic research on stored tissue samples. *JAMA* 1995, 274:1786–1792
5. Grizzle W, Grody WW, Noll WW, Sobel ME, Stass SA, Trainer T, Travers H, Weedn V, Woodruff K, Ad Hoc Committee on Stored Tissue, College of American Pathologists: Recommended policies for uses of human tissue in research, education, and quality control. *Arch Pathol Lab Med* 1999, 123:296–300
6. Caulfield T, McGuire AL, Cho M, Buchanan JA, Burgess MM, Danilczyk U, Diaz CM, Fryer-Edwards K, Green SK, Hodosh MA, Juengst ET, Kaye J, Kedes L, Knoppers BM, Lemmens T, Meslin EM, Murphy J, Nussbaum RL, Otlowski M, Pullman D,

- Ray PN, Sugarman J, Timmons M: Research ethics recommendations for whole-genome research: consensus statement. *PLoS Biol* 2008, 6:e73
7. Bevilacqua G, Bosman F, Dassel T, Höfler H, Janin A, Langer R, Larsimont D, Morente MM, Riegman P, Schirmacher P, Stanta G, Zatlouk K, Caboux E, Hainaut P: The role of the pathologist in tissue banking: European Consensus Expert Group Report. *Virchows Arch* 2010, 456:449–454
 8. Bledsoe MJ, Grizzle WE, Clark BJ, Zeps N: Practical implementation issues and challenges for biobanks in the return of individual research results. *Genet Med* 2012, 14:478–483
 9. Chan B, Facio FM, Eidem H, Hull SC, Biesecker LG, Berkman BE: Genomic inheritances: disclosing individual research results from whole-exome sequencing to deceased participants' relatives. *Am J Bioeth* 2012, 12:1–8
 10. Hull SC, Chan B, Biesecker LG, Berkman BE: Response to open peer commentaries on genomic inheritances: disclosing individual research results from whole-exome sequencing to deceased participants' relatives. *Am J Bioeth* 2012, 12:W9–W10
 11. Klitzman R, Appelbaum PS, Fyer A, Martinez J, Buquez B, Wynn J, Waldman CR, Phelan J, Parens E, Chung WK: Researchers' views on return of incidental genomic research results: qualitative and quantitative findings. *Genet Med* 2013, 15:888–895
 12. Ross LF, Saal HM, David KL, Anderson RR, Anderson RR, American Academy of Pediatrics, American College of Medical Genetics and Genomics: Technical report: ethical and policy issues in genetic testing and screening of children. *Genet Med* 2013, 15: 234–245
 13. Bledsoe MJ, Clayton EW, McGuire AL, Grizzle WE, O'Rourke PP, Zeps N: Return of research results from genomic biobanks: cost matters. *Genet Med* 2013, 15:103–105
 14. Holm IA, Savage SK, Green RC, Juengst E, McGuire A, Kornetsky S, Brewster SJ, Joffe S, Taylor P: Guidelines for return of research results from pediatric genomic studies: deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board. *Genet Med* 2014, 16:547–552
 15. Jarvik GP, Amendola LM, Berg JS, Brothers K, Clayton EW, Chung W, Evans BJ, Evans JP, Fullerton SM, Gallego CJ, Garrison NA, Gray SW, Holm IA, Kullo IJ, Lehmann LS, McCarty C, Prows CA, Rehm HL, Sharp RR, Salama J, Sanderson S, Van Driest SL, Williams MS, Wolf SM, Wolf WA, eMERGE Act-ROR Committee and CERC Committee; CSER Act-ROR Working Group, Burke W: Return of genomic results to research participants: the floor, the ceiling, and the choices in between. *Am J Hum Genet* 2014, 94:818–826
 16. Weiner C: Anticipate and communicate: ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts (December 2013 report of the Presidential Commission for the Study of Bioethical Issues). *Am J Epidemiol* 2014, 180:562–564.15
 17. Williams JK, Cashion AK, Brooks PJ: Return of anticipated and incidental results from next-generation sequencing: implications for providers and patients. *NAM Perspect* 2015. Discussion Paper. Washington, DC: National Academy of Medicine. <https://doi.org/10.31478/201502i>
 18. Fernandez CV, O'Rourke PP, Beskow LM: Canadian research ethics board leadership attitudes to the return of genetic research results to individuals and their families. *J Law Med Ethics* 2015, 43:514–522
 19. Beskow LM, O'Rourke PP: Return of genetic research results to participants and families: IRB perspectives and roles. *J Law Med Ethics* 2015, 43:502–513
