Do Institutional Review Boards Adequately Address the CLIA Regulations When Studies Return Individual Research Results?

A Document Analysis of IRB Policies and Guidance

by

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ABSTRACT

In 2014, the Centers for Medicare and Medicaid Services (CMS), which oversees the federal Clinical Laboratories Improvement Amendments (CLIA) program, issued guidance that the CLIA requirements apply when researchers seek to return individual-level research findings to study participants or their physician (Centers for Medicare & Medicaid Services, 2014). The present study explores the stance of U.S. Institutional Review Boards (IRBs) toward the applicability of and compliance with the CLIA regulations when studies plan to return individual research results (RIRR). I performed a document content analysis of 73 IRB policies and supporting documents from 30 United States (U.S.) institutions funded for biomedical research by the National Institutes of Health in 2017. Documents analyzed included policies, procedures, guidance, protocol and consent templates, and miscellaneous documents (such as IRB presentations) found to address the RIRR to study participants. I used qualitative content and document analysis to identify themes across institutions related to the CLIA regulations and the RIRR. Basic descriptive statistics were used to represent the data quantitatively.

The study found that 96.67% (n=29) of institutions had documents that addressed the RIRR to participants. The majority of the institutions had at least one document that referenced the CLIA regulations when discussing the practice of disclosing participant-specific results [76.67% (n=23)]. The majority of institutions [56.67% (n=17)] indicated that they require compliance with the CLIA regulations for returning individual study findings to participants, while 13.33% (n=4) recommended compliance. The intent of two (6.67%) institutions was vague or unclear, while seven (26.67%) institutions were silent on the topic altogether. Of the

23 institutions that referenced "CLIA" in their documents, 52.17% only mentioned CLIA in a one or two-sentence blurb, providing very little guidance to investigators.

The study results provide evidence that the majority of U.S. biomedical institutions require or recommend compliance with CLIA stipulations when investigators intend to return individual research results to study participants. However, the data indicates there is heterogeneity and variation in the quality of the guidance provided.

DEDICATION

This dissertation is dedicated to my family for their unwavering support. First and foremost, I would like to thank my husband - Steve - for sticking with me throughout this process. Steve: you have given me endless patience, support, and guidance; spent countless weekends as a solo parent; counseled me; edited numerous documents; talked me off the ledge; provided space when it was needed; inserted humor whenever possible; and, above all else, loved me. None of this would have been possible without you by my side. Thank you for giving me the motivation I needed to finish. I love you.

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LIST OF ACRONYMS

AAHRPP - Association for the Accreditation of Human Research Protection Programs

ACMG - American College of Medical Genetics

AER - Advancing Ethical Research

ANPRM - Advance Notice of Proposed Rulemaking

CAQDAS - Computer-Assisted Qualitative Data Analysis Software

CDPH - California Department of Public Health

CESR - Clinical Exploratory Sequencing Research

CLEP - New York's Clinical Laboratory Evaluation Program

CLIA – Clinical Laboratory Improvement Amendments

CMS - Centers for Medicare and Medicaid Services

ddNTP - Dideoxynucleotide Triphosphate

DNA – Deoxyribonucleic Acid

DRS - Designated Record Set

ELSI - Ethical, Legal, and Social Implications

FDA – Food and Drug Administration

FISH - Fluorescent in situ Hybridization

GDR - Genotype-Driven Recruitment

HHS – Health and Human Services

HIPAA - Health Information Portability and Accountability Act

HRPP - Human Research Protection Program

IDE - Investigational Device Exemption

IF – Incidental Findings

IRB - Institutional Review Boards

NASEM - National Academies of Sciences, Engineering, and Medicine

NBAC - National Bioethics Advisory Commission

NCATS - National Center for Advancing Translational Sciences

NGS – Next-Generation Sequencing

NHGRI – National Human Genome Research Institute

NHLBI – National Heart, Lung, and Blood Institute

NIH – National Institutes of Health

NPRM - Notice of Proposed Rulemaking

OCR – Office of Civil Rights

PCR - Polymerase Chain Reaction

PHI - Protected Health Information

PRIM&R - Public Responsibility in Medicine and Research

REB – Research Ethics Board

RFLP - Restriction Fragment Length Polymorphism

RIRR - Return of Individual Research Results

SACHRP - Secretary's Advisory Committee on Human Research Protections

SNF - Significant New Findings

SSCP - Single-Strand Confirmation Polymorphism

SWAN - Syndromes Without a Name

US – United States

WES – Whole Exome Sequencing

WGS – Whole Genome Sequencing

CHAPTER 1

INTRODUCTION

Advances in molecular and genomic biology have allowed scientists to make associations between specific genes and disease states at a rapid rate. As the potential benefits of genetic research are increasingly publicized, a growing number of physicians and their patients have been demanding genetic and genomic researchers disclose to them the results of genetic research studies. As a result, there has been a movement developing over the past ~15 years that has encouraged - out of respect for participants' autonomy - investigators to return both aggregate and individual research results to study participants. This movement has stimulated an energetic discussion about the practice amongst investigators, physicians, bioethicists, and study participants. Arguments on all sides of the debate call into question the roles and rights of the participant, the intent of research versus that of clinical practice, the investigator's obligations to the participant, the relevance and reliability of the molecular data, and the expected benefits and potential risks of participation in studies that ascertain new genetic information.

While numerous studies have concentrated on the ethical, legal, and social implications (ELSI) associated with the disclosure of research results, few have focused on the regulations mandated by the Clinical Laboratories Improvement Amendments (CLIA) of 1988, or the role and impact the regulations have on research studies that communicate individual genetic research findings to participants or their physicians. In the United States, the Centers for Medicare & Medicaid Services (CMS) oversee all clinical laboratory testing under the CLIA regulations (also referred to simply as CLIA). The CLIA program ensures quality laboratory testing by requiring laboratories performing clinical testing to meet the

requirements of CLIA set by CMS and the CLIA program; those that do receive certificates of compliance (CLIA certificates) for their clinical testing. Only CLIA-certified laboratories can return lab test results to patients and their physicians for clinical diagnosis, treatment, or management. Since most research laboratories are not CLIA-certified, questions can arise about the quality and validity of the research data in non-CLIA certified labs, and the legality of disclosure, if their data are to be returned to the subjects. Furthermore, due to the uncertainty and disagreement of what research results fall under the purview of the CLIA regulations, there appears to be no consistency in the practice of abiding by CLIA requirements when disclosing research findings to study subjects (Biesecker et al., 2009; Roberts et al., 2010).

Within the context of the CLIA regulations, my research addresses the practice of returning individual-level research results to study participants. [1] In this dissertation, I have: outlined federal regulations and guidance; highlighted key regulatory, ethical, and scientific issues; and conducted a study of whether current Human Research Protection Program (HRPP) and Institutional Review Board (IRB) policies, procedures, and supporting documentation are suitable for addressing CLIA compliance when investigators are inclined to disclose research results to study subjects. For this study, I consider individual research results to include results related to the study aims and incidental or secondary findings under the umbrella term of individual research results (to be referred to as RIRR for the purposes of this dissertation).

[1] Although returning research results encompasses both aggregate and individual results, this study focuses on the return of individual genetic research results.

Case Example

In 2007, a young man named Steven Keating found out he had a brain abnormality while participating in a research study involving MRI brain scans (Keating, 2016). While the abnormality was monitored, it wasn't until a follow-up brain scan in 2014 that he was diagnosed with a large brain tumor. At the time of his diagnosis, Mr. Keating was a Ph.D. student at the Massachusetts Institute of Technology. He wanted access to all medical and research data associated with his condition and eventually acquired access to over 200 gigabytes of medical data. As he was turned down to get his tumor sequenced clinically, he opted to participate in a research study that included somatic tumor sequencing analysis (Raths, 2016). In a 2016 interview, Keating said:

> I thought this is great; I will donate part of the tissue to science, and I can get my own genome back for my tumor, which can help me make decisions in the future about clinical trials and things like that (Raths, 2016, para. 7).

However, he ran into a barrier to getting access to the sequencing data as the sequencing was performed in a non-CLIA certified research laboratory.

> Of course, the sequencers at MIT were top of the line, but they weren't CLIA-certified because that costs thousands of dollars to do. What that meant was that everyone could see my genome except me. My doctors could see it, researchers at my university — people right around me — could, but I couldn't. And I am the one who gave them my own brain! Why can't I accept the liability of understanding it was done on this machine? (Raths, 2016, para. 8)

Eventually, the institute where the research took place agreed to pay to have Mr. Keating's tumor re-sequenced in a CLIA-certified clinical laboratory in order to give him access to the data. From his experiences, Mr. Keating became an advocate for

patient and participants' access to data and open data sharing (Keating, 2016; Lohr, 2015).

Steven Keating's story illustrates the complexity of returning individual-level study findings to participants. As I will show, it highlights the blurring of the lines between research and clinical testing, therapeutic misconception, the impact the return of results or incidental findings can have on a participant's life, and the issue of regulatory hurdles (to name a few). On the one hand, Mr. Keating benefited from his participation in research as his brain tumor may never have been discovered had he not been told of the abnormalities seen on his initial MRI. On the other hand, he purposefully participated in a tumor sequencing study with the expectation that he would receive the sequencing data back to help him "make decisions in the future about clinical trials and things like that" (Raths, 2016, para. 7). His statement from a 2016 interview demonstrates that he wanted the data for the management of his disease, which clearly places the use of the data under the auspices of the CLIA regulatory framework. Yet, he viewed the CLIA requirements as a bureaucratic process interfering in his ability to access data about himself.

Statement of the Research Problem

Lack of federal regulation and guidance on the disclosure of individual research results to study participants has created variety and diversity in practices across US institutions. Furthermore, lack of clarity and harmonization across federal agencies with respect to the applicability of the CLIA regulations when results are returned has led to confusion, uncertainty, and disagreement within the research community (Bookman et al., 2006; Evans & Wolf, 2020; National Academies of Sciences, 2018). As the primary role of IRBs is to ensure the protection of study participants' rights and welfare, one can envision that institutions may use the IRB approval pathway as a checkpoint for compliance with the CLIA regulations when

investigators return research results. Even the National Academies of Sciences, Engineering, and Medicine (NASEM) (2018) recently identified IRBs as a key stakeholder in the RIRR process and recommended that "institutions and IRBs should develop policies to support the review of plans to return individual research results". Additionally, the report specifically recommended that IRBs play a key role in reviewing and permitting "investigators to return individual research results" that are "high quality" (p. 17). To date, no published research studies have looked at extant IRB policies and procedures to understand if they are ready for such a role. This dissertation aims to fill this knowledge gap.

Purpose of and Need for this Study

Until recently, there had been no uniform policies or regulations that specifically addressed the return of research results. Although the 2018 Final Rule to update the Health and Human Services (HHS) policy for the Protection of Human Research Subjects asked investigators to add that RIRR may occur during the course of a study, it did not address the quality, accuracy, or validity of the data to be returned. In 2014, CMS released specific guidance outlining their expectation that laboratories obtain CLIA-licensure in order to disclose individual research results (Centers for Medicare & Medicaid Services, 2014). Although this guidance has been out seven years, there is considerable variation in practice, including deviation from the regulatory requirement.

As the role of genetics and genomics in research and clinical care continues to advance, the lack of consensus around the scope and applicability of CLIA in research will continue to become more prevalent. The arrival of whole-genome sequencing, in which investigators are able to look at the entire human genome of research participants, complicates the issue, given the immense amount of data generated, a large number of potential errors, and the increased frequency of

incidental findings.

The impact of the CLIA regulations on research is an essential issue that the research community is struggling to understand, and the federal government is failing to harmonize across regulations. Over the past twelve years, I have had countless informal discussions with colleagues within the IRB and research community regarding RIRR and compliance with CLIA regulations. These interactions have highlighted the lack of harmony and guidance amongst IRB practices when addressing compliance with CLIA in research protocol development and review. Further research needs to be conducted on the practices of IRBs in the United States regarding this important topic. IRB members, institutional officials, compliance officials, bioethicists, lawyers, and investigators have voiced their concerns and confusion over what the CLIA regulations mean to their research programs (Noren & Russell-Einhorn, 2010). Year-after-year the issue is discussed and debated at the annual Public Responsibility in Medicine and Research (PRIM&R) conference on Advancing Ethical Research (AER), as well as other national conferences, and most recently at the NASEM (Childers et al., 2019; Forster, 2016; Grienauer et al., 2017; National Academies of Sciences, 2018; Noren & Russell-Einhorn, 2010; Wolf, 2012).

The recent release of the NASEM report on the *Return of Individual-Specific Research Results Generated in Research Laboratories* (2018) illustrates the timeliness and relevance of this issue. While the committee recommendations create a path forward in which non-CLIA laboratory-generated data could possibly be returned to study participants, a change in current regulations would be needed. As the rulemaking process took the federal government over seven years to make changes to the Common Rule, I do not envision the NASEM committee's recommended changes will be implemented quickly, if at all. However, if they are implemented, they will significantly impact the research community, including

investigators, IRBs, and study participants. The time is ripe for a more in-depth look at IRBs' preparedness for the return of individual genetic research results. Hence this study.

Research Questions

Given the growing movement to return individual genetic research results to study participants, are IRBs' policies and supporting documentation suitable for addressing compliance with the CLIA regulations?

Additional Research Sub-Questions (RSQ):

RSQ 1: How do regulations and guidance from federal agencies address the issue of CLIA compliance when returning research results?

RSQ 2: How did disclosure of research results and compliance with the CLIA regulations become a highly debated topic?

RSQ 3: Do IRB policies and supporting documentation address key ethical principles regarding RIRR and/or complying with CLIA regulations? Do IRB policies address the guidance from federal agencies?

RSQ 4: How do results from this research project compare to previous research conducted on the topic of IRB policies and guidance documents addressing returning research results to study participants? (Kozanczyn et al., 2007)

Summary

In Chapter 1, I have described the context for and provided an overview of debates about the growing expectation from study participants that they are given access to their individual research data when they participate in a research study. I introduced the ongoing deliberations within the research community and federal

agencies about the applicability of the CLIA regulations when investigators disclose study findings.

Chapter 2 addresses RSQ 1, how regulations and guidance from federal agencies address CLIA compliance when returning research results. The chapter outlines the role federal agencies play in human subjects research and how they have (or have not) addressed the issue of RIRR. The chapter starts by examining the Office of Human Research Protection's (OHRP) Common Rule and recent federal changes implemented to increase participant protections. I touch briefly on the Food and Drug Administration's (FDA) regulations before delving into the Centers for Medicare & Medicaid Services (CMS) and Office of Civil Rights (OCR) Health Information Portability and Accountability Act (HIPAA) regulations. I introduce the CLIA regulations before the HIPAA regulations to set up the current perceived conflict around the RIRR between the two rules. I conclude the chapter by looking at additional guidance from the NIH and NASEM working groups and HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) recommendations on the return of individual research results.

Chapter 3 addresses RSQ 2, exploring how disclosure of research results and compliance with the CLIA regulations became a highly debated topic. The chapter explains how the genetics community became the center of the return of research results debate due to their interactions with the rare disease community. It briefly covers additional scenarios that have added to the push for RIRR, including the introduction of genotype-driven recruitment and the discovery of incidental findings in the sheer amount of genomic data that new sequencing technologies can generate. Next, I present the perspectives on RIRR of the research community, including study participants, investigators, and IRBs. Finally, I review some relevant law cases that provide some insight into the legal issues that may come into play in

the courts.

Chapter 4 describes the design and methods I used to (1) select the institutions included in my sample set; (2) identify and collect the documents for my analysis; (3) employ a software system for document organization, management, and coding; (4) identify and archive online document location; and (5) code data for analysis. Finally, I review the validity and reliability of the data.

Chapter 5 provides a detailed review of the results from my analysis, including (1) institutional demographics; (2) document characteristics; (3) emerging themes for returning research results and CLIA compliance from content analysis; (4) how documents address key ethical principles regarding RIRR and /or CLIA compliance as well as guidance from federal agencies (RSQ 3); and (5) a comparison of this study's findings to previously published research (RSQ 4).

Finally, in chapter 6, I provide a brief summary of the study findings and describe some outstanding research questions that must be resolved to address the return of individual research results and compliance with the CLIA regulations adequately and ethically.

CHAPTER 2

FEDERAL REGULATIONS AND GUIDANCE

Understanding the regulatory environment of research involving human subjects is critical to my research as institutional policies and procedures are used to communicate requirements from federal regulations. Historically, the three main federal agencies that oversee research with human subjects (OHRP, the FDA, and the OCR) had not directly addressed the topic of returning research findings to study subjects. Until recently, the CMS was the only federal regulatory agency that was not silent on the topic. While federal statutes have hardly addressed disclosure of individual-level findings back to study participants, advisory committees, and working groups have released guidance documents and position statements to try and fill in the gaps.

The Office of Human Research Protections (OHRP) and the Common Rule

The OHRP provides oversight for the HHS's policy for the Protection of Human Research Subjects, often referred to as the Common Rule. The Common Rule applies to research studies involving human subjects that are federally funded or take place at an institution that has agreed to abide by the Common Rule for all human subjects research, regardless of funding source ("Protection of Human Subjects," 1991). In essence, the Common Rule establishes the policies for obtaining the informed consent of the study participants and review of research involving human subjects by independent committees known as Institutional Review Boards (IRB). The primary role of the IRB is to ensure that the rights and welfare of study participants are protected. IRBs do so by reviewing the study objectives, protocol, and involvement of human subjects, including risks and benefits, consent, and subject selection procedures.

Up until 2018, the Common Rule had not directly addressed the disclosure of research results to study participants. The only language included in the Common Rule that addressed "research results" was in section 46.116(b)(5), which stated that subjects will be informed of "significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation" ("Protection of Human Subjects," 2009, p. 138). While the term "significant new findings (SNF)" is not defined in the rules and interpretation can vary by IRB, it has traditionally been construed to mean "new side effects of experimental drugs, changes in the frequency of side effects, major changes in study design, and changes in standard of care, such that subjects may be placed at more risk if participation in the study continues" (Simon et al., 2012, p. 421). While the SNF language was not designed to address the disclosure of individual-specific research data during or at the completion of the study, Simon et al. (2012) raised concerns that SNF language may be interpreted differently by study subjects leading to an expectation of the return of research results.

Final Common Rule Changes

On July 26, 2011, the HHS published an Advance Notice of Proposed Rulemaking (ANPRM) to request comment on how current regulations for the protection of human subjects and the Common Rule may be updated, streamlined, and improved. The ANPRM recognized that some IRBs make determinations regarding whether clinical results should be returned to study participants (U.S. Department of Health and Human Services, 2011). Therefore, one question the ANPRM sought comment on was whether standard algorithms could be developed to guide IRBs on when research results should be provided to participants and when they should not. While this was the only question that addressed the return of research results in the ANPRM, it demonstrates that HHS was aware of the issue.

When the Notice of Proposed Rulemaking (NPRM) was finally released on September 8, 2015, the return of results was addressed in a number of places, including (1) requiring the IRB to review the plan to return results; and (2) restricting the regulatory approval pathways that could approve studies intending to return results (*Federal Policy for the Protection of Human Subjects: Notice of Proposed Rulemaking*, 2015). The proposed rule recognized that:

> Challenges can arise regarding return of individual research results when it is not clear if the findings have clinical validity or utility or when the knowledge imparted may cause psychological distress or social harm. These issues have been the subject of frequent discussion, particularly regarding the Clinical Laboratory Improvement Amendments of 1988 (*Federal Policy for the Protection of Human Subjects: Notice of Proposed Rulemaking*, 2015, p. 53988).

In all, HHS received more than 2,100 public comments to the NPRM ("Federal Policy for the Protection of Human Subjects," 2017). There was a mixed response with regards to proposed changes addressing the return of research results. Passionate, pro-disclosure proponents often cited respect for the participants and questioned the ethics of not disclosing clinically relevant findings (Angrist, 2016; Geisinger Health System, 2015; Harvard Personal Genome Project, 2016; Keating, 2016; PersonalGenomes.org, 2016). The American College of Medical Genetics (ACMG) expressed their concern that there would ever be a situation where clinically relevant results may not be returned, stating "the idea that an investigator could learn something about an individual that might be important to that individual's health and not be allowed to provide the individual with this information is profoundly disturbing" (American College of Medical Genetics, 2016, p. 9).