 20. Tassé A-M, Bledsoe MJ, Giepmans L, Rahimzadeh V: Legal and ethical implications of data sharing in international biobanking research: toward a global response. *Biopreserv Biobank* 2016, 14: 193–194
 21. Bledsoe MJ: Ethical legal and social issues of biobanking: past, present, and future. *Biopreserv Biobank* 2017, 15:142–147
 22. Bledsoe MJ: The final common rule: implications for biobanks. *Biopreserv Biobank* 2017, 15:283–284
 23. Sobel ME, Dreyfus JC: Disruptive influences on research in academic pathology departments: proposed changes to the common rule governing informed consent for research use of biospecimens and to rules governing return of research results. *Am J Pathol* 2017, 187:4–8
 24. ACMG Board of Directors: Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics. *Genet Med* 2017, 19:721–722
 25. Botkin JR, Appelbaum PS, Bakken S, Brown C, Burke W, Fabsitz R, Gamble VN, Gonsalves G, Kost R, Leonard DGB, McGuire A, Nichols JH, Patrick-Lake B, Wilkins CH, Zikmund-Fisher BJ: Standardizing return of participant results. *Science* 2018, 362: 759–760
 26. Evans BJ: HIPAA's individual right of access to genomic data: reconciling safety and civil rights. *Am J Hum Genet* 2018, 102:5–10
 27. Dreyfus JC, Sobel ME: Concern about justifying the release of genomic data as a civil right. *Am J Hum Genet* 2018, 103:163–165
 28. Wolf LE, Beskow LM: New and improved? 21st century cures act revisions to certificates of confidentiality. *Am J Law Med* 2018, 44: 343–358
 29. Wong CA, Hernandez AF, Califf RM: Return of research results to study participants: uncharted and untested. *JAMA* 2018, 320: 435–436
 30. Secretary's Advisory Committee on Human Research Protections: Letter to Secretary of Health and Human Services, the Honorable Sylvia Burwell. 2016 July 21, Attachment B: Return of Individual Research Results. Available at <http://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-return-individual-research-results/index.html> (accessed December 2019)
 31. Secretary's Advisory Committee on Human Research Protections: Letter to Secretary of Health and Human Services, the Honorable Sylvia Burwell. Attachment C: Return of Individual Results and Special Consideration of Issues Arising from Amendments of HIPAA and CLIA. September 28, 2015. Available at <http://www.hhs.gov/ohrp/sachrp-committee/recommendations/2015-september-28-attachment-c/index.html> (accessed December 2019)
 32. Tandy-Connor S, Gultinan J, Krempeley K, LaDuca H, Reineke P, Gutierrez S, Gray P, Tippin Davis B: False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med* 2018, 20:1515–1521
 33. US Food and Drug Administration: The FDA Warns against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication (2018). Available at <https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-many-genetic-tests-unapproved-claims-predict-patient-response-specific> (accessed December 2019)
 34. US Code: Clinical Laboratory Improvement Amendments of 1988, 42 USC. Available at <https://www.cdc.gov/clia/law-regulations.html> (accessed December 2019)
 35. US Code: Clinical Laboratory Improvement Amendments of 1988, Certificate Requirement, 42 USC 263(b). Available at <https://www.cdc.gov/clia/law-regulations.html> (accessed December 2019)
 36. Office of Human Research Protections: Guidance on research using coded private information or specimens. October 16, 2008. Available at <http://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html> (accessed December 2019)
 37. Code of Federal Regulations: The HIPAA Privacy Rule, Title 45 CFR 160 (2013) Available at www.hhs.gov/hipaa/for-professionals/privacy/index.html (accessed December 2019)
 38. Code of Federal Regulations: The HIPAA Privacy Rule, Title 45 CFR 164 (2013). Available at www.hhs.gov/hipaa/for-professionals/privacy/index.html (accessed December 2019)

39. Code of Federal Regulations: The HIPAA Privacy Rule, Title 45 CFR 164 (2013). Available at www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html (accessed December 2019)
40. Gymrek M, McGuire AL, Golan D, Halperin E, Erlich Y: Identifying personal genomes by surname inference. *Science* 2013, 339:321–324