While the majority of respondents who addressed the issue agreed there was a benefit to participants, some cited the complexity of returning research results and concerns over implementation, including administrative and financial burden and liability (Remick, 2015; Schulman IRB, 2015). The concern that researchers would return non-CLIA-certified findings was another common theme expressed in the comments (American Society for Investigative Pathology, 2015; Duke University & Duke Medicine, 2015; McCall, 2016).

> We encourage clear guidance from OHRP that such Information should be confirmed in a CLIA-accredited laboratory prior to releasing results to patients. This protects patients from unnecessary re-contact, burden, and worry that could result from incorrectly generated or interpreted results generated in a research context. (Duke University & Duke Medicine, 2015, p. 16)

The amendment to the Common Rule (known as the Final Rule) was published on January 19, 2017, with an expected implementation date of January 21, 2019. The Final Rule did not adopt the proposed change that would have had IRBs reviewing plans to return clinically relevant results to participants. There was public concern that this requirement would place a burden on IRBs to find experts to assess RIRR and clinically relevant findings ("Federal Policy for the Protection of Human Subjects," 2017).

The Final Rule created a new exemption category (exempt from IRB review) for secondary use of identifiable data or biospecimens for which broad consent was obtained originally ("Federal Policy for the Protection of Human Subjects," 2017). This exemption would not apply if the investigator planned to return individual research results to participants as a part of the study design. However, this

exemption does not prevent investigators from returning individual research results when required by law ("Federal Policy for the Protection of Human Subjects," 2017).

With respect to the consent, the Final Rule addresses the issue of return of results as an additional element that should be provided to participants if applicable. The Final Rule stated, "a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions" ("Federal Policy for the Protection of Human Subjects," 2017, (§ __.116(c)(8)).

For studies that choose to utilize a broad consent for the collection of identifiable biospecimen or data for future use, the Final Rule requires a blanket statement that clinically relevant results may not be returned unless there is a plan to return such results in all circumstances:

> 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 must be included in the broad consent. ("Federal Policy for the Protection of Human Subjects," 2017, § __.116(d)(6))

In the end, although the return of results was incorporated into the Final Rule as a trigger for specific approval pathways and an element of some consent, there was no guidance provided on the quality of the data returned or how to review RIRR plans. With the Final Rule failing to address the CLIA debate, institutions are still left with inconsistency in IRB practices between institutions.

Association for the Accreditation of Human Research Protection Programs (AAHRPP). AAHRPP is a non-profit organization that accredits human research protection programs that meet high standards in quality, effectiveness, and efficiency in the protection of human subjects in research (Association for the

Accreditation of Human Research Protection Programs, n.d.). While AAHRPP does not fall under OHRP or the Common Rule, it does play an important role in guiding IRBs on policy development and best practices.

In order to obtain accreditation, organizations must meet certain standards and elements outlined by AAHRPP, which incorporate international and U.S. government requirements for the protection of human subjects along with best practices (Association for the Accreditation of Human Research Protection Programs, 2015). The standards, elements, and information needed to fulfill each element are outlined in AAHRPP's *Evaluation Instrument for Accreditation* document. Prior to the February 2018 version, the concept of returning research results to study participants was not discussed in the evaluation instrument (Association for the Accreditation of Human Research Protection Programs, 2015). However, starting in 2018, the instrument included language dealing with the "broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained" ("Federal Policy for the Protection of Human Subjects," 2017, § __.116(d)). The new instrument asks investigators to include a "statement regarding whether clinically relevant research results, including individual research results, will be disclosed to the participant, and if so, under what conditions" (Association for the Accreditation of Human Research Protection Programs, 2018, p. 117). This language was included in the evaluation once the revised Common Rule took effect. Prior to the common rule changes, there was no AAHRPP standard or element that addressed the return of research results.

The Food and Drug Administration (FDA)

The second regulatory agency that has oversight of research with human subjects is the Food and Drug Administration (FDA). The FDA regulations protect human subjects in any research study that involves an FDA-regulated drug, device,

biologic, food additive, color additive, electronic product, or other test article ("Protection of Human Subjects," 1980). FDA regulations do not directly address the disclosure of research results to study participants. That being said, some have raised the point that the FDA would consider research that returns laboratory data for clinical care to fall under the scope of an FDA investigational device exemption (IDE) (Secretary's Advisory Committee on Human Research Protections, 2015a). The IDE regulation allows investigational devices - not yet approved by the FDA - to be used in clinical studies (Food and Drug Administration, 2018; National Human Genome Research Institute, 2017). In the case of genomics research, the sequencing test would be considered a device. The 2017 NHGRI Points to Consider webpage addresses the IDE regulations in the context of genomic research. The site states:

> In the context of genomics research, the purpose of the IDE process is to demonstrate that a test has plausible analytical validity and to protect the interests of study participants who might receive test results that could affect their clinical care. (National Human Genome Research Institute, 2017)

Centers for Medicaid and Medicare Services (CMS) and the Clinical Laboratory Improvement Amendments (CLIA)

Until recently, the research community has not typically viewed CMS as an agency that has oversight of research involving human subjects. Nevertheless, CMS regulations are applicable when research results are disclosed to participants in some instances.

CMS oversees and administers the CLIA program that governs clinical laboratory testing in the United States. Congress passed CLIA in 1988 after an article in *The Wall Street Journal* raised concerns over laboratory errors occurring in medical offices where physicians were performing Papanicolaou smear (pap smear) testing to detect cervical cancer (Bogdanich, 1987). The CLIA regulations establish quality

standards for laboratories performing clinical testing to ensure "accuracy, reliability, and timeliness of patient test results, regardless of where" the specimen analysis occurs (Centers for Medicare & Medicaid Services, 2012, para. 1). CMS considers data generated during laboratory testing and then returned to a patient or physician for the diagnosis, treatment, or management of disease to fall within the scope of the CLIA regulations. The CLIA regulations define a laboratory as:

> …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. ("Clinical Laboratory Improvement Amendments: Laboratory requirements," 2010, p. 512)

CLIA-certified laboratories have quality standards and processes in place to reduce errors in the pre-analytical, analytical, and post-analytical phases of clinical testing. These quality standards address testing for personnel qualifications and responsibilities, quality controls, patient test management, proficiency testing, and quality assurance.

CMS makes an exception for research laboratories that analyze human specimens but do not report patient-specific results "for the diagnosis, prevention, or treatment of any disease or impairment, or the assessment of the health" of the research participant ("Clinical Laboratory Improvement Amendments: Laboratory requirements," 2010). Research laboratories that meet this definition do not have to obtain CLIA certification in order to perform laboratory testing on human specimens.

Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations

Interestingly, as the debate over CLIA's applicability to research results ramped up within the research community, CMS announced its position on the issue in a "lowly PDF file posted unsigned on its website on or about December 2014" (Evans & Wolf, 2020, p. 1293). The document is titled "Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations". It states that CMS's interpretation of the statute to be that laboratories returning individual results that "**will be or could be** used 'for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings are presumed to be subject to CLIA absent evidence to the contrary" (emphasis added) (Centers for Medicare & Medicaid Services, 2014, p. 2). Evans and Wolf (2020) are highly critical of the 2014 document and CMS's stance in which they feel CMS is asserting broader jurisdiction than what was originally intended:

> This explanation interprets CLIA's research exception as giving rise to a rebuttable presumption that any patient-specific results that a laboratory reports [sic] "will or could be" misused for a clinical purpose, with the laboratory bearing the burden of proof to rebut the presumption with contrary evidence. The CLIA regulation creates no such presumption or burden of proof, nor does the CLIA statute. (Evans & Wolf, 2020, p. 1323)

The 2014 Guidance document also addressed the often cited, "I don't need to worry about CLIA, I have IRB approval" stance.

> So what if the research testing has Institutional Review Board (IRB) approval? IRBs do not generally assess whether or not CLIA would apply to a given testing situation, and they do not have authority to determine CLIA applicability on behalf of the CLIA program. The Federal regulations that

> govern human research subject protection are unrelated to the CLIA requirements, and the IRBs that consider human research subject protection considerations would not be expected to consider the applicability of the CLIA regulations. And, even if they did, IRBs would have no authority to authoritatively opine on the applicability of those CLIA provisions. (Centers for Medicare & Medicaid Services, 2014, p. 2)

State Laws Equivalent to CLIA

Washington and New York have state laboratory licensing programs that CMS has deemed to be equivalent to the CLIA regulations, and therefore they are exempt from CLIA (Centers for Medicare & Medicaid Services, n.d.). Both programs have rules "prohibiting the return of research results generated by unlicensed laboratories" that are identical or comparable to the CLIA prohibition (National Academies of Sciences, 2018, pp. 307-308). While Washington's licensure only applies to laboratories performing testing in the state, New York's Clinical Laboratory Evaluation Program (CLEP) applies to "clinical laboratories located in or accepting specimens from New York State" and is more stringent than the CLIA regulations (Department of Health Wadsworth Center, n.d., para. 1; Washington State Department of Health, n.d.).

The Office for Civil Rights (OCR) and the Health Insurance Portability and Accountability Act (HIPAA)

The final regulatory agency with oversight of research with human subjects is the Office of Civil Rights (OCR), which oversees the Health Insurance Portability and Accountability Act (HIPAA). Congress passed HIPAA in 1996 in order to increase the efficiency of the healthcare system. HIPAA includes various rules that set national standards for the security and privacy of patient health care information, including electronic information. The Privacy Rule essentially defines how covered entities or

business associates to a covered entity can use protected health information (PHI). A covered entity is an institution or individual that is "1) a health care provider that conducts certain transactions in electronic form; 2) a health care clearinghouse; or 3) a health plan" (U.S. Department of Health and Human Services, 2017, § 160.103). A business associate is defined as a "person or entity that performs certain functions or activities that involve the use or disclosure of protected health information for a covered entity" (U.S. Department of Health and Human Services, 2017, § 160.103). With respect to research, HIPAA comes into play when researchers are collecting, generating, and sharing a subject's identifiable PHI for the purposes of research (Office for Civil Rights, 2002).

The Privacy Rule grants individuals the right to inspect and obtain a copy of their designated record set (DRS) from a covered entity - known as the right of access ("Standards for Privacy of Individually Identifiable Health Information," 2000). An individual's DRS includes (1) medical and billing records; (2) enrollment, payment, claims adjudication, and case or medical management record systems; and (3) other records that are used to make decisions about individuals. It is this third category in the DRS definition that is obscure as it can be interpreted differently by different institutions, especially when it comes to next-generation sequencing (NGS) data. What exactly from the NGS testing was included in the DRS? Was the raw sequencing data included? What about the variant call files? In 2016, HHS clarified that the DRS "includes not only the laboratory test reports but also the underlying information generated as part of the test" (Office for Civil Rights, 2016, para. 1). HHS further clarified that for NGS, this would include "a copy of the completed test report, the full gene variant information generated by the test, as well as any other information in the designated record set concerning the test" (Office for Civil Rights, 2016, para. 1).

Under the right of access provision, investigators working at an institution that is a HIPAA-covered entity may be required to disclose research findings to participants in order to be in compliance with the Privacy Rule. However, given that the majority of data generated in research laboratories are not used in the participant's treatment or disease management, the data does not typically end up in the participant's DRS. Consequently, participants would not have a right to access non-clinical research data under the 1996 Privacy Rule. However, if the study involves a treatment (such as in a clinical trial) and the research data are incorporated into the participant's medical record, investigators may be subject to disclosure of the research data under the Privacy Rule.

In an acknowledgment that the CLIA regulations did not allow research laboratories to return individual-specific results to patients or physicians, the 1996 Privacy Rule had a CLIA-exception written into the rule:

> … for certain research laboratories that are exempt from the CLIA regulations, the Privacy Rule does not require such research laboratories, if they are also a covered health care provider, to provide individuals with access to protected health information because doing so may result in the research laboratory losing its CLIA exemption. (Office for Civil Rights, 2006)

This "CLIA-exception" provided harmonization between the CLIA and HIPAA regulations by prohibiting non-CLIA certified laboratories from having to adhere to the right-to-access requirement.

CLIA and HIPAA Discordance

On February 6, 2014, HHS released modifications to both the Privacy Rule and CLIA laboratory requirements with the intent to improve a patient's abilities to access their test reports directly from clinical laboratories ("CLIA program and HIPAA Privacy Rule; Patients' access to test reports," 2014). Prior to the 2014 change, an

individual's right to access their test results directly from laboratories varied by state, with some states only permitting the physicians that ordered the test to access the reports. The 2014 modifications corrected this patchwork of state laws with respect to access rights and empowered patients "to take a more active role in managing their health and health care" ("CLIA program and HIPAA Privacy Rule; Patients' access to test reports," 2014, p. 7290).

As a part of the 2014 rule changes, HHS removed the CLIA-exception from the right-to-access requirement in the Privacy Rule. Consequently, if a research laboratory is part of a HIPAA-covered entity, the laboratory could be obligated to honor a study participant's request to access their data, regardless of whether it was generated in a clinical laboratory or not (Evans et al., 2014). On the contrary, under the CLIA regulations, a laboratory would not be allowed to return data "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of individual patients" without CLIA certification (Secretary's Advisory Committee on Human Research Protections, 2015b, p. 17). Researchers could argue that providing the data would not be for clinical purposes but rather to meet the patient's access rights. Although this may be true in terms of the researcher's motivation for returning the data, CMS has indicated that they would consider disclosure to trigger the need to comply with CLIA as the data could be used for clinical purposes (Centers for Medicare & Medicaid Services, 2014; Evans, 2018).

Due to the discordance between the HIPAA and CLIA regulations, the HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) held a special panel to explore the issue at their March 24-25, 2015 meeting (Secretary's Advisory Committee on Human Research Protections, 2015b). Notably, at the meeting, a representative from CMS pointed out that "attorneys counseled that there

is no conflict in the Final Rule because labs can comply with both rules by fulfilling their obligations under HIPAA and becoming CLIA certified" (Secretary's Advisory Committee on Human Research Protections, 2015b, p. 19). In my opinion, this sentiment suggests that CMS does not understand how expensive, time-intensive, and impractical it is to expect all research labs performing genetic analysis on human samples to simply "become CLIA certified". This is precisely what was at issue in the Keating case introduced earlier.

Some scholars disagree that there is discordance between the HIPAA and CLIA statutes as, in their opinion, CMS is incorrectly interpreting the CLIA statute to claim oversight of all research findings if returned to a subject (Evans & Wolf, 2020).

Additional Guidance

Despite the fact that federal regulations had not specifically addressed the RIRR until the recent Final Rule changes, various organizations spoke to the issue in working groups or guidance documents. The National Bioethics Advisory Commission (NBAC) (1999), President Clinton's bioethics committee, met to establish guidelines for returning data to study participants. The NBAC suggested that the disclosure of research results to subjects should be "an exceptional circumstance" and occur only when "a) the findings are scientifically valid and confirmed; b) the findings have significant implications for the subject's health concerns; and c) a course of action to ameliorate or treat these concerns is readily available" (National Bioethics Advisory Commission, 1999). Interestingly, the CLIA regulations were not mentioned once in the NBAC's guidelines.

A working group for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) made almost identical recommendations in 2005, and most organizations have adopted these principles as the standard (Bookman et al., 2006). In 2009, the NHLBI convened a new working group

composed of leading experts in the fields of genetics, law, public policy, and patient advocacy (Fabsitz et al., 2010). The working group was tasked with updating the 2005 guidance on returning research results to study participants. The group identified four criteria to be used to determine whether individual genetic results should be offered to study participants. The criteria included making sure "the test is analytically valid, and the disclosure plan complies with all applicable laws" (p. 575). Interestingly, the working group could not agree on what compliance with applicable laws entailed. The group was split over the interpretation of the CLIA regulations and whether they applied to the disclosure of research results. They highlighted CLIA as a "high-impact issue" that needs further legal review and clarification (p. 576).

Two recent guidance documents that highlight the relevance of RIRR and CLIA compliance include (1) the 2015 Health and Human Services (HHS) SACHRP letter to the HHS Secretary on the Return of Individual Results and Special Consideration of Issues Arising from Amendments of HIPAA And CLIA (Secretary's Advisory Committee on Human Research Protections, September 28, 2015), and (2) the 2018 NASEM consensus report titled *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm* (National Academies of Sciences, 2018).

The Secretary's Advisory Committee on Human Research Protections (SACHRP)

SACHRP "provides expert advice and recommendations to the Secretary of HHS on issues and topics pertaining to or associated with the protection of human research subjects" (U.S. Department of Health and Human Services, 2018). The committee is comprised of lawyers, bioethicists, IRB professionals, and researchers. Realizing that the issue of returning research data was gaining "significant attention," SACHRP began looking into the matter (Secretary's Advisory Committee on Human Research Protections, April 25, 2015). SACHRP identified and addressed three areas

of importance including in the RIRR discussion: (1) return of general study results to subjects (Secretary's Advisory Committee on Human Research Protections, April 25, 2015); (2) return of individual study results to subjects (Secretary's Advisory Committee on Human Research Protections, July 21, 2016); and (3) return of incidental findings to subjects (Secretary's Advisory Committee on Human Research Protections, August 2, 2017). From these discussions that started in March of 2011, a central theme in the discussions around the return of individual results and incidental findings: the role the CLIA regulations should play when investigators are deciding whether they should return results. Meeting minutes highlight the varying – and often conflicting - opinions expressed by committee members, outside speakers, and regulators on the issue (Secretary's Advisory Committee on Human Research Protections, 2011, 2015a, 2015b). Pertinent to this research project is the SACHRP reports on (1) return of individual results to subjects (which addresses IRB roles in RIRR but not necessarily CLIA); (2) return of individual results and special consideration of issues arising from amendments of HIPAA And CLIA (which addresses CLIA but not necessarily the IRB), and (3) reporting incidental findings (which addresses both CLIA and the IRB) (Secretary's Advisory Committee on Human Research Protections, April 25, 2015, August 2, 2017, September 28, 2015).

National Academies of Sciences, Engineering, and Medicine

In July of 2018, the NASEM released a consensus report titled *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm* (National Academies of Sciences, 2018). The report stemmed from a yearlong study sponsored by the NASEM, CMS, the FDA, and the NIH in which a multi-disciplinary committee was tasked with considering "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" (National Academies of Sciences, 2018, p. xxv).

While the regulatory environment and CLIA's role in the disclosure process is a focal point throughout the document, the study sponsors advised the committee to avoid examining and scrutinizing "CMS's current interpretation of the scope and applicability of CLIA" in the return of research findings (p. 9). The task force was informed that there were limitations in what they were being asked to report on. The report noted, "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" (National Academies of Sciences, 2018, p. 9). In other words, the sponsors did not want the committee diving into the debate regarding whether compliance with CLIA is actually needed when disclosing individual research results. While the committee did discuss the conflicting viewpoints of compliance with the CLIA regulations throughout the report, they did not delve into CMS's actual interpretation of the statute as it applies to RIRR. In a scathing review of the report, Evans and Wolf (2020) opine that CMS's directive to their current interpretation of CLIA's applicability when returning research results was basically "instruction for the committee to take sides in a legal dispute by describing a contested agency position about the law (the PDF position) as if it really were the law" (p. 1294). They went on to state, "for the Academies to agree to include an agency's disputed views in the Academies' own 'description of the current regulatory environment,' with no fact-checking, makes the Academies a captive mouthpiece for a federal agency under fire" (Evans & Wolf, 2020, p. 1295).

Recommendations of the Committee. The report covered ethical and societal considerations for returning research results, laboratory quality systems,

decision-making processes, advancing consent and communication strategies, and the legal and regulatory environment. Overall, the report outlined 12 recommendations resulting from the study (National Academies of Sciences, 2018, pp. 33-37). There were three recommendations relevant to this work. First, the committee advises that research institutions, investigators, and IRBs should "consider whether and how to return individual research results on a study-specific basis" (p. 81). Second, research institutions and IRBs are asked to "ensure the high quality of individual research results that are returned to participants" (p. 121). This recommendation would instruct institutions and IRBs to allow investigators to return results if they are of high quality. Quality could be determined if the results were (1) being generated in a CLIA-certified laboratory or (2) generated in a lab under a proposed "to-be-developed" quality management system. Additionally, the IRB could determine the results may be returned if they are not "intended for clinical decision making" (p. 125).

The third recommendation most relevant to this discussion was that research institutions should "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" (p. 181). This point recognizes the importance that policies and procedures provide to IRBs and researchers in support of implementing the practice of returning research results to subjects.

The report, taken as a whole, illustrates the committee's viewpoint that change is needed to the current process in response to the evolving relationship between investigators and research participants. Additionally, the committee felt that the benefits of disclosure to study participants had been understated while risks have been overstated. The committee recommended that institutions and IRBs allow the

return of non-CLIA laboratory-generated results with the implementation of a "process-based approach" that takes into account a case-by-case assessment of what will be disclosed, the risks and benefits to participants, the quality of the laboratory, and proper communication strategies (National Academies of Sciences, 2018, p. x).

Summary

In this chapter, I have laid out how the federal agencies with oversight of human subjects research have historically been silent on the practice of returning individual research results. Accordingly, the research community filled in the need for guidance through working groups, position statements, and peer-reviewed publications. While the Centers for Medicare & Medicaid Services (CMS) was not traditionally viewed as a player in the research protections space, their stance that the CLIA regulations apply any time individual-specific laboratory findings are returned to a physician or patient/participant quickly moved them into the arena. CMS's 2014 document on Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations coupled with the update to HIPAA's right of access provision has placed even greater confusion on institutions conducting biomedical research. In this context, many within the research community view the two policies to be discordant and in conflict. In the next chapter, I discuss how the movement to return research results to study participants started and grew into an expectation by participants. I also summarize the perspectives and practices of the research community.

CHAPTER 3

LITERATURE AND CASE LAW REVIEW

Disclosure of Research Results in Literature

Due to the inherently hypothetical nature of research, results generated in research studies are traditionally not returned to individual subjects. The overall goal of research, after all, is to contribute scientifically accurate, generalizable knowledge that may benefit society or a population, not individual study participants (Clayton & McGuire, 2012). When research findings are reported back to study participants, they can be communicated as either aggregate or individual results. Aggregate results are general conclusions drawn from the study as a whole, while individual results are findings with personal relevance to the participant. Individual results generated can vary by study and data type including imaging results, non-genetic clinical lab results (such as HIV status), and genetic results. The present study focuses only on the disclosure of individual research data.

A review of existing literature makes it apparent that disclosure of individual research results is a controversial topic that elicits strong responses from both sides of the debate. Some argue that investigators are obligated to return results to study participants (Fernandez et al., 2003; Ravitsky & Wilfond, 2006), while others believe that the disclosure of such results should not be routine practice (Clayton & McGuire, 2012; Ossorio, 2006; Parker, 2006). The foundations for most of the debates surrounding the return of research results are the ethical principles of respect for persons, beneficence, and justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Respect for persons holds that each person is an autonomous being entitled to make decisions about his or her own life and body. Beneficence requires that investigators have a duty to maximize the benefits for the study participants while minimizing the risks as much as

possible. Finally, the principle of justice honors the participants by ensuring a fair distribution of risks and benefits across all prospective study participants and the general population.

The push toward disclosing research findings to study participants out of respect for persons appears to have gained traction with a 2003 publication by Fernandez, Kodish, and Weijer (Fernandez et al., 2003). Fernandez et al. challenged the traditional nondisclosure model by claiming that the ethical principle of respect for persons obligated researchers to disclose results to study participants. They argued that by returning study findings, either in aggregate or individual form, researchers recognized the study participant as an integral part of the research study and not merely a means to an end. According to Fernandez et al., while compliance with CLIA-mandates is important, they do not believe it to be a critical factor when deciding to disclose research results. In other words, investigators should not let the issue of CLIA compliance be why they choose not to return research results to study participants. [2]

Application of Disclosure of Research Results

Various circumstances within or surrounding genetic or genomic research studies may compel an investigator to disclose research results. For instance, the research may reveal rare genetic mutations for which clinical testing is not available, the results may be used for recruitment into additional research studies or therapeutic selection (genotype recruitment), or the investigator may discover an incidental finding that they believe should be communicated to the subject. Each of these cases represents ethically interesting challenges.

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[2] Two of the three authors of this article are from Canada, where CLIA does not apply.

Rare Genetic Disorders. Historically, the debate over returning genetic research results to subjects has centered on disclosing genetic mutations that cause rare disorders. The Genetic and Rare Diseases Program at the National Center for Advancing Translational Sciences (NCATS) at the NIH, defines rare genetic disorders as disorders that affect <200,000 people in the United States (National Center for Advancing Translational Sciences, 2021). In addition, a subset of rare disorders is classified as undiagnosed rare disorders, of which ~80% are believed to have a genetic etiology (Chong et al., 2015).

A report by an international team of patient organizations in 2016 outlined the needs for patients with undiagnosed conditions (Genetic Alliance UK et al., 2016). The report placed undiagnosed patients into one of two categories; the "not yet diagnosed" and the "undiagnosed (Syndromes Without a Name or SWAN)" (pg. 2). The "not yet diagnosed" patients have not been able to find a diagnosis because they have not been referred to the appropriate clinical providers. Conversely, SWAN patients do not have a diagnostic test available yet "since the disease has not been characterized and the cause(s) not yet identified" (pg. 2). The report went on to identify the needs of each group to improve outcomes:

(1) To improve outcomes for the 'not yet diagnosed' group, both the route to, and the quality of, diagnostic tools and also access to extensive genomic data need to be improved.

(2) To improve outcomes for the 'undiagnosed'/'SWAN' group, more diagnostic testing methods, including genomics, need to be integrated within clinical practice, and underpinned by genomic data sets, to facilitate the diagnosis of novel conditions. (Genetic Alliance UK et al., 2016, p. 2)

While the "yet to be diagnosed" and SWAN patient groups require different measures for improvement, both populations rely on diagnostic tools.

The Diagnostic Odyssey. Patients and families not yet diagnosed' or 'undiagnosed' (hereafter referred to as undiagnosed) often have a long, complex, and expensive journey while looking for answers. The time spent by these patients searching for a diagnosis is often referred to as the diagnostic odyssey (Basel & McCarrier, 2017). It may involve multiple doctor's visits, consultations, specialists, a battery of medical testing, misdiagnoses, and costly medical expenses for patients and families. Delays in diagnosis may prevent patients from receiving proper clinical management and care, leading to poor outcomes, including death (Grosse & Khoury, 2006). A survey conducted by the National Commission on Orphan Diseases (1989) found that it took up to five years to get a diagnosis in nearly 1 in 3 patients (n=801) while "15% went without a diagnosis for six or more years" (National Commission on Orphan Diseases, 1989, p. 17). A 2013 survey of 631 patients in the United States and the United Kingdom found the average time to diagnosis for a rare disease varied between 5.6 and 7.6 years (Shire, 2013).

A 2017 publication on McArdle disease (GSDV) highlights the struggles patients face when searching for a diagnosis (Scalco et al., 2017). The study looked at 50 patients with a confirmed GSDV diagnosis. GSDV is an autosomal recessive disorder with impaired muscle metabolism due to an absence of muscle glycogen phosphorylase. The study found that despite the average age of onset for symptoms being three years old, the median age of diagnosis was 33 years old. Additionally, 90% of patients were misdiagnosed, with 62% having more than one misdiagnosis. There was a rapid increase in diagnoses made after genetic testing became available in the 1990s. 46% of study participants reported that they had been diagnosed as being lazy or unfit, while 14% were given a psychiatric or psychological misdiagnosis. In addition, 47% of the participants were provided with incorrect

disease management such as exercise training advice or intervention (antibiotic treatment or surgery).

Diagnostic Genetic Testing for Rare Genetic Diseases. There is no question that the emergence of DNA sequencing technologies has made a significant impact on our understanding of rare diseases. Early genetic analysis techniques included karyotyping to interrogate chromosomal abnormalities, fluorescent in situ hybridization (FISH) to look at specific nucleic acid sequences in chromosomes, array-based comparative genomic hybridization to detect tumor cell genomic imbalances, restriction fragment length polymorphism (RFLP), and single-strand confirmation polymorphism (SSCP) (Durmaz et al., 2015). While RFLP and SSCP were the primary mutation screening methods used by diagnostic laboratories, Sanger sequencing automation was a game-changer in both research and diagnostic genetic testing (Durmaz et al., 2015).

In 1977, Frederick Sanger and colleagues published a method to read the nucleotide base pairs of DNA called Sanger sequencing (Sanger et al., 1997). The Sanger method used the polymerase chain reaction (PCR) technique to make copies of the desired segment of a DNA sample. During the PCR amplification of the DNA chain-terminating inhibitors called dideoxynucleotide triphosphates (ddNTPs) would stop the elongation of DNA at varying nucleotides. This produced DNA fragments of varying lengths that could then be separated by size using gel electrophoresis. Sanger sequencing could produce DNA sequences of 250-750 base pairs in length (Metzker, 2005).

In 1986, Applied Biosystems automated Sanger sequencing methods by attaching a fluorescent dye to the nucleotides and eventually the ddNTPs that could be read by an instrument (Pareek et al., 2011). The fluorescent dye also allowed for DNA samples to be run in a single lane and read by color rather than fragment size.

Sequencing automation increased sequencing read lengths to 750-1,000 base pairs, which reduced the costs of testing (Metzker, 2005). Further advances in sequencing technologies led to the development of massive parallel sequencing technology referred to as next-generation sequencing (NGS). NGS uses a multiplexing technique in which DNA fragments adhere to a two-dimensional surface, and all DNA templates are available in a single reaction (Shendure et al., 2017). NGS allows laboratories to sequence the entire exome (whole-exome sequencing or WES) and genome (whole genome sequencing or WGS) of an organism in a single workflow and, in some cases, in as little as 13 hours. (Illumina, 2019). The next, next-generations of sequencing (3rd and 4th generation sequencing) are already in development and use. This includes nanopore sequencing and single-cell sequencing in real-time (McGinn & Gut, 2013). Sequencing capabilities have advanced at a breakneck pace. Between 2004 to 2010, sequencing capabilities doubled every five months (Heather & Chain, 2016). As sequencing capabilities have advanced with technology, the costs have dramatically decreased. Whereas the cost of sequencing a human genome in 2001 was around $100,000,000, it was estimated to cost around $1,000 in 2020 (National Human Genome Research Institute, 2020).

Clinical Testing. Clinical interest in developing diagnostic tests to look for such rare disorders is generally low. During the 1990s and early 2000s, this was due to multiple factors, including the small volume of test requests for rare mutations and the complexity of the testing methods that related to a test's profit potential (Biesecker, 1996). Therefore, families turned to research scientists studying their orphan disease or disease-causing genes for answers. The implied practice of these laboratories was to communicate the research findings "even in the absence of compliance with CLIA regulations" (Pelias, 2005). Investigators may have felt a

strong pressure or obligation to reveal mutation or carrier statuses to families since no diagnostic test was available for patients with rare diseases.

Leslie Biesecker (1996) highlighted the "urgent need for standards and guidelines on genetic testing" due to the rapid pace of the Human Genome Project (p. 300). In particular, the author was concerned with the transfer and uptake of rare disease genetic testing (which he coined "orphan tests") by clinical laboratories due to regulatory thresholds that would be impractical for orphan testing to meet. Biesecker put forward two proposals to manage orphan tests: (1) developing standards for clinical testing in research laboratories and (2) developing laboratories that focus on offering orphan tests (pp. 303-304). The first solution centered around acknowledging that orphan tests may never move into a clinical setting; therefore, the author proposed developing "CLIA guidelines for the research-clinical testing interface" (p303). Biesecker outlined a two-phase process in which the test's validity, quality control, and clinical use would be determined. Interestingly, Biesecker suggested using an institution's IRB - or similar committee - to determine the test's validity through peer-review of the research. The IRB's role in protecting subjects from unjustifiable risk suits them for the task.

> Some of the evaluation in the first stage could be performed by individual institutional review boards (IRBs), human subjects committees, or similarly constituted groups. This would be necessary for tests that are still considered to be in the research stage. Although this activity may be considered outside the current mission of IRBs, they have the advantage of being familiar with the research environment and have a demonstrated ability to protect patients from undue or inappropriate risks. Approval by the IRB would be contingent upon demonstration that the test has the potential to be a valid assay for the

> disorder in question and that subjects enrolled in the study are subject to reasonable risks. (Biesecker, 1996, p. 303)

In 2005, the American College of Medical Genetic's (ACMG) Ultra-Rare Disorders Working group of the Laboratory Quality Assurance Committee was tasked with developing technical standards and guidelines for laboratories conducting molecular genetic testing for patients with ultra-rare disorders (Maddalena et al., 2005). Understanding that most CLIA-certified laboratories do not offer clinical testing for rare genetic conditions, ACMG recommended that clinical laboratories partner with research laboratories studying rare diseases in order to provide a CLIA outlet for validation of the research findings. An alternative model to a research laboratory obtaining CLIA certification is custom mutation analysis, in which external clinical laboratories confirm or validate research findings under proper CLIA conditions. To date, this model has been implemented successfully in several research studies (Biesecker et al., 2009; de Gouyon et al., 1997; Lo Nigro et al., 1997).

Genotype-Driven Recruitment. Many genomic studies are beginning to enroll participants based on the presence or absence of a particular genotype or gene variant. This genotype-driven recruitment (GDR) approach allows researchers to study a genotype-rich population for diseases or variants of interest, which may significantly increase the pace for advances in genetic research (McGuire & McGuire, 2008). For example, an investigator studying Alzheimer's disease may choose to enroll individuals that carry an APOE4 allele. Because GDR participants are recruited into a study due to their genotype, disclosure of individual genetic information is highly likely (Budin-Ljøsne et al., 2013). Considering that the mere eligibility for entry into a GDR study may disclose participants' genetic information (such as APOE status), does the genotyping need to be performed in a CLIA-certified laboratory?

In May of 2011, Beskow et al. (2012) held a workshop at Duke University to develop recommendations for approaching genotype-driven research recruitment ethically. The multi-disciplinary workshop participants included IRB leaders, study subjects, researchers, study coordinators, and bioethicists. To avoid deception and be transparent with prospective subjects regarding why they are eligible to participate in a genotype-driven study, attendees believe it is "appropriate to offer individual genetic research results in most cases" (Beskow et al., 2012). Beskow et al. (2012) recognized that the role of the CLIA regulations in this situation is an important topic but believe that the "workshop was not constituted to meaningfully address this regulatory issue" (p. 6). Although the workshop did not weigh in on the CLIA issue, the authors acknowledged the contention around non-CLIA-certified research laboratories returning individual-level results. Beskow et al. suggest that there may be cases where the ethical motivation for disclosing non-CLIA research results outweighs the regulatory requirements.

> However, we believe the explicit motivation for offering results in the context of genotype-driven recruitment—to achieve a scientific goal in an ethical manner, not for the participant's health-related benefit—is highly pertinent to this issue and merits further exploration. (Beskow et al., 2012, p. 6)

Incidental Findings. From time to time, researchers will come across a finding they were not anticipating and must face the moral dilemma of what to do with the results. Deciding how to handle these incidental findings, as they have come to be known, is the topic of many discussions and debates (Cho, 2008; Kohane et al., 2006; Wolf et al., 2008). Investigators conducting genetic studies, especially studies that look at large portions of a person's DNA, may be faced with a finding that is out of the scope of the original research goal. For instance, an investigator

may be looking for a gene associated with bipolar disorder and stumble upon a mutation in the BRCA gene associated with an increased risk of developing breast cancer. How should the investigators handle this finding? Are they obligated to return this research finding to the participant? What if the participant does not want to know this information? Is the disclosure of such serious information the responsibility of the researcher?

Given that most research laboratories do not have CLIA certification, can the data legally be returned to the participant (since it is diagnostic in nature), or does the participant have to be retested in a clinical lab? Although there are currently no federal regulations on how investigators should handle incidental findings, guidance documents by special interest groups strongly recommend that only CLIA-certified data be returned to the participants (Bookman et al., 2006; College of American Pathologists, n.d.; National Bioethics Advisory Commission, 1999; Secretary's Advisory Committee on Human Research Protections, August 2, 2017). For studies with a likelihood of identifying incidental findings, SACHRP recommends investigators address the issue in IRB protocols and consent forms. Similarly, SACHRP recommends institutions, IRBs, and sponsors consider developing "standard procedures for incidental findings that can be applied across protocols" (Secretary's Advisory Committee on Human Research Protections, August 2, 2017).

Study Participants' Perspectives on the Return of Research Results

Explorations of study participants' desire to receive individual research results have shown that most subjects want the information returned (Bollinger et al., 2013; Burnett-Hartman et al., 2020). Bollinger et al. (2013) surveyed 1,523 adults and found that 78% would be interested in receiving individual research findings, with 57% wanting access to all of their results. Burnett-Hartman et al. (2020) surveyed 10,369 adults regarding barriers to genetic research participation. The study found

that the return of results greatly influenced individuals' willingness to participate in research. Only 22% were willing to participate if no results were returned versus 87% if results were returned. RIRR also increased the diversity of study subjects as non-Hispanic blacks and Hispanics were more likely to participate if individual findings were to be disclosed.

In their focus group-based research, Bollinger and colleagues (Bollinger et al., 2012) found that the majority of the eighty-nine participants expressed a desire to receive individual study findings. The central values the subjects expressed included improvement of health, non-health-related benefits such as personal empowerment, and a sense that there was an obligation of investigators to disclose the information to them. As one participant aptly put it, "Why would the information be more important to you all than for us, our individual information? The specifics would be more important to us than to the study, I think" (Bollinger et al., 2012).

While research has shown a high public interest in study participants' desire to receive their individual research results, there is also a strong minority position that this should not be the case. In a recent study, Bradbury et al. (2018) looked at the uptake of individual genetic breast cancer research results in women that had previously enrolled in a research repository study. Out of the 402 potential participants contacted, 107 consented to the study, and eighty-three chose to receive their research results. Of the 295 potential participants that did not enroll in the study, 48% (n=194) did not respond to contact attempts, and 21% (n-85) actively or passively declined participation. The authors concluded that the number of participants that did not enroll, in conjunction with the individuals that enrolled but declined to receive their research results, showed that public interest in receiving individual research findings might not be as high as previously reported.

Interpretation of the CLIA Regulations by the Research Community

Since there is no uniform policy for the return of research results to date, it is usually left up to the investigators and their respective IRBs to determine whether or not to disclose results. In addition, interpretations of the applicability of the CLIA regulations when communicating research results are inconsistent. This is more than likely due to the lack of knowledge or the misunderstandings that many researchers, clinicians, and IRBs have regarding the implications that CLIA has for genetic testing and research (Ledbetter & Faucett, 2008). Often, there is a false impression that CLIA regulations apply only to laboratories that bill Medicaid or Medicare for their testing. Another incorrect belief investigators often have is that if they place a disclaimer on the results to identify that they are for "Research use only" and "Not to be used for diagnostic or treatment purposes," then they do not have to abide by the CLIA regulations (Ledbetter & Faucett, 2008).