41. Weil CJ, Mechanic LE, Green T, Kinsinger C, Lockhart NC, Nelson SA, Rodriguez LL, Buccini LD: NCI think tank concerning the identifiability of biospecimens and “-omic” data. *Genet Med* 2013, 15:997
42. US Code: Federal Food, Drug, and Cosmetic Act, Title 21 USC 351–352, 360. Available at <https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act> (accessed December 2019)
43. Code of Federal Regulations: CLIA Regulations, Title 42 CFR 493. Available at <https://www.cdc.gov/clia/law-regulations.html> (accessed December 2019)
44. US Food and Drug Administration: Laboratory Developed Tests 2014. Available at <https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests> (accessed December 2019)
45. Ioannidis JPA, Allison DB, Ball CA, Coulibaly I, Cui X, Culhane AC, Falchi M, Furlanello C, Game L, Jurman G, Mangion J, Mehta T, Nitzberg M, Page GP, Petretto E, van Noort V: Repeat-ability of published microarray gene expression analyses. *Nat Genet* 2009, 41:149–155
46. Begley CG, Ioannidis JPA: Reproducibility in science: improving the standard for basic and preclinical research. *Circ Res* 2015, 116:116–126
47. Ioannidis JPA: The reproducibility wars: successful, unsuccessful, uninterpretable, exact, conceptual, triangulated, contested replication. *Clin Chem* 2017, 63:943–945
48. Hunter JE, Irving SA, Biesecker LG, Buchanan A, Jensen B, Lee K, Martin CL, Milko L, Muessig K, Niehaus AD, O’Daniel J, Piper MA, Ramos EM, Schully SD, Scott AF, Slavotinek A, Sobreira N, Strande N, Weaver M, Webber EM, Williams MS, Berg JS, Evans JP, Goddard KAB: A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Genet Med* 2016, 18:1258–1268
49. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O’Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG: CORRIGENDUM: ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2017, 19:606
50. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med* 2017, 19:249–255
51. Ormond KE, O’Daniel JM, Kalia SS: Secondary findings: how did we get here, and where are we going? *J Genet Couns* 2019, 28:326–333
52. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O’Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG, American College of Medical Genetics and Genomics: ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013, 15:565–574
53. Hofbauer GF, Kamarashev J, Geertsen R, Boni R, Dummer R: Melan A/MART-1 immunoreactivity in formalin-fixed paraffin-embedded primary and metastatic melanoma: frequency and distribution. *Melanoma Res* 1998, 8:337–343
54. Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, Cho MK, Christman MF, Green RC, Hall R, Illes J, Keane M, Knoppers BM, Koenig BA, Kohane IS, Leroy B, Maschke KJ, McGeveran W, Ossorio P, Parker LS, Petersen GM, Richardson HS, Scott JA, Terry SF, Wilfond BS, Wolf WA: Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med* 2012, 14:361–384
55. Bombard Y, Brothers KB, Fitzgerald-Butt S, Garrison NA, Jamal L, James CA, Jarvik GP, McCormick JB, Nelson TN, Ormond KE, Rehm HL, Richer J, Souzeau E, Vassy JL, Wagner JK, Levy HP: The responsibility to recontact research participants after reinterpretation of genetic and genomic research results. *Am J Hum Genet* 2019, 104:578–595
56. David KL, Best RG, Brenman LM, Bush L, Deignan JL, Flannery D, Hoffman JD, Holm I, Miller DT, O’Leary J, Pyeritz RE: Patient recontact after revision of genomic test results: points to consider—a statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2019, 21:769–771
57. Office of Human Research Protections, Vulnerable Populations. Available at <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/vulnerable-populations/index.html> (accessed December 2019)
58. McCarty CA, Garber A, Reeser JC, Fost NC, Personalized Medicine Research Project Community Advisory Group and Ethics and Security Advisory Board: Study newsletters, community and ethics advisory boards, and focus group discussions provide ongoing feedback for a large biobank. *Am J Med Genet A* 2011, 155A:737–741