Investigators. Wolf et al. (2018) surveyed investigators from the Clinical Exploratory Sequencing Research (CESR) Consortium regarding challenges genomic researchers face when navigating the interface between research and the clinic in CSER-funded projects (n=9). A recurring question raised by respondents was whether the results returned to study participants had to come from a CLIA-certified laboratory. While all respondents answered that they either generated results or confirmed returned findings in a CLIA-certified lab, one respondent highlighted the complexity of the CLIA issue:

> The return of non-CLIA data continues to be a HUGE issue. I think that ethically it is clear that subjects/parents want research data, I think they have a right to it and in particular the fact that some IRB's [sic] absolutely refuse disclosure

and others allow it makes the situation, particularly for a multi-institutional study, extremely difficult. (Wolf et al., 2018, p. 549)

The vastly differing opinions regarding the applicability of CLIA regulations when disclosing genetic information made front-page news in California with the controversial Bring Your Genes to Cal program at the University of California (UC), Berkeley (College of Letters & Science, 2010). In the summer of 2010, researchers at UC Berkeley planned a research study in which incoming freshmen would undergo genotyping for three genes that metabolize lactose, folic acid, and alcohol. Investigators planned to return the genotyping results to the study participants with the hope that they may select a healthier lifestyle according to their genotypes. However, the California Department of Public Health (CDPH) decided that disclosure of genotyping results crossed the line between research and medical practice. As a result, CDPH informed study investigators that the study was out of compliance with CLIA regulations, and they could not return the results to participants under the current study design. In light of the ruling, UC Berkeley altered its original research plan and provided aggregate data only to study participants. Dean Mark Schlissel informed the students of the changes to the program in a letter in which he stated, "This ruling relies on an interpretation of legal statutes that is entirely different from the interpretation of the same statutes by UC's top lawyers" (Sanders, 2010b, para. 27). The letter was followed up by a press release in which the university continued to defend their actions by stating, "Because the UC Berkeley program is an educational experiment, the students are not patients, and the three specific genetic variants are not disease-related, CLIA rules and the California statute do not apply" (Sanders, 2010a, para. 10). This scenario is a perfect illustration of the need for clarification and guidance on how CLIA regulations apply to genetic data when labs wish to disclose data to subjects and/or their physicians.

While my review of scientific literature of compliance with the CLIA-regulations in RIRR did not return a plethora of results, several studies addressed confirmation testing (Biesecker et al., 2009; Bradbury et al., 2018; Graves et al., 2014; Laurino et al., 2017; Roberts et al., 2010; Siegfried et al., 2013). One article that specifically addressed the issue was Roberts et al. (2010), in which researchers decided not to validate the research results that they disclosed due to the non-clinical value the results carried. For their study, investigators disclosed cyclin-dependent kinase inhibitor type 2A (CDKN2) genotype results to study participants from an epidemiology research study of melanoma in which participants had previously participated. Investigators had to decide whether or not to retest the biospecimens for validation, given that the original genotyping had not been performed in a CLIA-certified laboratory. The team chose not to validate the results in a CLIA lab since the results were not disclosed for clinical use but rather to assess the participants' responses to receiving the research results. Interestingly, investigators retested thirty-six of the samples in a non-CLIA laboratory to look for discordant results. They found one result to be discordant out of the 36 samples retested. This finding supports the practice of validating the return of results in cases where the data is or may be clinically relevant.

In contrast to the previous examples, Biesecker et al. (2009) wrote CLIA validation of participant disclosed research findings into the study design of the NIH ClinSeq Study. The ClinSeq Study is a pilot project in which investigators seek to learn about the role genes play in health through next-generation sequencing (n=1500) (National Human Genome Research Institute, 2014). The study was designed with the intent to disclose results to subjects. At the time of sample collection, duplicate samples were collected, with one sample sent to the research laboratory and a second sample sent to a CLIA-certified diagnostic laboratory. Initial

sequencing was performed in a research laboratory with relevant findings validated in a CLIA laboratory before results were returned to the participants. Investigators reported that their decision to disclose CLIA-validated data was simply due to their interpretation of the CLIA regulations, which prevented them from returning the data generated in the research laboratory.

Oftentimes, investigators opt to return non-CLIA research findings with a notation that the results were generated in a research laboratory and should not be used to make clinical decisions without first being validated in a clinical laboratory. Laurino et al. (2017) conducted a study in order to understand if participants pursue CLIA verification of genetic results received in a research setting when recommended by the research team. Subjects for the study were participants enrolled in a familial colon cancer registry (including cases and related family members) in which cases were identified as having a pathogenic variant in a mismatch repair gene associated with Lynch syndrome. Family members included in the study were tested for the same pathogenic variant and irrespective of genetic test result status. Participants were offered non-CLIA research findings and counseled on "the importance of verifying the results in a CLIA-certified laboratory" (p. 701). Of the 26 participants who received individual research results and completed required 2- and 12-month surveys, only four individuals surveyed (15.4%) reported obtaining CLIA-laboratory-verified results. The major reasons identified by participants for not following through with CLIA-validation included insurance-related concerns and limited belief of personal or clinical benefit.

In the previously discussed Bradbury et al. (2018) study that looked at the uptake of individual genetic breast cancer research results, CLIA-confirmation played a key role in the study design. The results were not generated in a CLIA-certified laboratory; however, participants with a “deleterious or likely deleterious research

result in any gene and a variant of uncertain significance (VUS) in a high penetrance gene were recommended to have" the result confirmed in a clinical laboratory (n=22) (pg. 2). The study found that fourteen (64%) of the participants where clinical confirmation was recommended followed through with obtaining clinical testing. Interestingly they did not recommend confirmation testing for participants with negative research results or VUS in moderate penetrance genes. However, fifteen participants that fell into the "not recommended" category followed through with additional clinical testing "as covered by clinical care" (pg. 22). The study found 94 percent concordance between the research and clinical testing results and 75 percent concordance with variant call interpretation. Regardless of the imperfect concordance findings, the authors concluded that "returning only results obtained in a CLIA-certified research laboratory would deny some individuals critical medically actionable information that could be relevant to their health if subsequently confirmed in a clinical laboratory" (pg. 9).

Institutional Review Boards. In addition to the lack of knowledge on the part of investigators, IRBs have a deficit in understanding the CLIA regulations (Ledbetter & Faucett, 2008). Periodically, IRBs may require investigators to disclose research information with the belief that the subjects will benefit from the information. This mandate, however, is often in conflict with the law under the CLIA rule and may expose the subjects to risk in the form of returning non-validated results. Risks may include the return of inaccurate results due to sample mix-up or misannotation, leading to incorrect diagnosis or treatment (Green, 2013; Lohr et al., 2015; Toker et al., 2016).

A survey of 79 Canadian University Research Ethics Board (REB)[3] chairs revealed that they personally were highly supportive (94.8%) of the investigators' offer to disclose results to research participants (REBs are the Canadian equivalent of the US IRBs) (MacNeil & Fernandez, 2006). Moreover, only 19.5% of the chairs responded that a policy or guideline that governed the return of such results existed at their institution.

In the United States, Dressler and colleagues (2012) interviewed 31 IRB professionals at six US institutions to explore their views and experiences with studies returning research results (Dressler et al., 2012). The study found that overall, most respondents were supportive of the disclosure of research results but with provisions. The provisions mentioned by some respondents included clinical utility of the findings, personal utility, and returning results only to the subjects that want the information returned. An additional condition raised was the analytical validity of the results and the need to validate the findings in a CLIA-certified laboratory. While 94% of respondents agreed that preliminary, non-validated results should not be returned, they did not define preliminary and non-validated. While discussing validation, some respondents mentioned institutional policies that addressed the need for CLIA-validation of results. One respondent reported that their institution did not allow non-CLIA validated results to be returned to participants. Interestingly, two respondents noted that even though their institutions had policies preventing investigators from disclosing non-CLIA validated results, exceptions had been made at both institutions. While Dressler et al.'s study did not specifically ask questions regarding CLIA, answers that included the topic of CLIA demonstrate the inconsistencies in applying the CLIA regulations when disclosing research findings.

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[3] REBs in Canada perform virtually the same role as IRBs in the United States.

While only a handful of studies have looked into IRB members' attitudes and perspectives towards disclosure of research findings to study participants, even fewer have examined IRB policies, procedures, and supporting documentation to look at institutional requirements or guidance on the practice.

MacNeil and Fernandez (2006) surveyed 22 Canadian research ethics boards (REB) coordinators to understand their institution's policies on returning research results. This study was interested in (1) the practice of returning new findings that may affect a participant's willingness to continue in a clinical trial; and (2) returning results at the completion of a study. They found that seven (31.8%) of the 22 REBs had policies or statements embedded in IRB applications or sample consent forms that discussed returning results to participants at the completion of the study. Only 2 REBs (9.1%) provided guidelines that mentioned the return of results to participants while on the study, and in these cases, it was in the context of studies that used diagnostic testing. Interestingly, the IRBs that did ask investigators to outline how they would return results did not provide guidance on how to do so. There was no discussion in the study regarding the analytic or clinical validity of the results, as the study was not necessarily focused on the return of individual-level results.

In 2007, a review of IRB policies from 207 US medical schools, industrial, and non-medical schools found a lack of consistency in IRB policy or guidance regarding the return of research results to study participants (Kozanczyn et al., 2007). 56% had no available policy on the return of research results to study participants. Of the remaining 44%, 36.3% were found to have vague policies that mentioned RIRR, while only 7.7% were found to have existing policies on RIRR. While this study looked for the presence of additional policy details (including what information is returned, who disclosed the findings, and budget requirements for the return of results), it did not look for any requirements around the quality or validity of the

data. Therefore, there was no mention of the CLIA regulations in this study.

In addition to IRB policies addressing the return of results, many have suggested that the informed consent form should discuss the possibility that results will be disclosed (Bookman et al., 2006; Fabsitz et al., 2010; Secretary's Advisory Committee on Human Research Protections, July 21, 2016). Simon et al. (2012) were interested in what type of guidance IRBs provided researchers around the use of informed consent to communicate intent to return research findings. Using a content analysis approach, they examined 45 informed consent templates from 20 institutions to look for references of individual research results, incidental findings, and significant new findings. The study found that 39 documents (87%) across all 20 institutions referenced individual research results, while only 22% of documents across six organizations referenced incidental findings. Of the 39 documents that discussed individual research results, 49% included language suggesting that individual research results "disclosure was *not* an option," while 26% suggested it was an option (Simon et al., 2012, p. 5). The researchers concluded that IRBs tended to overemphasize nondisclosure of research findings.

Additionally, the study looked at the prevalence of informed consent documents that mention disclosure of the risks and benefits. The study found that 18% of analyzed documents referenced risks associated with the subject receiving results, while only 2% referenced benefits. The emphasis on risks associated with the return of results as well as nondisclosure consent language suggests IRBs view nondisclosure as a means of participant protection. It is worth noting that while the study used the search terms "CLIA" and "clinical laboratory" to identify relevant documents, there is no mention of data quality, accuracy, validity, or use of CLIA-certified laboratories in the publication.

Beskow and O'Rourke (2015) surveyed IRB chairs and vice chairs to understand IRB leaders' perspectives on the "proper role of the IRB in addressing" the RIRR (p. 502). Fully 91% (n=30) of surveyed IRB leaders felt "whether the results were generated (or confirmed) in a CLIA certified laboratory" was somewhat or very important when deciding if results should be returned (p. 505). However, when asked what the IRB's role should be in "defining the general characteristics of individual results that should be offered to participants (example: results are analytically valid…)," 34% (n=22) felt the IRB should have full authority while 51% (n=33) believed the IRB should have input only (p. 507). When asked who should have the authority to develop policy on the RIRR, 45% (n=17) said an existing or ad hoc institutional entity, while 34% (n=13) said the responsibility lies with a national entity (Beskow & O'Rourke, 2015).

Case Law Review

As concerns over legal liability or obligations may motivate or deter an investigator or institution's willingness to return research results, it is essential to look at how the courts have ruled in past cases. To date, there have been no court cases that have specifically addressed the issue of RIRR from non-CLIA certified laboratories. However, several court cases provide some insight into how the judiciary may view lawsuits dealing with a researcher's putative legal obligation to disclose participant-specific findings. Pike et al. (2014) wrote extensively about the topic of researchers' legal duties to disclose incidental findings (IFs) in genomics research. They pointed out that the push to disclose may eventually create a legal duty:

> Nevertheless, as additional voices call for an ethical obligation to return IFs, and as this emerging ethical obligation increasingly becomes standard or customary practice in research, the emerging ethical obligation could give rise

to a legal obligation to return IFs, the failure of which could result in legal liability. (Pike et al., 2014)

While this section is not meant to be a comprehensive review of all legal issues surrounding the RIRR, I touch on a handful of cases I find relevant to the discussion of researchers' relationships with participants, the hotly contested duty to disclose, and the potential liability implications of the complexity of next-generation sequencing (NGS) and variant classification.

Special Relationships: Blaz v. Michael Reese Hospital Foundation and Grimes v. Kennedy Krieger Institute

Courts have ruled that non-clinician researchers and study participants do not have a physician-patient relationship, and therefore participants cannot sue for medical malpractice. However, two court cases, *Blaz v. Michael Reese Hospital Foundation* (1999) and *Grimes v. Kennedy Krieger Institute* (2001) acknowledged that there is the potential for a "special relationship" between researchers and study participants which impose duties on the investigators ("Blaz v. Michael Reese Hospital Foundation," 1999) ("Grimes v. Kennedy Krieger Institute," 2001). The *Blaz v. Michael Reese Hospital Foundation* case found that a physician-investigator had a duty to warn patients of the risk of developing certain sorts of tumors from previous radiation exposure at a hospital after the correlation was found by an investigation into the hospitals retrospective data ("Blaz v. Michael Reese Hospital Foundation," 1999).

In *Grimes v. Kennedy Krieger Institute,* the Maryland Court of Appeals opinioned that non-therapeutic research studies create a "special relationship between research entities and human subjects" that "will almost always impose duties" ("Grimes v. Kennedy Krieger Institute," 2001). In this case, the Kennedy Krieger Institute (KKI) was looking at the effectiveness of lead-based paint

abatement procedures in low-cost housing where children lived. Some families received comprehensive lead abatement while others received varying lesser degrees of abatement. The success of the abatement strategies was determined by comparing the lead level in the resident children's blood with the lead levels from samples taken around and in the houses (National Academies of Sciences, 2018). The plaintiff in the case claimed KKI was negligent in warning her about the dangers posed by the lead hazards in her house ("Grimes v. Kennedy Krieger Institute," 2001). Initially, a lower court had ruled there was no duty to warn; however, on appeal, the Court of Appeals of Maryland found that "a duty to warn may exist a matter of law" and therefore summary judgment was incorrectly granted (National Academies of Sciences, 2018). In describing the "special relationship" created between the investigators and subjects in non-therapeutic studies, the appeals court stated:

> This duty requires the protection of the research subjects from unreasonable harm and requires the researcher to completely and promptly inform the subjects of potential hazards existing from time to time because of the profound trust that participants place in investigators, institutions, and the research enterprise as a whole to protect them from harm. ("Grimes v. Kennedy Krieger Institute," 2001 at 214)

Subsequent to the ruling, there was considerable criticism of the "duty to warn" finding as the court applied it broadly to non-therapeutic research and called for "the disclosure of risks that may not be a result of participation in the research project" (Hoffmann & Rothenberg, 2002, p. 111).

Medical Malpractice: Ande v. Rock

Ande v. Rock ("Ande v. Rock," 2002) is the only published opinion from the courts dealing specifically with the return of genetic research results to study participants, and as such, I will go into details about the case.

In 1985, a research study was ongoing at the hospital in which investigators hypothesized that early nutritional intervention in newborns with cystic fibrosis would lead to better health outcomes (Andrews et al., 2015). To test their theory, leftover blood from standard newborn screening tests was used to look for cases of cystic fibrosis, which was not a part of the state newborn screening panel. All parents were provided with information about the research study as a part of the newborn screening pamphlet that is given to parents prior to testing. The parents of half of the newborns were told if their child tested positive and offered a nutritional plan to begin immediately, while the other half of the parents were not informed whether their child had a positive test. The non-informed group was considered the "blinded control" group for the study. While the newborn samples were tested for cystic fibrosis before the babies were one month of age, defendants claimed that results from the control group were not reviewed. Therefore, investigators did not know who was positive or negative in this arm of the study.

In 1993, CEA was born to Linda and Charles Ande and enrolled in the study. However, as she was in the control blinded group, her primary care physician and parents were not informed of the research study test result. At the age of two, CEA was diagnosed with cystic fibrosis and her mother, at the time, was pregnant with her second child (who later was also diagnosed with cystic fibrosis).

The Andes brought a lawsuit against the state employees, researchers, and institutions involved in the research study. The lawsuit alleged that the defendants: (1) failed to obtain proper informed consent; (2) withheld treatment that may have

reduced the severity of CEA's condition; and (3) caused harm by withholding CEA's test results ("Ande v. Rock," 2002). The plaintiff's maintained that they were harmed by these acts as (1) they would have accepted treatment to lessen the severity of her illness, and (2) they would not have conceived their second child had they known the test results.

The court found that there was no physician-patient relationship between the Andes and any of the researchers involved. Therefore, the medical malpractice claim was not valid and did not apply in this case. On appeal, the higher court affirmed the circuit court's ruling. While this precedential case established that study participants could not sue researchers for medical malpractice as there is no physician-patient relationship, Marchant et al. (2020) note that the court did not consider whether the researchers were negligent in their duties as researchers.

Laboratory Liability with Variant Classification: Williams v. Quest Diagnostics, Inc. and *Belser v. Quest Diagnostics, Inc.* [4]

While not specifically related to research, the *Williams v. Quest Diagnostics* case (2018) addressed the challenges clinical laboratories face in variant classification. At the heart of the case was the question of liability for clinical laboratories related to their variant interpretation and classification system.

In 2007, a young boy referred to as CM, who had been suffering from seizures since infancy, underwent genetic sequencing of the SCN1A gene at Athena Diagnostics, Inc. (Athena). His doctors suspected he might have had severe

[4] H. Freeman Belser, Esquire was substituted as the current personal representative of Mrs. Williams by order filed October 1, 2020 Belser v. Quest Diagnostics, Inc., (D.S.C. November 4, 2020). The Plaintiff alleged "negligent misrepresentation, constructive fraud, civil conspiracy, and violation of the Unfair Trade Practices Act" in her lawsuit Williams v. Quest Diagnostics, Inc., (D.S.C. 2018).

myoclonic epilepsy of infancy (also known as Dravet syndrome). The diagnosis was important in CM's clinical management as sodium channel blocking anticonvulsant medications can exacerbate seizures in Dravet syndrome (Guerrini et al., 1998). The clinical report CM's sequencing identified a mutation (1237T>A; Y413N) in the SCN1A gene that Athena classified as a variant of unknown significance (VUS). As CM's diagnosis was uncertain and non-sodium channel blocking medications had been unsuccessful in his treatment, his physician prescribed the sodium channel blocking drug carbamazepine. Unfortunately, CM passed away in 2008 from a "traumatic seizure" ("Belser v. Quest Diagnostics, Inc.," D.S.C. November 4, 2020, p. 3).

It wasn't until CM's mother sought genetic counseling in 2014 that she found out that CM's VUS had been reclassified to pathogenic and that at the time of his 2007 report, there had been two recent publications linking his variant to Dravet syndrome, including one authored by Athena's Chief Director of Genetics, Dr. Sat Dev Batish (Berkovic et al., 2006; Harkin et al., 2007).

CM's mother (the plaintiff) filed suit against Quest Diagnostics, Athena Diagnostics, and ADI Holdings (the defendants) for negligence/gross negligence resulting in the wrongful death of her son. The plaintiff's expert witness, Dr. Robert Cook-Deegan, argued that Athena was negligent in updating their variant lists and databases. He also believed that Dr. Batish's authorship on the Harkin et al. paper was evidence that they had "access to and knowledge of this variant's disease-associated nature" and yet "failed to properly categorize the mutation in its original report" ("Belser v. Quest Diagnostics, Inc.," D.S.C. November 4, 2020, p. 15). To counter Dr. Cook-Deegan's conclusions, the Defense's expert witness argued that although the 2007 article was available, she did not believe "it was not enough to classify the variant" ("Belser v. Quest Diagnostics, Inc.," D.S.C. November 4, 2020,

p. 16). An additional expert witness for the Defense added that Athena's classification system exceeded the standard of care for classification systems, and she believed the laboratory correctly classified the variant as uncertain ("Belser v. Quest Diagnostics, Inc.," D.S.C. November 4, 2020). The court concluded "that no reasonable jury could find Defendants erred in classifying Decedent's variant as a VUS, or that any misclassification was the result of nonmedical, administrative, ministerial, or routine care" ("Belser v. Quest Diagnostics, Inc.," D.S.C. November 4, 2020, p. 19).

The *Williams v. Quest Diagnostics* cases drew the scientific community's attention (Ashford, 2017; GenomeWeb, 2018; Ray, 2020). The case brought to light the potential legal risks groundbreaking technology can raise for the biomedical community (Ashford, 2017). Turna Ray (2020) highlights some of the challenges revealed by the case when dealing with incorporating cutting-edge technology and genomic information into healthcare. In Ray's article, John Conley's quote captures the uncertainty many are feeling:

> What's our expectation of something that's at the very edge? Do we want to demand that it's got to be perfect? … Or do we, as a society and as a legal system, want to say to people, "You're on the edge [of medical care] and the edge is always a little bit dangerous" (Ray, 2020, para. 3)?

Summary

As I have outlined in this chapter, the practice of RIRR stemmed from a need within the rare disease community to get access to testing. The rapid advances in genomic technology and slow uptake within the clinical environment forced the rare disease community to turn to researchers for answers and insight into their conditions. The research community was further confronted with participants' expectations for the RIRR as next-generation sequencing capabilities generated more

and more genetic data on study participants. Research into RIRR has underscored the complexity of the issue with varying perspectives and practices from participants, investigators, and IRBs. Although the courts have not specifically addressed the research findings and CLIA discourse, it may only be a matter of time before they have to speak and act, on the issue. In the next chapter, I address the methodology used to answer the questions posed in the introduction.

CHAPTER 4

STUDY METHODOLOGY

Previous research studies utilizing document analysis of IRB policies and guidance have varied by topic and sample size. McMillan (2020) compared IRB policies for obtaining informed consent from non-English speaking subjects with a sample size of 21 institutions with one policy per institute. Barnes, Carrithers, and Sugarman (2020) analyzed IRB policies from the top 20 NIH funded institutions in 2018 to understand restrictions put in place by IRBs on the use of research data. Wolf, Zandecki, and Lo (2005) examined IRB guidance for pediatric research with a sample size of 39 institutions. Wolf (2009) examined how IRB policies addressed conflicts created by finder's fees in recruiting research participants (n=117 institutions).

In 2007, Kozanczyn, Collins, and Fernandez identified the IRB review process as "a key opportunity to support researchers offering research results to participants" (p. 2). By the same token, the IRB review process can provide researchers with guidance on the types of data that can be returned, including the accuracy and validity of the data. A document analysis of HRPP and IRB policies and supporting documentation will shed light on an organization's stance with respect to whether individual research findings can be disclosed to study participants, and if so, do the findings have to be compliant with the CLIA regulations.

Research Design

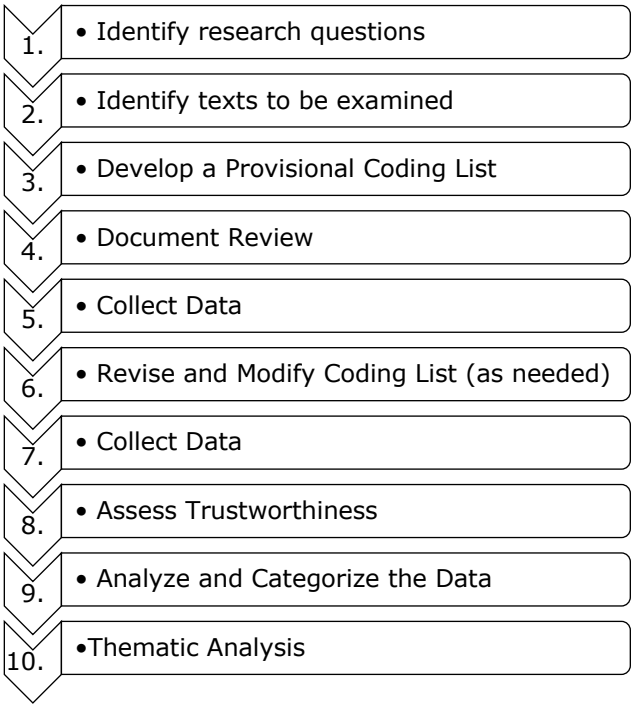
This study used a mixed qualitative and quantitative document analysis of biomedical institutions' HRPP and IRB policies and supporting documents with respect to the return of research results to study participants and addressing

compliance with the CLIA regulations. [5] I employed a document analysis approach that combined elements of content analysis and thematic analysis. I modified the content analysis process suggested by Insch, Moore, and Murphy (1997) and outlined in Figure 1 to include document review and thematic analysis (p. 8). I used basic descriptive statistical analysis to discuss the coded data by document and institutions.

Data was obtained from online, publicly available IRB policies and supporting documents using the criteria outlined below to increase the breadth of coverage.

Figure 1

Document Analysis Approach



Insch, Moore, and Murphy (1997) define content analysis as a method for "studying the content and themes of written or transcribed text" that can be used to

[5] For the purposes of this project, I refer to human research protection programs (HRPP) and IRB websites and documents simply as IRB documents.

"identify intentions and other characteristics of the communicators" (pp. 2-3). Content analysis involves identifying texts to analyze and breaking the texts down into manageable content through coding and categorizing the data (Busch et al., 1994-2012). Data coding involves the identification of codes, often a word or short phrase, in text or documents (Saldana, 2016). Coded data are then grouped into categories that allow patterns of the data to emerge. Used in conjunction with content analysis, thematic analysis can help investigators "uncover themes pertinent to a phenomenon" with the documents' data (Bowen, 2009, p. 32). Thematic analysis looks for emerging themes which can then be formed into new categories for additional analysis (Fereday & Muir-Cochrane, 2006). To further describe the data, I included basic descriptive statistics and frequencies of codes, categories, and document types. Therefore, my overall analysis involves a mixture of both qualitative and quantitative methods.

Sample Set

I used homogenous purposeful sampling to select institutions involved in biomedical research to include in my study. Purposeful sampling allows for the "identification and selection of information-rich cases related to the phenomenon of interest" (Palinkas et al., 2015, p. 533). Homogenous sampling is utilized to select organizations with similar characteristics and reduce variation. This method of sampling increased the likelihood that the organization's HRPP and IRB documents analyzed would address the return of research results to study participants (RIRR).

To identify the biomedical institutions to include in my sample set, I selected the top 25 institutions in the United States (US) funded by the National Institutes of Health (NIH) in 2017 (Appendix A). This information was obtained using the NIH Research Portfolio Online Reporting Tools (RePORTER) website, which "provides access to reports, data, and analyses of NIH research activities" (National Institutes

of Health, 2011). Two institutions, Massachusetts General Hospital and Brigham and Women's Hospital, use the same IRB through Partners Healthcare (now called Mass General Brigham) and therefore have the same HRPP policies and procedures. Hence, I selected the next institution on the list that had its IRB policies publicly available online. Additionally, I selected five IRBs from US institutions that fell outside of the top 25 to increase the heterogeneity of my sample.[6]

Document Identification

I undertook a preliminary analysis of websites from the top 25 institutions to assess the accessibility of IRB policies and supporting documents. All websites had their HRPP and IRB policies, procedures, and supporting documents publicly accessible.

I used the following process to collect documents for each selected institution. First, I located each institution's IRB's website through a Google search. Second, I used the search tool bar on the IRB website to search the site for all documents that contained keywords relevant to the return of research results (Table 1). This list of key terms later served as my initial provisional coding list. Third, I manually reviewed each search hit to determine if retrieved hits were relevant to the scope of the research study. Hits that were not relevant were excluded from the document set. For example, the words "confirmation" and "return" were broadly used in the context of IRB application submissions, and many of the hits had no relevance to the issue of returning research results. Finally, I downloaded documents or saved websites as .pdf documents to include in my document set.

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[6] It is important to note that I did not select independent (commercial) IRBs for inclusion in this research. In my experience, independent IRB policies do not typically address compliance with the CLIA regulations as compliance with return of results and data quality are not a requirement of the Common Rule.

I aimed to include documents that were pre-2018 Common Rule changes (which took effect January 21, 2019). For institutions that had already changed their documentation to reflect the 2018 Final Rule requirements, I used the Wayback Machine to access older versions of the document. There were two institutions that did not have pre-2018 Final common rule documents available. This is noted in Appendix B. When institutions had multiple versions of a document available on their website, I chose the most recent version to include in my analysis. Unless otherwise noted, documents were collected between January 2018 and January 2019.[7]

Table 1

Search terms used to find IRB Documents that Address the Return of Research Results to Study Participants

CLIA	gene(s)	return
Clinical Laboratory Improvements Amendments	genetic(s)	secondary
confirmation	genomic(s)	sequencing
confirmatory	incidental Finding(s)	validation
disclose	individual-Level	validity
DNA	result(s)	

Retrieved documents were categorized by document type, which included (1) policies, (2) standard operating procedures, (3) guidance documents, (4) protocol and consent form templates, and (5) other documents which mentioned returning

[7] I did not include IRB documents that were specific to in vitro diagnostics (IVDs) and investigational device exemptions (IDEs) as the FDAs oversight of laboratory developed tests was outside the scope of this project. Additionally, I did not include text that dealt with a patient's right to access medical information generated as a part of a clinical trial and placed in their medical records. The only exception was where the text addressed the CLIA regulations as a part of the discussion.

research results that did not fit into categories 1-4 (including IRB presentations and reports). Table 2 provides a definition for each document type and examples of the kinds of documents I included in each category. Appendix B provides the complete list of documents in my sample set alphabetically by institution along with the title of the document, the date of the document, and the archived web address of the document.

Table 2

Definitions and included documents by document type

Document Type	Definition	Included documents
Policy	A document that defines an organization's position on a particular issue and provides a governing framework.	✓ Policies ✓ All-in-one policy and procedure manuals
Procedure	A document that defines the process for supporting and carrying out a policy.	✓ Procedures ✓ Standard Operating Procedures ✓ Procedure manuals
Guidance	A document that provides clarity or advice on existing policies and procedures. Can serve as a reference when no standards exist. Often used to provide best practices on a given topic.	✓ Guidance documents ✓ Checklists ✓ Flow charts
Template	A document that models appropriate formatting, elements, and sample language on a given topic.	✓ Informed consent templates ✓ Protocol templates ✓ Supplemental forms requiring written responses
Other	Documents found to be relevant to this study that did not fit into other document types.	✓ PowerPoint trainings ✓ Reports to convey information

Retrieved documents were downloaded or saved as a PDF from the institution's website or using archived websites from the Internet Archive. All documents were imported into the MAXQDA software analysis system for data coding.

Instrumentation

MAXQDA

I used a Computer-Assisted Qualitative Data Analysis Software (CAQDAS) called MAXQDA Analytics Pro 2018 (VERBI Software, 2018a) for document text storage and data analysis. MAXQDA is a "social science-oriented data analysis" software that allows for the "management and systemic evaluation of texts, [and] documents" (VERBI Software, 2018b, p. 1). The software automated the process of text searching and coding search terms. The program allowed me to load multiple file formats, including text and PDF documents.

The Internet Archive and Wayback Machine

I used the Internet Archive's Wayback Machine to find records of old documents that are no longer available on IRB websites and to upload IRB documents used in my analysis that could not be found in the archives (Internet Archive, n.d.-b). The Internet Archive is a 501(c)(3) non-profit organization that has been "building a digital library" of web content and internet sites since 1996 (Internet Archive, n.d.-a, para. 1). The Internet Archive is accessible using the Wayback Machine, which is an internet tool that allows users to search and visit archived websites and content, and capture and save current websites of interest. The Internet Archive also allows the public to upload media, including text documents, into the archive.

Data Coding and Analysis

Data Coding and Collection

Data coding is a research tool used to label and organize data. Codes are "most often a word or short phrase" that "attributes interpreted meaning to each individual datum for later purposes" (Saldana, 2016, p. 4). Saldana (2016) notes that "coding is a cyclical act" that involves multiple cycles of coding and re-coding the data for generating "categories, themes, and concepts, grasping meaning, and/or building theory" (p. 9).

I used provisional coding as my first cycle coding method, which starts with a predetermined list of codes prior to data collection (Saldana, 2016). As data is collected, "codes can be revised, modified, deleted, or expanded to include new codes" (Saldana, 2016, p. 168).

Development and Refinement of Provisional Code List

Provisional coding allows researchers to generate their initial code list from preparatory work prior to the investigation (Saldana, 2016, p. 168). To start, I developed my provisional list of keywords (Table 3) to code my data from a review of relevant literature and published research exploring consent and/or policy guidance for the return of results (Kozanczyn et al., 2007; Simon et al., 2012). I used this list initially to identify documents on HRPP websites included in my sample set.

This list was modified and refined to remove keywords that yielded search hits that were too broad or not found in my sample set. For example, the keyword "genomic" yielded 198 hits in 19 documents. However, this term was found to mainly be related to the NIH's genomic data sharing policy for depositing data into data repositories. The instances where the keyword was associated with the return of research results were captured with the keywords "genetic" and "sequencing."

Additionally, the coding list was modified to add new keywords that were identified when reviewing the documents, or coded segments related to other hits conveyed a similar meaning as a keyword. For example, my initial coding list did not include the words "share" or "communicate". However, both words were used to convey returning findings or results. Therefore, these words were added to my code list and used for a keyword search. Appendix C presents the overall coding schematic used for this study along with the definition of each code and example text from my document sample set.

Table 3

Provisional and Refined Coding Lists

Provisional Coding List	**Modified List #1**	**Modified List #2**
CLIA	accuracy	Accuracy
Clinical Laboratory Improvement Amendments	CLIA	be given
confirmation	clinical laboratory	CLIA
confirmatory	clinically relevant	clinical laboratory
disclose	communicate	Clinically
DNA	confirmation	clinically relevant
gene(s)	disclose	Communicate
genetic	disclosure	Confirm
genomic	finding(s)	Disclose
incidental finding(s)	genetic	Genetic
individual-level	incidental finding(s)	incidental finding(s)
results(s)	inform	individual result(s)
Return	offer	Inform
secondary	patient specific	Offer
sequencing	reliability	other for disclosure
validation	report	other for individual
validity	research finding(s)	participant specific
	research result(s)	patient-specific
	result(s)	Provide
	return	Reliability
	secondary finding(s)	Report
	sequencing	research finding(s)
	valid	research result(s)
	validity	Return
		secondary finding(s)
		Sequencing
		Share
		valid

Note. Keyword stems and variations of words were searched and/or combined (e.g., valid/validity, confirm/confirmed/confirmation, disclose/disclosed/disclosure).

Concept Matrix

I developed a concept matrix to track and show the codes present in each document (Appendix D). A concept matrix is a tool used to organize and visually present concepts present in a group of documents. The documents in my sample set were listed on one side of the matrix, and each coding term or concept was listed at the top. I recorded a "1" in the cells where the coding term or concept was present in a document. I further refined the findings into a second matrix representing the connections between the documents and identified categories (Appendix E). Appendix F delineates the categories by institution.

Institutional CLIA-Specific Requirements in Policies & Supporting Documentation

The codes and categories allowed me to identify and focus on areas of text that would shed light on my research questions. Careful reading and review of these texts allowed me to identify themes around how institutions communicated their stance on the return of research results and compliance with the CLIA regulations. Details associated with these topics - such as the need to confirm returned findings in a CLIA-certified laboratory – were further investigated for patterns and frequency of reference.

Reliability and Trustworthiness

Krefting (1991) has outlined four strategies and criteria that could be used to show the quality and trustworthiness of qualitative data: credibility, transferability, consistency, and confirmability. *Credibility* can be achieved by "spending sufficient time" with the data source to "identify reappearing patterns" (Krefting, 1991, p. 217). I attempted to achieve credibility through a detailed literature review search spanning seven years, collection of document sources at two different time points to ensure reproducibility in finding and pulling the documents, and reanalysis of the

data at different periods. Regarding *transferability*, Lincoln and Gaba note that in qualitative research, this can be addressed through adequate data description that allows others to use the findings for comparison (Guba & Lincoln, 1981). Using dense or thick data description, "judgments about the degree of fit or similarity may be made by others who may wish to apply all or part of the findings elsewhere" (Guba & Lincoln, 1981, p. 77). I have field notes detailing thick descriptions of the documents in my analysis, along with descriptions of my content and thematic analysis. For *confirmability*, along with the reflexivity described below, I used a computer-assisted qualitative data analysis software (CAQDAS) for document and data management which created an audit trail of my coded documents and memos. Finally, for the sake of *consistency*, I ensured that all documents used in my analysis were archived in the Internet Archives and therefore were accessible to other scholars. To look at the consistency and reliability of codes, I had a colleague in human subjects research protections perform an intercoder reliability evaluation on a small sub-set of my documents (as described below, on page 65).

Ideally, this study would have used triangulation of collection methods and data sources as another means to test the trustworthiness of the data. Triangulation allows researchers to look for convergence of data and do "cross-data validity checks" (Patton, 1999, p. 1192). In order to triangulate in this context, I would have needed interviews or surveys of IRB members and staff at the institutions in my sample set, for instance. While beyond the scope of the current project, this additional data collection should prove worthwhile in future research.

While I was not able to collect data through different methods, I collected different document types. Previous research using IRB document analysis has primarily focused on policies and guidance documents or consent form analysis. This study assessed a diversity of types of IRB documents, including policies, procedures,

guidance, template consent forms, template protocol forms, checklists, and other sources of documentation (e.g., PowerPoint training presentations). Expanding the types of documents beyond what has previously been studies adds variety to the analysis and can capture a broader spectrum of IRB communication outlets.

Intercoder Reliability

Reliability is associated with "the extent to which a measuring procedure yields the same results on repeated trials" (Neuendorf, 2017, p. 165). To asses intercoder reliability, I had a colleague independently code 5% (n=4) of my study documents. I provided her with my coding schematic (Appendix C) and asked her to code the document and then complete a content matrix to signify if the code was present or absent in the document. Her findings were then compared to my findings for the same documents. Out of 104 codes across four documents (27 codes per document), there was only one code that my colleague coded as present, and I coded as absent. The single discrepancy noted was for the word "sharing". My colleague marked the word for a document section that discussed broad genomic data sharing submitted to NIH genomic data repositories.

Reflexivity

Finlay (2002) describes reflexivity as examining the researcher's relationship with the object being studied, including unconscious reactions. In this case, means examining my relationship with HRPP policies and procedures and the applicability of the CLIA regulations. As a research compliance professional at a genomic research institution, I have a personal interest in the extent that the CLIA regulations apply when research results are disclosed to study participants. Over the course of working on this dissertation, I have helped build three CLIA-certified laboratories at my institution. Additionally, I have first-hand experience writing policies, procedures, protocols, consent forms, and training that addresses human subjects research. My

experiences could lead to interpretational bias as I may interpret the text to mean more or less than the authors intended. I have tried to minimize it through sound study design similar to previous work examining IRB policies and procedures and the use of a CAQDAS. While I recognize my bias may be perceived as a concern, I believe it has allowed me to better understand the topic being studied. Thirsk and Clark (2017) point out that "a priori knowledge (preunderstanding) of the topic allows the researcher to explore a topic further and deeper, carefully balancing what is already believed, with what new might be learned" (p. 3). Throughout this project, I have been open to moving beyond my own preconceived notions and allowing a new understanding of the topic to be discovered.

Study Design Limitations

One potential limitation to the study design was the use of only publicly available documents resulting in insufficient detail. Publicly available IRB documents may be aligned with the federal regulations governing human subjects research (such as the FDA and OHRP). Given that, to date, these regulations have been silent on the topic of RIRR, institutional IRB policies may be silent on the issue as well. To reduce this limitation, I analyzed "other" documents found through the institutions' websites - such as IRB training or template forms – to capture instances when the IRB appears to mention RIRR and/or CLIA compliance outside the scope of an actual policy.

Another potential limitation was selection bias due to an incomplete collection of documents. As this study relied only on publicly available documents that were found online, selection bias may have been introduced. In recent years, most large institutional IRBs have moved away from paper submissions of IRB applications and submissions and moved towards using electronic IRB compliance software modules or systems for the management of IRB protocols and supporting documents. These

systems have their submission applications embedded in the software and are therefore not publicly available to download. Consequently, institutions included in my sample set may ask questions regarding an investigator's intention to return research results to study participants in their application. That information would not be included in my analysis.

Another study limitation is that some or all of the policies examined may no longer be available on the Institution's IRB website as documents change over time as updates and newer versions are released. I used the document's internet archive web address documented in Appendix B to account for these changes. For documents that were not found in the internet archive, I used the archives upload feature to save a copy of the document used in my analysis. The uploaded documents are now publicly available for others to access.

As this research focused on the top NIH-funded research institutions, it may not be representative of all IRBs. However, selecting the top NIH-funded institutions for IRB policy analysis makes sense due to the sheer amount of research carried out at these institutions (Wolf, 2009; Wolf et al., 2005). Wolf et al. (2005) point out that the top NIH-funded institutions are also "likely to devote more resources to their IRBs than other institutions" (p. 88). Future research that includes a more extensive selection of institutions from further down the NIH funding list could provide a more generalizable, cross-sectional analysis of IRB practices across the United States.

Another possible source of data that would contribute to our understanding of IRB policies and practices with respect to RIRR and CLIA compliance would be interviews with IRB Chairs and IRB staff. While this proposed research focused on document analysis as the first step to understanding the problem, I acknowledge that additional research (including interviews) would complement the current project.

Summary

Analysis of IRB policies and supporting documentation concerning CLIA compliance when investigators return research results to participants can help determine the nature and variety of policies and practices amongst the top NIH-funded biomedical institutions. I used a mixed qualitative and quantitative document analysis that combined content and thematic analysis elements to collect, code, and categorize. Descriptive statistics provide additional insight.

CHAPTER 5

STUDY RESULTS

The purpose of this research study is to determine whether online human research protection programs and Institutional Review Board policies, procedures, and supporting documentation addresses the return of individual research results (RIRR) to research participants and the CLIA regulations. The focus of the study was on RIRR for genetic or genomic results; therefore, I excluded documents that exclusively focused on non-genetic or genomic results, which primarily consisted of incidental imaging findings. I looked at five types of documentation that included policies, procedures, guidance, templates, and "other" documents that did not fall into one of the other document type categories but discussed the practice of returning research results.

In this chapter, I present the results of the document analysis. The chapter starts with a description of the institutions' demographics and the document characteristics. Next, I present the findings from the content analysis and describe the data using descriptive statistics.

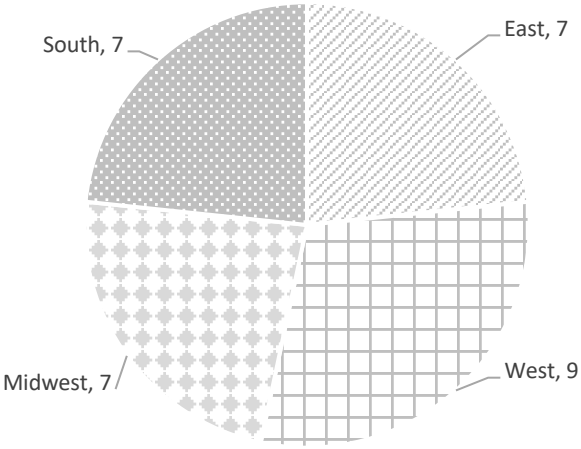
Institutional Demographics

My sample set consisted of 30 institutions that received NIH funding in 2017 (27 degree-granting, three non-degree-granting) (Appendix A). [8] The majority of the institutions were medical schools or teaching hospitals (n=28). The range of NIH funding was $651,844,903-$1,350,077 (median=$342,648,390.53). All four regions of the United States (East, West, South, and Midwest) were represented (Figure 2).

[8] Note: I chose not to anonymize the institutions included in this study as I used text taken directly from the publicly available IRB documents to support my research.

Figure 2

Institution Locations by Region



Document Characteristics

All 30 institutions had their IRB policies, procedures, and supporting documentation publicly available online. Across the 30 institutions, a total of seventy-three documents were collected that addressed returning research results to study participants, with an average of two documents collected per institution (min=0, max=6, mode =2). Only one institution, the University of Pittsburgh, had no documents publicly available that addressed the return of research results. [9] Table 4 represents a breakdown of the number of documents collected by document type.

[9] The University of Pittsburgh's Human Research Protection Office's (HRPO) website does provide access to their policies, procedures, guidance, and forms. However, the only search hits with the initial search terms returned (1) a guidance document on the Genetic Information Non-discrimination Act (GINA); and (2) a Genomic Repository Guidance (dbGap/other NIH-repositories). A search for the word "CLIA" returned only an "Additional Resources" webpage with a link to the "Clinical Laboratories Improvement Amendments (CLIA)" Act listed under Federal Resources. There was no additional information provided.

Guidance and template documents were the most prevalent type of documents that discussed returning findings with twenty-seven (38.03%) documents for each type, while the "other" category only had three (4.23%) documents. Documents classified as "other" included a PowerPoint presentation on genetic research and informed consent, an IRB's Genetics Research Advisory Panel report, and the Presidential Commission for the Study of Bioethical Issues' IRB Primer for Incidental and Secondary Findings (Emory University, 2016; Massachusetts General Hospital, n.d.; Presidential Commission for the Study of Bioethical Issues, 2014). The majority of the template documents were for consent forms (74.07%).

Table 4

Number of Document Types That Address Return of Research Results to Study Participants

Document Type	n	%
Policy	8	10.96
Procedure	6	8.22
Guidance	29	39.73
Template	27 [a]	36.99
Other	3	4.11
Total	73	100

[a] 20 consent form templates (74.07%), 5 protocol templates (18.52%), and 2 supplemental protocol checklists/forms (7.41%).

Table 5 shows the number of institutions that had a specific document type. 66.67% of institutions had at least one guidance document available that discussed the return of results, while 53.33% of the institutions had at least one template document. Twenty percent of the institutions (n=6) only discussed the return of results in template documents.

Table 5

Numbers of Institutions that Address the Return of Research Results to Study Participants by Document Type

Document Type	N	%
Policy	7	23.33
Procedure	6	20.00
Guidance	20	66.67
Template	16 [a]	53.33
Other	3 [a]	10.00

[a] Six of the institutions only addressed the return of research results to study participants in template documents.

Content Analysis

I identified five coding categories in the documents that are associated with the topic of returning study findings. These categories are: providing findings, research findings, data quality, genomic data, and individual-level. Table 6 presents the coding terms that emerged throughout the document analysis and their associated category.

Table 6

Terms Searched that Represent Thematic Categories

Providing Findings	**Research Findings**	**Data Quality**	**Genomic Data**	**Individual-Level**
communicate	clinically relevant	CLIA	genetic	individual-level
disclose	incidental finding	clinical laboratory	sequencing	patient-specific
be given	research result [c]	clinically		participant-specific
inform	secondary finding	accuracy		other identifiable
offer		reliability		
provide		confirmation [a]		
return		validity [b]		
report				
share				

[a] Included the search term "confirm"

[b] Included the search term "valid"

[c] Included the search term "results", "findings", and "research findings"

[d] Included the search term "results"

Table 7 presents the frequency of the different categories that appeared in the documents and institutional policies and practices. As I selected my document sample set for the presence of the topic of returning research results, it is no surprise that 100% (n=73) of documents addressed providing findings to participants. However, one institution in my sample set did not have any documents that addressed returning research results to participants; therefore, only 96.67% (n=29) of institutions had these themes present. Policies and practices at 83.33% (n=25) of institutions mentioned the quality of the data; at 96.67% (n=29) of the institutions, genomic data were a focus; and at 43.33% (n=13) of institutions, the individual level of the data was mentioned.

Table 7

Number and Frequency of Thematic Categories by Institution and Total Documents

Category	Data quality		Providing Findings		Genomic data		Research findings		Individual -level	
	n	%	n	%	n	%	n	%	n	%
Institution [a] (n=30)	25	83.33	29	96.67	29	96.67	29	96.67	13	43.33
Documents (n=73)	50	68.49	73	100	61	83.56	73	100	22	30.14

[a] One institution did not have any documents that addressed returning research results to study participants.

Below I provide a deeper look into the five categories I identified that were associated with the return of research results and provide additional insights into the data.

Category 1: Providing Findings

Documents were coded for terms related to the action of providing findings back to study participants. Table 8 provides the various terms of different institutions and documents used to describe the act of returning results. An initial observation: many words convey the act of returning results to subjects. It was important that I capture the various terms used to represent the act of returning results as they helped me identify meaningful units of text within my documents relevant to the RIRR discussion.

Table 8

Terms Found that Described the Act of Providing Research Findings to Study Participants

disclose	inform	offered
provide	be given	relayed
return	receive	transmitted
share	conveyed	release
report	discussing	revealed
communicate	notification	

The top most frequently used terms are presented in Table 9. The majority of institutions used the words "disclose", "provide", or "return" when discussing RIRR.

Table 9

Number and Frequency of Top Five Terms for Providing Findings by Institution and Total Documents

Code [a]	Disclose		Provide		Return		Share		Report	
	n	%	n	%	n	%	n	%	n	%
Institution [b] (n=30)	24	80	19	63.33	17	56.67	13	43.33	13	43.33
Documents (n=73)	34	46.57	29	39.73	34	46.57	19	26.03	16	21.91

[a] The top 5 codes in the Providing Findings category are listed.

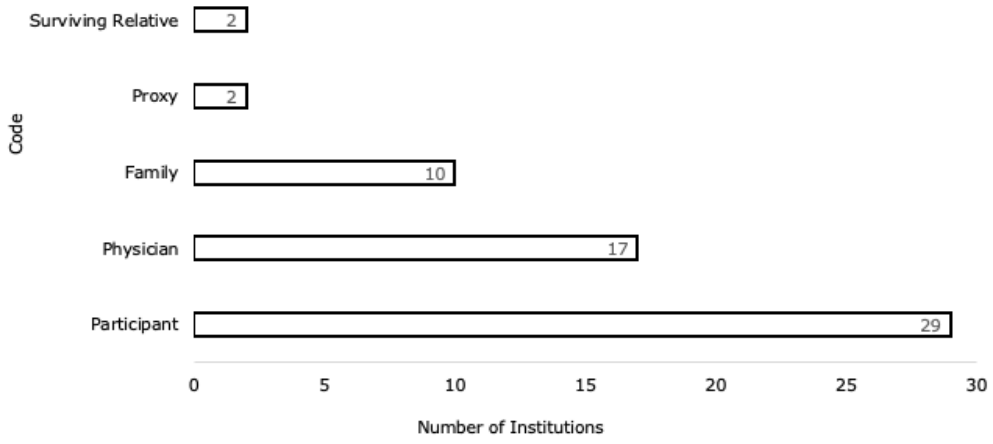
[b] One institution did not have any documents that addressed returning research results to study participants.

Two themes emerged from my data regarding the act of providing findings back to study participants: (1) discussion of to whom the findings would be returned, and (2) identification of who would return the findings.

The first theme references to whom findings should be returned. Figure 3 depicts the categories of individuals the institutions listed as possible recipients. Twenty-nine (96.67%) of the thirty institutions addressed in at least one document that referenced the participant as the intended recipient of the findings. Seventeen (56.67%) of institutions included the participant's physician, and ten (33.33%) had the participant's family in the reference.

Figure 3

To Whom Institutions Mentioned Results May be Returned



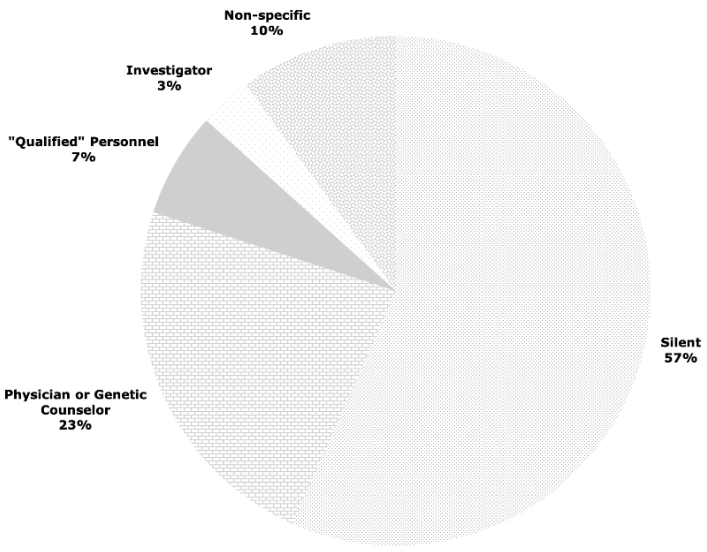
Guidance documents often asked investigators to consider how results would be returned and by whom, e.g., "If applicable, how will you return results to subjects, family members, and/or the subject's physician"? By contrast, consent form templates provided optional text that researchers could include in the consent form if relevant to their study.

Two (6.67%) institutions allowed participants to designate a proxy to receive the results if they were incapacitated or died during the study. In addition, two (6.67%) institutions asked investigators to consider if there would be a benefit to provide surviving family members with participant data of deceased subjects.

The second theme that emerged was about who would be communicating the study findings to the participant, illustrated by Figure 4. 56.67% (n=17) of institutions were silent on addressing who should return results to the subject. 23.33% (n=7) of institutions specified that results should be communicated by a physician or genetic counselor, while 6.67% (n=2) of institutions simply stated that results should be returned by "qualified" personnel. One institution (3%) placed the responsibility to return the results squarely on the investigator. Three institutions (10%) asked investigators to address who would return the study findings but provided no additional details.

Figure 4

Recommendations of Who Should Return Results to Participants by Number of Institutions [a]



[a] Percentages are rounded to the nearest ones

While the questions of to whom the research results are returned and by whom may not appear to tie directly into the question of compliance with the CLIA regulations, they do provide insight into institutional intentions regarding returning individual-level research results. Over 50% of institutions mentioned returning results to the participant's physician, indicating that the data to be returned has clinical value. Similarly, while most institutions were silent on addressing who should return the results, 26.67% mentioned a physician, genetic counselor, or other "qualified personnel". Under CMS's interpretation of the CLIA regulations, if the results returned have the potential to be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health," then the CLIA requirements are meant to apply (Centers for Medicare & Medicaid Services, 2014, p. 2).

Category 2: Research Findings

Multiple working groups - including the Presidential Commission for the Study of Bioethical Issues (2013), which was active during the term of then-President George W. Bush, Wolf et al. (2008) - typically classify the types of returnable individual findings from research as primary findings, incidental findings, and secondary findings. Primary findings are results related to the goals and aims of the research study. Wolf et al. (2008) defined incidental findings 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" (p. 219). Finally, secondary findings are " actively sought but not the primary reason for testing" (Ells & Thombs, 2014, p. 655).

I analyzed how institutions categorized findings to be returned (Table 10). The word "primary" in relation to findings was rarely used in my document set. Instead, all documents (n=73) simply referred to research results or findings, which

I categorized as "research results". 56.67% (n=17) of institutions addressed the return of incidental findings, while only 13.33% (n=4) addressed secondary findings. Based on the context of the usage of the term "secondary finding", it appears two of the four institutions are using it interchangeably or in place of the term "incidental finding". An additional category emerged in my analysis which was findings that are "clinically relevant". This term was used by 40% of institutions (n=12) as a qualifier to returnable findings.

Table 10

Number and Frequency of Research Findings Codes by Institution and Total Documents

Code	Research Results		Incidental Findings [b]		Secondary Findings		Clinically Relevant	
	n	%	n	%	N	%	n	%
Institution [a] (n=30)	29	96.67	17	56.67	4	13.33	12	40
Documents (n=73)	73	100	26	35.62	5	6.85	17	23.29

[a] One institution did not have any documents that addressed returning research results of any kind to study participants.

[b] This category only included incidental findings that were not specific to imaging incidental findings.

Category 3: Data Quality

One of the main ethical and clinical concerns with returning individual-level results generated in a research laboratory is the data's quality (or lack thereof) (National Academies of Sciences, 2018). Thus, one of the hallmark recommendations from the NASEM report regarding returning individual research results was to support the development of a well-resourced infrastructure to enable research

laboratories to return "high-quality individual results" (National Academies of Sciences, 2018, p. 124).

68.49% (n=50) of the documents across 83.33% (n=25) of institutions addressed data quality as a point to consider when returning study findings to participants (Table 11). The majority of institutions (76.67%) raised "CLIA" as a point to consider or a requirement when discussing disclosure of results to subjects. "The IRB typically does not allow the release of laboratory analyses to subjects unless they are performed by a CLIA-approved entity" is an example of a point to consider statement (University of Wisconsin Madison, 2018b, p. 2).

Table 11

Number and Frequency of Data Quality Codes by Institution and Total Documents

Code [a]	CLIA		Confirmation		Accuracy		Validity		Reliability		Clinical Lab	
	n	%	n	%	n	%	n	%	n	%	N	%
Institution (n=30)	23	76.67	15	50	4	13.33	15	50	7	23.33	9	30
Documents (n=73)	41	56.16	19	26.03	5	6.85	21	28.77	9	12.33	9	12.33

[a] One institution (3.33%) used the word "clinically" to describe the quality of the data

Exactly 50% (n=15) of institutions referenced the confirmation of research findings. While the majority of the institutions coupled confirmation testing with a clinical or CLIA-certified laboratory, one institution simply asked investigators to consider confirmatory testing, "the investigator should also consider whether they will provide additional confirmatory testing to the participants, whether they are willing to test family members, and how the cost for such testing and counseling will be covered" (Washington University, 2011, p. 8).

Additionally, 50% (n=15) of institutions discussed the validity of the data. Thirteen of the 15 institutions that discussed validity also discussed CLIA; however, two institutions never mentioned CLIA or CLIA-certified laboratories in any of their documents. They simply referred to the data or tests being validated for clinical use as exampled by the University of Alabama text, "most research data derived from tissue specimens has not been validated for clinical decision-making and should not be disclosed to the participant under most circumstances" (University of Alabama at Birmingham, 2013, para. 5).

Category 4: Genomic Data

As the ongoing debate around CLIA compliance when returning study findings has centered primarily around genetic data, I looked at the frequency documents and institutions associated with the return of results guidance or questions around the context of genetic data. 96.67% (n=29) of the institutions addressed genetic data as a type of data to which the return of results guidance applied. [10] While 29 institutions (96.67%) highlighted genetic data (often by referring to genetic test results), only 46.67% (n=14) of them specifically addressed whole genome or whole exome sequencing data. Additional types of data called out in some documents as examples of what may be disclosed included imaging data (i.e., MRI incidental findings), non-paternity, STD status, positive pregnancy tests, or sleep analysis.

Category 5: Individual-Level

The majority of institutions did not specifically identify results to be returned were individual-level. Rather, the documents simply discussed results being returned

[10] The one institution that did not have any documents associated with the return pf research results did have guidance documents associated with genomic data sharing in the context of data repositories (like the NIH dbGap) as well as guidance on the Genetic Information Non-discrimination Act (GINA).

to the participant. 43.33% (n=13) of institutions specified the "individual-ness" of the data. Documents that explicitly identified the results as being individual primarily discussed individual or patient-specific results. Seven (23.33%) asked investigators to consider if aggregate results would be returned. Data quality metrics for aggregate data were not included in any documents discussing disclosure of aggregate results. One institution asked investigators to think about how results would be returned to communities: "How will the results of the research be shared with the participants and/or the target community/ies?" (Emory University, 2015, p. 2)

Policy Format Used by Institutions to Communicate Topic-Specific Guidance

To understand how institutions communicated their stance and expectations for certain topics, I categorized the documents into one of four policy-type categories: focused, inclusionary, tangential, or silent. Table 12 indicates the definitions of the policy-type categories.

Table 12

Definitions of Policy Format Types

Policy-Type Category	Definition
Focused	A document that's primary purpose or focus is to address the specified issue or topic. This includes document that were written specifically to provide guidance on a topic.
Inclusionary	A document that includes the specified issue or topic but it is not the primary focus of the document.
Tangential	A document that peripherally mentions the specified issue or topic but is not really related to the overall document purpose.
Silent	A document that does not address or mention the specified issue or topic.

The three topics I explored were the return of research results, CLIA, and genetics/genomics. Appendix G presents the policy type for the three focused topics

by document. Table 13 shows the number and frequency of documents categorized by policy type for the three focused topics. The data indicates that the majority of documents were not focused on any one topic. The documents categorized as focused were primarily dealing with genetics/genomics (28.77%) or returning research results (19.18%). Most documents were categorized as inclusionary for each topic.

Concerning the topic of CLIA, only 6.85% (n=5) of documents were primarily focused on providing guidance on the applicability of the CLIA regulations for research testing. 49.31% (n=36) of documents referenced the CLIA regulations in either inclusionary or tangential format, and 43.83% (n=32) of documents were silent on the topic altogether. Of the 36 documents that referenced CLIA in inclusionary or tangential documents, 72% (n=26) consisted of one or two sentences that simply mentioned the regulation. This was usually in the context of a laboratory or certification such as "CLIA-certified laboratory", "CLIA Laboratory", "CLIA approved", or "CLIA certification":

> The IRB typically does not allow the release of laboratory analyses to subjects unless they are performed by a CLIA-approved entity (University of Wisconsin Madison, 2018b, p. 2).

Table 13

Number and Frequency of Policy Format Types by Document for the Topics of the Return of Research Results, CLIA, and Genetics

Topic	Focused		Inclusionary		Tangential		Silent	
	N	%	n	%	n	%	n	%
Return of Research Results	13	19.18	58	79.45	1	1.37	0	0
CLIA	5	6.85	33 [a]	45.21	3 [a]	4.11	32	43.83
Genetics	21	28.77	37	50.68	5	6.85	10	13.7

Note: n=73

[a] Of the CLIA inclusionary or tangential documents (n=36), 26 were brief blurbs that consisted of one or two sentences that referenced the CLIA regulation.

Table 14 presents the primary policy type the institutions use to communicate the specified topics. While 40% (n=12) of institutions had IRB-focused documents on the return of research results, and 50% (n=15) had IRB-focused documents on genetics, only 16.67% (n=5) had an IRB document that focused on compliance with CLIA when returning research results. Most institutions addressed returning research results (56.67%) and compliance with the CLIA regulations (60%) in documents that were not primarily focused on these topics. The topic of genetics was not far behind, with 46.67% of documents labeled as inclusionary.

All but one institution had either a focused policy or inclusionary policy on the return of research results and genetics. 23.33% (n=7) institutions did not have any policy or documentation addressing compliance with the CLIA regulations. Twelve institutions (40%) only referenced CLIA with one or two sentences that simply mentioned the regulation.

Table 14

Number and Frequency of Policy Types by Institution for the Topics of the Return of Research Results, CLIA, and Genetics

Topic	Focused		Inclusionary		Tangential		Silent	
	N	%	n	%	n	%	n	%
Return of Research Results	12	40	17	56.67	0	0	1 [a]	3.33
CLIA	5	16.67	18	60	0	0	7 [a]	23.33
Genetics	15	50	14	46.67	0	0	1 [a]	3.33

Note: n=30

[a] Includes the University of Pittsburgh which had no documents in the document set.

Identified Themes Around Reference to CLIA and the Return of Individual Research Results

I identified two themes when analyzing the data for reference to the CLIA regulations when researchers plan to return individual findings to the subject. These are (1) the requirement to comply with the CLIA regulations; and (2) the mention of confirming the results in a CLIA-certified laboratory and identification of who is responsible for covering the costs of CLIA certification.

Documents Addressing Compliance and/or the Applicability of the CLIA Regulations

In reviewing the documents to understand if the institutions require compliance with the CLIA-regulations when research results are returned to study participants, several positions emerged. This included requiring compliance, recommending compliance, ambiguous or unclear messaging about compliance, and institutions that were silent on the CLIA regulations. The "Required" and "CLIA Silent" codes were further delineated into sub-codes to capture the variation

identified in institutional documentation. Table 15 provides the coding scheme, definitions, and example text for the positions identified.

Table 15

Coding Scheme for Compliance with the CLIA Regulations When Results are Returned to Study Participants

Code	Definition	Document Language
Required: Full Stop [a]	Institution uses language that makes compliance with the CLIA regulations officially compulsory, or otherwise considered essential. Document uses words like must or required.	Under the current interpretation of these requirements, the Organization will not permit researchers to disclose or report results of research tests when such tests have been performed in laboratories that have not been CLIA-certified and do not have a state laboratory license (Johns Hopkins University, 2013, para. 1).
Required: Exceptions [a]	Institution uses language that makes compliance with the CLIA regulations officially compulsory, or otherwise considered essential. Document uses words like must or require(d). However, language is included that makes an exception to the requirement.	The results of clinically-available tests performed for research purposes may be returned to individual research subjects only when the test is performed in a laboratory which is CLIA certified or meets CLIA quality standards (Mayo Clinic Rochester, 2018, p. 1). If the test is not available in the clinical setting and, in the opinion of the investigator, returning the test result would be in the best interest of the research subject, the investigator must obtain IRB approval before returning the result. The return of such a result may be approved by the IRB if it is deemed to be in the best interest of the research subject, have a high degree of validity, and be actionable (Mayo Clinic Rochester, 2018, p. 1).
Required: Qualified [a]	Institution uses language that makes compliance with the CLIA regulations officially compulsory for specific types of data (such as clinically relevant or health related).	For diagnostic or health-related uses, the tests must be physician-ordered and performed at a CLIA-certified laboratory (University of California Berkley, 2017, p. 7).

Code	Definition	Document Language
Required: PI determines [a]	Institution places responsibility of determining if the CLIA regulations are relevant or appropriate on the researcher	4.1 Researchers are responsible for complying with the CLIA requirements, when applicable: 4.1.1 Deciding whether their laboratories require certification 4.1.2 Obtaining and maintaining certification, as necessary (p. 2) 5.1.1 CLIA applicability: Researchers determine the applicability of CLIA to their labs. This is best done by referring to the information provided by CMS at the CLIA website: http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html (University of Washington, 2014, p. 3).
Recommended	Institution uses language that encourages compliance with the CLIA regulations. Document uses words like should, recommends, or encourages.	Labs that are providing research findings for medical use (e.g., affected patients will be recommended for surgery, drug therapy or the research result will be used to guide other aspects of medical management) should be encouraged to obtain CLIA certification for the test. When available, subjects should be advised that they can be retested by a commercial CLIA certified lab (University of Michigan, 2002, p. 5).
Ambiguous/Unclear	The institution's expectation is unclear or not obvious based on the wording of the document.	Does the PI intend to return results from research using the stored samples? If YES, need to address the following issues: ☐ Results validated in a CLIA laboratory (if not already performed in one) (Northwestern University at Chicago, 2018, p. 2)?
CLIA Silent: Full Stop [b]	No mention of CLIA or data quality	N/A
CLIA Silent: Data quality [b]	The institution does not specifically mention the CLIA regulations but does discuss the quality of the data (such as valid or accurate).	Most research data derived from tissue specimens has not been validated for clinical decision-making and should not be disclosed to the participant under most circumstances (University of Alabama at Birmingham, 2013, para. 5).

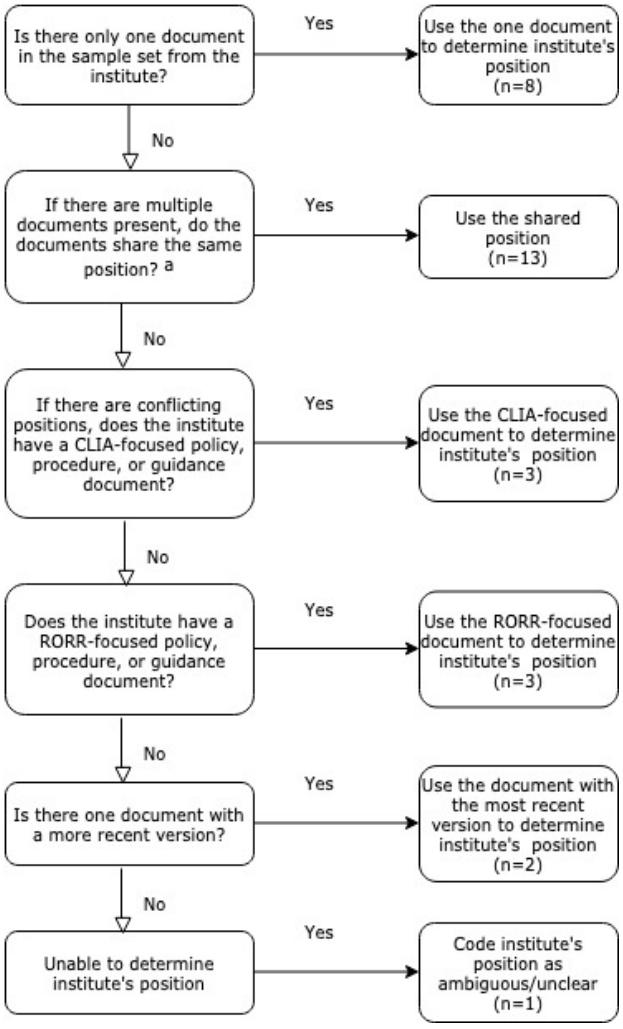
[a] The code for "required" was further delineated into the listed sub-codes

[b] The code for "silent" was further delineated into the listed sub-codes

Appendix H presents the assigned code for all documents concerning if and how the document addressed compliance with the CLIA regulations. After I assigned each document a code, I determined the overall code for the institution's position (Appendix I) following the process outlined in Figure 5.

Figure 5

Process Used to Determine an Institution's Position on Compliance with the CLIA Regulations When Returning Research Results to Study Participants



[a] In cases where an institution had documents silent on CLIA and documents with a position, the documents with a position trumped the silent document.

Table 16 shows the number and frequency of institutions by code for compliance with the CLIA regulations. At the same time, Table 17 provides the delineation of the "Required" and "CLIA Silent" codes into sub-codes. Overall, 56.67% of institutions (n=17) used language in their policies and supporting documentation that required compliance with the CLIA regulations. This intent is evidenced by the use of such words as "must" or "required" when discussing the use of a CLIA-certified laboratory when returning results. While 23.33% of institutions (n=7) had no language related to the CLIA regulations, 13.33% of institutions used language that encouraged the use of a CLIA-certified laboratory, and 6.67% of institutions' expectations were ambiguous or unclear. [11]

Table 16

Number and Frequency of Institutions by Code for Compliance with the CLIA Regulations

Code/Position	Institutions (n=30)	
	n	%
Required [a]	17	56.67
Recommended	4	13.33
Ambiguous/Unclear	2	6.67
Silent on CLIA [a]	7	23.33

[a] Codes were further delineated into sub-codes presented in Table 17.

Table 17 provides the delineation of the "Required" and "CLIA Silent" codes into sub-codes. Of the 17 institutions that required compliance with the CLIA

[11] One institution (Stanford University) had two template consent forms accessible on their website. One consent form was for the Department of Veterans Affairs research and the other was their standard consent form template. Both consent forms discussed the return of research results but only the Veterans Affairs template noted that the CLIA regulations applied if individual results would be returned for the diagnosis, treatment, or management of the participant. Accordingly, I coded this institution as **"**ambiguous/unclear**"**.

regulation, nine institutions considered compliance to be essential and did not provide an alternative, five institutions required compliance but included language that allowed for exceptions to the rule. One institution required compliance but qualified that requirement by specific use of the data. In this case, the document used the qualification of "for diagnostic or health-related uses" (University of California Berkley, 2017, p. 7). Finally, two institutions required compliance but put the responsibility to interpret and determine the applicability of the CLIA regulations on the study principal investigator.

I delineated the "CLIA Silent" category into two sub-codes to distinguish between truly silent documents on the quality of the data returned versus institutions that referred to data quality metrics but did not specifically address the CLIA regulations. Of the seven institutions coded as silent on the CLIA regulations, five were silent on the discussion of any data quality metrics, while two institutions addressed the validity of the data when discussing the return of research results.

Table 17

Number and Frequency of Institutions by Sub-Code for Compliance with the CLIA Regulations

Category	Sub-category	Institutions (n=30)	
		n	%
Required	Required [a]	9	30
	Required: exceptions [b]	5	16.67
	Required: qualified [c]	1	3.33
	Required: PI interprets [d]	2	6.67
Silent on CLIA	Silent [e]	5	16.67
	CLIA Silent: Data Quality [f]	2	6.67

[a] Required, full stop

[b] Required but references exceptions

[c] Required but qualifies the type or use of the data

[d] Required but puts the interpretation of CLIA applicability back on the researcher

[e] Silent on the CLIA regulations

[f] Silent on the CLIA regulations but references the validity of the data or test

Documents Addressing Confirmation of Research Results in a CLIA-Certified Laboratory

As confirmation of research findings in a CLIA-certified laboratory has been a commonly accepted method to ensure CLIA compliance, I examined all documents for discussion of confirmation testing. Confirmation of research results in a clinical laboratory was discussed in 19 documents across 13 institutions (43.33%). Table 18 shows a breakdown by document type. Of the seven template documents that referenced confirmation testing, five were consent templates, while four institutions provided model consent language to inform study participants that research results needed to be confirmed by a clinical lab. Only one institution provided guidance to investigators that a new sample may need to be obtained if the research was done in a non-CLIA certified laboratory. One institution provided model consent language to inform study participants that they may need to collect additional sample(s) for the confirmation testing.

Table 18

Reference to Confirmation Testing by Document Type

Document Type	n
Policy	3
Procedure	0
Guidance	8
Template	7
Other	1
Total # of Documents	19
Total # of Institutions	13

Associated with the concept of CLIA confirmation of research results, the cost of confirmation testing emerged as a linked attribute that 26.67% of institutions

addressed. Table 19 defines the scheme I used to code the documents for who was responsible for covering the cost of CLIA confirmation of research findings. The codes that surfaced during the document review included (1) the participant being responsible for confirmation testing; (2) the study sponsor being responsible; (3) not specific (documents that did not specify who would be responsible, vague documents that mentioned costs of returning results in a more general context); and (4) silent (documents that did not discuss the costs of confirmation testing).

Table 19

Coding Scheme for Addressing the Cost of Confirming Research Results and Who is Responsible for Paying

Code	Definition	Document Language
Confirmation cost: participant	The cost of confirming research results in a CLIA-certified lab is the participant's or their insurance's responsibility	If this happens, then you may want to get a second test from a certified clinical laboratory, consult your own doctor, or get professional genetic counseling. You may have to pay for those additional services yourself (University of Minnesota, 2018, p. 14).
Confirmation cost: not participant	The cost of confirming research results in a CLIA-certified lab is the study's responsibility	You will not be charged for the costs of confirming in a clinical laboratory any findings to be used in research (Columbia University, 2016a, p. 30).
Confirmation cost: not specific	The document discusses the cost of confirming research results in a CLIA-certified lab but is silent on who the responsibility lies with	The investigator should also consider whether they will provide additional confirmatory testing to the participants, whether they are willing to test family members, and how the cost for such testing and counseling will be covered (Washington University, 2011, p. 8).
Confirmation cost: vague	The document mentions cost in the context of returning results but is vague on specific details.	What are the Costs Associated with Finding/Returning Research/Incidental Findings (University of California San Diego, 2018, p. 3)?
Confirmation cost: silent	The document is silent on confirmation cost.	

The data in Table 20 indicates that 23.33% (n=7) of institutions addressed the cost of CLIA confirmation compared to 76.67% (n=23) of institutions that did not. An equal number of institutions (n=2) were coded as "confirmation cost: participant", "confirmation cost: not specific", and "confirmation cost: vague". Appendix J provides the documents addressing the cost of CLIA confirmation and their assigned code. Columbia University was the only institution that specifically stated that the costs of confirmation testing would not be the participant's responsibility (Columbia University, 2016a).

Table 20

Number and Frequency of Institutions that Address the Cost of Confirming Research Results

Category	Institutions	
	n	%
Confirmation cost: participant	2	6.67
Confirmation cost: not participant	1	3.33
Confirmation cost: not specific	2	6.67
Confirmation cost: vague	2	6.67
Confirmation cost: Silent	23	76.67

Additional Features of IRB Policies and Supporting Documentation

Research Sub-Question 3: (a) Do IRB policies and supporting documentation address key ethical principles regarding RIRR and/or complying with CLIA regulations? (b) Do IRB policies address the guidance from federal agencies?

Policy Ethical Justification for Return of Research Results (Question 3a)

The Belmont Report outlines the basic ethical principles underlying research: respect for persons, beneficence, and justice. As these principles are the basis for human subjects protections, I wanted to explore whether they were cited in the

documentation in the context of the return of research results. Table 21 presents the number and frequency of institutions that address the Belmont ethical principles.

Table 21

Number and Frequency of Institutions that Address Research Ethics Principles with respect to the Return of Research Results

Research Ethics Principle	Institutions	
	n	%
Respect for Persons	28	93.33
Consent process [a]	28	93.33
Right not to know [b]	19	63.33
Other/direct reference	4	13.33
Beneficence	2	6.67
Other/direct reference	2	6.67
Justice	1	3.33

[a] Institutions that addressed respect for persons indirectly through the concept of informing participants if they will or will not receive research results as a part of the study.

[b] Institutions that addressed respect for persons indirectly through the concept of allowing participants to opt-in or out of receiving results.

The vast majority - 93.33% (n=28) - of institutions included the concept of respect for persons in their documentation. Twenty-eight institutions (93.33%) demonstrated this principle through guidance that investigators needed to inform subjects whether research results would be returned. Fifteen institutions (50%) asked investigators to clearly state when results would *not* be returned, not just when they would be returned. Nineteen (63.33%) institutions asked investigators to consider whether participants can opt-in or out of receiving results, often referred to as the "right not to know". Four institutions (13.33%) directly addressed the "respect for persons" principle outside the context of the option to receive test results. This

included the right to be informed about the research they participate in, the right to information about themselves, and the right to honor children's future autonomy.

Two institutions (13.33%) discussed beneficence, maximizing the benefits, and minimizing the risks of study participation as consideration for disclosing research findings. Only one institution (3.33%) addressed the principle of justice in that investigators should consider "the intent for reciprocity and justice to benefit participants based in part on the contribution that participants' involvement has provided to the research study" (Yale University, 2013a, p. 3).

Review of Policies for CLIA Guidance from Federal Agencies (Question 3b)

Of the 23 institutions that mentioned the CLIA regulations in one or more documents (Table 22), eight referenced the CLIA or state clinical testing regulations with a more detailed explanation. This was defined as documents that provided definitions taken directly from the CLIA regulations for research and clinical laboratories. Out of the other 15 institutions that mentioned CLIA, only four institutions (13.33%) provided a link to the Centers for Medicare & Medicaid Services and/or CLIA regulations website. Two institutions (Johns Hopkins University and Emory University) referenced other federal agency guidance to the CLIA rule. One institution referenced guidance from the National Human Genome Research Institute (Emory University, 2018b). Another institution referenced the outdated "CLIA-exception" rule to the right-to-access requirement in the Privacy Rule removed from the HIPAA regulations in 2014 (Johns Hopkins University, 2015).

Table 22

Number and Frequency of Institutions that Address CLIA Guidance from Federal Agencies

Guidance from Federal Agencies	Institutions (n=30)	
	n	%
References to State and/or CMS CLIA regulations & guidance [a, b]	8	26.67
Provides link to CLIA regulations/CMS.gov	4	13.33
References to other Federal agency guidance on CLIA regulations [c]	2	6.67

[a] Institutions included in this category directly cited the CLIA or State testing regulations.

[b] Two institutions were located in New York, which is CLIA-exempt as their state regulations for clinical testing are equivalent or more stringent than federal regulations.

[c] One institution cited genome.gov for issues on incidental findings. One institution cited the outdated CLIA-exception rule for HIPAA right to access.

Comparison of Study Findings to Previous Peer-Reviewed Research

Research Sub-Question 4: How do results from this research project compare to previous research conducted on the topic of IRB policies and guidance documents addressing returning research results to study participants?

In 2007, Kozanczyn, Collins and Fernandez conducted a similar study in which they looked at IRB policies or standard operating procedures from 207 institutions in the United States to understand how they addressed the return of research results

(Kozanczyn et al., 2007). [12] The authors classified documents into one of three categories; (1) yes, the policies referenced return of research results, (2) No they did not reference the return of research results, and (3) they were vague. The authors defined vague as "guidelines or SOPs referring to return of research as an abstract concept with no details provided" (p. 259). In order to understand how IRB policies at US institutions have changed on this issue since 2007, I performed a similar analysis to compare findings. Kozanczyn et al. did not include template or "other" types of documents in their analysis. In order to replicate their process, I performed two sets of calculations. The first involving only the policies, procedures, and guidance documents in my sample set and the second including all documents in my sample set (Table 23).

Kozanczyn, Collins, and Fernandez (2007) found that only 7.7% (n=16) of US IRBs had the return of results present in policies and guidance documents. 56% (n=116) had no reference to the return of research results and an additional 36.3% (n=75) had a vague reference in which the return of results was an "abstract concept with no details" (p. 259). Therefore, 44% of institutions evidenced that they had at least thought about the issue, even if only abstractly. Looking at only medical schools (n=123), they found that 9.8% (n=12) referenced the return of results, 38.2% (n=47) made no reference, and 52% (n=64) had a vague reference. This resulted in 68.2% (n=76) medical school IRBs having had considered the issue of returning research results in their policies.

[12] The Kozanczyn, Collins and Fernandez study was not focused solely on the return of individual research results. They included overall study results in their definition of results.

Table 23

Number and Frequency of Institutions that addressed the Return of Research Results using the methods described by the Kozanczyn et al. Study

	No		Yes		Vague	
Study	n	%	n	%	n	%
Kozanczyn et al. [a] ROR Analysis (n=207)	116	56	16	7.7	75	36.3
Buchholtz ROR Analysis (limited [b]) (n=30)	7	23.33	23	76.67	0	0
Buchholtz ROR Analysis (all [c]) (n=30)	1	3.33	29	96.67	0	0
Kozanczyn et al. [a] ROR Med-Schools Only (limited [b]) (n=123)	47	38.2	12	9.8	64	52
Buchholtz ROR Analysis Med-Schools Only [d] (limited [b]) (N=28)	6	21.42	22	78.57	0	0
Buchholtz ROR Analysis Med-Schools Only [d] (all [c]) (n=28)	1	3.57	27	96.43	0	0

[a] (Kozanczyn et al., 2007)

[b] The "limited" sample set only contained the policies, procedures, and guidance documents from my sample set.

[c] The "all" sample set contained the policies, procedures, guidance, template, and "other" documents from my sample set.

[d] Includes medical schools and hospitals

Looking only at the policies, procedures, and guidance documents in my sample set, I found 76.67% (n=23) of institutions discussed the return of research results while 23.33% (n=7) of institutions had no reference. If I look only at medical schools and hospitals (n=28) in my sample set, 78.57% (n=22) of institutions referenced the return of results, and 21.42% (n=6) had no reference. When I expanded the analysis to my complete sample set for medical schools, including

policies, procedures, guidance, templates, and other documents, only one (3.57%) institution did not have any documents that addressed the return of research results. By contrast, 96.43 % (n=27) had referenced the return of results in at least one document.

In 2007, 36.3% of all IRB and 52% of medical school IRBs were classified as vague in addressing the return of results and only included the return of results as an "abstract concept" in their documents (Kozanczyn et al., 2007). My analysis found that no institutions were vague or abstract in their reference to the return of results.

Summary

The main objectives of this chapter were to report the findings from the document analysis. Terms used to code the data were categorized into five categories: Providing findings, research findings, data quality, genomic data, and individual-level. The frequency of each category appearing in documents and by institution was discussed in detail, along with any key observations identified around each category. Focusing specifically on how documents referenced the CLIA regulations, I identified several themes addressed with relation to CLIA compliance. Additionally, I looked at whether the documents referenced the bioethical principles of respect for persons, beneficence, and justice in the return of research results sections. I also investigated whether the documents cited the federal regulations or guidance to frame the CLIA discussion. Finally, I compared my findings to the 2007 study by Kozanczyn, Collins, and Fernandez, which looked at U.S. IRB's policies around the return of research results. (Kozanczyn et al., 2007). In the next chapter, I discuss the results of my analysis.

CHAPTER 6

DISCUSSION AND CONCLUSION

This study aimed to understand if and how US IRBs address the applicability and compliance with the CLIA regulations when researchers plan to return individual research results to study participants.

Despite a growing movement by many within the research community to encourage investigators to return individual-level research results (RIRR) to study participants, United States federal agencies have been slow to address the topic. A common point of contention around the RIRR discussions was the applicability of the Clinical Laboratory Improvement Amendments (CLIA) regulations when participant-specific results were to be returned. In 2014, the Centers for Medicare and Medicaid Services (CMS), which oversees the federal CLIA program, issued guidance that the CLIA requirements apply when individual-level findings are returned to a subject or their physician (Centers for Medicare & Medicaid Services, 2014). Even with this guidance, however, there remains significant debate around the topic, culminating with a National Academies of Sciences, Engineering, and Medicine (NASEM) working group recommending that the NIH develop a CLIA-alternative for research laboratories to return data not intended for clinical decision-making (National Academies of Sciences, 2018).

The Current State of US IRBs addressing Return of Results

To understand how IRBs address compliance with the CLIA regulations when investigators return research results to study participants, we must first understand the IRB guidance landscape on returning research results to study participants. Previous research by Kozanczyn, Collins, and Fernandez (2007) found that there was no "systemic approach to the return of results to study participants within guidelines provided by U.S. IRBs" with only 43.3% of institutions having clear or vague

guidance on the issue (p.262). Looking specifically at medical schools, Kozanczyn et al. found 61.8% of institutions had clear or vague guidance, although 52% were classified as vague. My research indicates that, during the intervening decade, U.S. IRBs have significantly improved their approach to the return of research results with 96.67% of all institutions, and 96.43% of medical schools/hospitals, providing some type of IRB guidance on the issue to their investigators. What has changed since 2007 to account for the ~34-53% increase in IRB Guidance for investigators returning research results to study participants?

The surge in the generation of individual genetic research data and the growing movement to disclose research findings to study participants can explain the increase in IRB guidance between 2008 to the present. As discussed in Chapter Two, advances in genetic and genomic technology have been one of the main driving forces behind the growth in the return of research results movement. Since the completion of the human genome project in 2003, there has been an exponential growth in genetic and genomic sequencing capabilities. In turn, this has led to researchers being able to generate a vast amount of individual genetic data on study participants.

Around the same time as the completion of the human genome project, Fernandez, Kodish, and Weijer published a paper challenging the nondisclosure model and calling the return of results to study subjects an ethical obligation (Fernandez et al., 2003). While the idea of returning research results to participants was not new in the genetics community, the Fernandez et al. paper was published in the *IRB: Ethics and Human Research* journal and was therefore highly visible to the IRB community. Discussions on the practice and ethical obligation to disclose research results continued to grow both in the literature and federal working groups and agencies (Angrist, 2011; Bookman et al., 2006; National Academies of Sciences,

2018; Ravitsky & Wilfond, 2006). The topic gained even further visibility in the IRB community at the Public Responsibility in Medicine & Research (PRIM&R) annual conferences as it was a frequent focus of breakout sessions (Childers et al., 2019; Forster, 2016; Grienauer et al., 2017; Noren & Russell-Einhorn, 2010; Wolf, 2012).

When looking specifically at how IRBs are communicating the return of results, 40% of the institutions (n=12) had guidance that is focused primarily on the return of results. In comparison, 56.67% (n=17) had the topic included in a more general document, such as a procedure manual, or in documents specifically addressing genetic/genomic research. Not surprisingly, focused guidance on the return of results was primarily centered around disclosing incidental or secondary findings. Overall, however, only 60% of institutions (n=18) mentioned incidental or secondary findings in their documents. This is a surprising finding in that so much of the debate regarding returning results has centered on incidental findings that may have clinical implications for subjects. Perhaps the IRBs are simply lumping all findings returned to participants together and not distinguishing between the different types of data that can be discovered and returned. However, I find this is worrisome as best practices call for investigators to plan for and anticipate incidental or secondary findings (Presidential Commission for the Study of Bioethical Issues, 2013).

While not the focus of this research study, I observed that there is a lot of variation in the guidance provided to investigators with respect to returning research results. This can vary from one or two sentences in a consent form that simply reminds investigators to inform participants if their results will be returned to detailed supplementary IRB submission forms asking investigators the who, what, where, and how questions related to returning the results. While several groups have addressed the importance of the return of research results and the need for

guidance from Health and Human Services (HHS), the federal government has yet to issue formal guidance on the practice (Presidential Commission for the Study of Bioethical Issues, 2014; Secretary's Advisory Committee on Human Research Protections, July 21, 2016).

How Well Do IRB Policies and Supporting Documentation Address Key Ethical Principles?

Before addressing whether and how IRBs handled compliance with the CLIA regulations, it is important to understand whether and how institutions framed the ethical principles of respect for persons and beneficence in the context of returning results.

The literature primarily tends to cite respect for persons/autonomy as the primary ethical principle that supports a participant's right to receive their individual research results (Ossorio, 2006). Interestingly, only 13.33% (n=4) of institutions directly referenced the respect for persons or autonomy principles in the context of returning research results to participants. The primary reason cited was a participant's right to be informed about the research they are participating in, including receiving results that could be relevant and useful. One institution specifically asked investigators to consider if returning results about the risk of adult-onset conditions would "honor future autonomy" of the child (Emory University, 2018b, p. 9).

More common in the documentation was how institutions would address respect for persons indirectly by guiding investigators toward informing participants whether they will or will not receive results. 93.33% of institutions (n=28) had some sort of guidance related to this practice. While much of the guidance centered around informing participants whether results would be disclosed, 50% of institutions (n=15) asked investigators to clearly state whether results would *not* be disclosed.

Being clear and upfront with participants about the potential – or not – to receive results allows them to make an informed decision regarding participation (National Academies of Sciences, 2018). Finally, 63.33% of institutions indirectly addressed the ethical principle of respect for persons through guidance that participants have the right to opt-in or out of receiving research results. This concept of individuals having the "right not to know" their genetic testing results is "grounded in respect for decisional autonomy and/or an interest in protecting individuals from receiving unwanted and potentially harmful information" (Berkman & Hull, 2014, p. 29). Interestingly, two institutions (Yale University and Massachusetts General Hospital) cautioned investigators that there might be times it is inappropriate to provide the option to opt-out of receiving results as the results may have clinical significance:

> Some studies may offer a choice of whether or not to receive their study results. However, when the study by its nature may yield results with possible health or safety significance, it may be appropriate for participants who do not wish to receive their study results to simply not participate in the study. (Yale University, 2013a)

Only two institutions (6.67%) directly addressed the principle of beneficence, which is to "maximize possible benefits and minimize possible harms" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). One institution emphasized the benefit aspect of returning study results:

> The principle of Beneficence requires that benefits to the subjects be maximized while risks are minimized. Providing subjects with experimental test results may provide them with benefit, even if it is only the intellectual satisfaction and feeling of control of learning difficult-to-interpret information about themselves. (Yale University, 2013a, p. 3)

If we look at the act of returning research results as a way to maximize a participant's benefit from research, then 96.67% of institutions (n=29) indirectly addressed the principle as all but one institution addressed returning research results. Looking at the principle of beneficence instead as underscoring the need to minimize risks posed to participants, 83.33% of institutions (n=25) asked investigators to consider the quality and validity of the data being returned to study participants, with 76.67% (n=23) of institutions directly addressing CLIA as a quality metric. One of the primary concerns with returning non-CLIA generated data involves the quality and reliability of the data (National Academies of Sciences, 2018). That over three-fourths of the institutions inquire about the quality suggests that the IRBs are weighing the benefits against the risks of returning results, the primary concept in the principle of beneficence.

Out of all discussions on the ethical reasons for returning research results, only one institution provided direct ethical justification for returning non-CLIA generated study findings:

> The Belmont Report cites basic ethical principles which may be seen as supporting research subjects? Right to have access to information about themselves. The principle of Respect for Persons establishes the right of individuals to be fully informed about research in which they participate. The principle of Beneficence requires that benefits to the subjects be maximized while risks are minimized. Providing subjects with experimental test results may provide them with benefit, even if it is only the intellectual satisfaction and feeling of control of learning difficult-to-interpret information about themselves. Because individual interests may vary, studies may need provisions that allow individual subjects to decide whether or not to receive results. (University of California San Francisco, 2015, pp. 3-4)

The Current State of US IRBs addressing Return of Results and Compliance with the CLIA Regulations

The present study found that 76.67% of biomedical IRBs (n=23) address the CLIA regulations in the context of returning research results to study participants in their policies, procedures, guidance, template, and other supporting documentation. Despite this high frequency of institutions addressing the CLIA regulations, I found there to be varying degrees of detail provided on the topic. Only 16.67% of institutions (n=5) had policies or guidance documents explicitly focused on the CLIA requirements. 52.17% of institutions (n=12) that reference CLIA in their IRB documentation do so with only one or two-sentences and very little detail.

There is considerable heterogeneity in how institutions address CLIA and their requirements or expectations of CLIA-compliance for RIRR. On the whole, 56.67% of institutions (n=17) required the use of a CLIA-certified laboratory to generate or confirm research results when returned to participants with an additional 13.33% (n=4) recommending or encouraging the use of a CLIA-certified lab. There was further variation between the institutions that require CLIA compliance. The majority of institutions in the required category (52.94% [n=9]) expectations were that only CLIA-certified results would be returned to participants. However, 29.14% (n=5) used language that hinted at exceptions to the CLIA rule or directly provided examples of cases in which there is justification to provide non-CLIA certified results to subjects:

> Ethical Justifications for Providing Results in the Absence of CLIA Certification: There are situations in which it is unethical to withhold all results. However, citing one or more of the following ethical justifications for providing results is not in itself sufficient to ensure IRB approval. The IRB

must consider the overall context of the study and will make decisions on a case-by-case basis. (University of California San Francisco, 2015, p. 3)

One institution qualified that the CLIA regulations specifically applied to data that would be used for clinical care; "Note: if a CLIA approved lab is not being used the test results cannot be used for medical treatment" (University of California Irvine, n.d.-a, p. 2). Two institutions (6.67%) had IRB procedures on CLIA Lab Certification that outlined the requirement of CLIA certification for research labs but did not provide an interpretation of when it applied. Instead, the procedures put the responsibility of deciding whether CLIA applies to their laboratory squarely on individual investigators. One institution specifically stated that it was the human subjects research program's responsibility for "ensuring that researchers are aware of the CLIA certification requirement" but not to interpret or enforce the CLIA regulations and requirements (University of Washington, 2014, p. 2). Both institutions clearly stated that "IRB approval is not conditional upon obtaining CLIA certification, even when CLIA certification is required" but that the IRB would consider the "information about the validity and reliability of the analysis" (University of Colorado Colorado Springs, 2018, p. 86; University of Washington, 2014, pp. 2-3). Seven institutions (23.33%) offered no guidance that mentioned the CLIA regulations or requirements, although two institutions did address the validity of the data.

In addition to variation in stance on requiring compliance with the CLIA requirement, there was a sizable difference in what type of additional detail accompanied the reference to or discussion of the CLIA regulations. In particular, I looked at details with respect to confirmation or verification of research findings. Confirmation of research findings in a CLIA-certified laboratory is a commonly adopted practice for studies that did not use a CLIA laboratory to generate the initial

data (Das et al., 2008; Siegfried et al., 2013). This is especially true when unanticipated, clinically relevant findings have been discovered in a study in which the investigator perceives a need to return individual-level results. Only 43.33% of institutions (n=13) mentioned confirmation or verification of research results in a state or CLIA-certified laboratory. This number seems low considering 76.67% (n=23) of institutions discuss compliance with the CLIA requirements. Of these thirteen institutions, only four provided investigators with model consent language to inform participants that research findings may need to be retested or verified in a clinical laboratory.

An additional consideration has to do with the potential for the need to collect a new sample to perform the confirmation testing. Clinical labs will not accept a research specimen for clinical testing as it has broken the CLIA chain-of-custody. Therefore, if a researcher wants to obtain confirmation testing before results are returned, they would need to obtain a new sample from the study participant if the sample has been stored in a research setting. While this may be easily done with a blood sample, it may not be possible to obtain a new tissue sample such as a biopsy or tumor sample. With this in mind, I found it interesting that only one institution provided guidance to their investigators on the issue of CLIA chain-of-custody:

> If the original clinical sample was not obtained in a CLIA certified laboratory, a new sample must be obtained. If this is not possible (e.g., with tissue biopsies obtained through an invasive procedure), then the protocol should be designed so that initial samples are received in an established CLIA-approved clinical laboratory (such as a clinical pathology laboratory). (Massachusetts General Hospital, n.d., p. 33)

Informing study participants that they may need to provide an additional sample for clinical confirmation is another consideration investigators should take into account. During the informed consent process, investigators should disclose to prospective participants the procedures involved with participation in the study. If a new sample may be needed at some point, this should be communicated. Only one institution provided model consent language to inform subjects of the potential for additional sample collection (Columbia University, 2016a, p. 33).

Finally, there is a general expectation in human subjects research that investigators will inform study participants if they will incur any costs associated with participating in a research study. In the case of confirmation testing, I analyzed the documents to see if the responsibility of covering the costs of CLIA confirmation was discussed. Only 20% of institutions (n=6) addressed the cost of confirming the research results in a CLIA-certified laboratory. In all, two institutions mentioned the participant covering the costs of testing, two discussed the costs but were not specific as to who was responsible, one institution specifically said the costs were not the participant's responsibility, and one was vague in mentioning costs of returning findings but not specifically calling out the cost of CLIA-confirmation testing itself. In my sample, therefore, there was little consistency in how this issue was addressed, and there was evident variety in discussing who is responsible for covering the costs. Three institutions provided model consent language that directly informed the participants whether they were expected to pay – or not – for the cost of verifying results in a clinical lab. The other three institutions asked investigators to consider who would pay for confirmation testing in guidance documents.

It is unclear why there is such heterogeneity in the degrees of detail provided to investigators with respect to the CLIA regulations. One explanation may be the lack of guidance from the federal Office of Human Research Protections with respect

to human subject protections. Without a federal requirement to address the issue in IRB policies, institutions may see no reason to address the topic. Another plausible explanation is that IRBs may not be (or see themselves as not being) responsible for oversight or enforcement of the CLIA regulations. As the CLIA rule applies to clinical laboratory testing, IRBs may not view their position as having a role in providing guidance. However, as human subjects' welfare and protection are the responsibility of the IRB, one can argue that it is necessary for them to address the return of results in the context of CLIA. Another, less likely, explanation may be that the IRBs included in my sample set have not had to deal with the issue of return of research results or compliance with the CLIA regulations, and therefore have had no need to develop guidance. However, this is an unlikely explanation as I purposefully selected institutions whose IRBs are most likely to have reviewed large volumes of biomedical protocols.[13] Finally, there is a chance that institutions did have IRB guidance documents that were not publicly available and therefore excluded from my analysis. With the increase in the use of electronic IRB submission systems, institutions could address some of the return of results and CLIA questions in online applications or consent-form building software programs.

Recommendations

While the majority of IRBs referenced the CLIA regulations in at least one document, IRB policies and supporting documentation were inconsistent across the institutions, with most institutions providing very little substantive guidance. IRB guidance should address (1) an institution's expectations concerning CLIA

[13] Twenty-six of the institutions in my sample set are ranked in the top 200 of U.S. News Best Global Universities for their molecular biology and genetic programs. The four institutions not ranked include three institutions that are not universities and one institution that does not have a molecular biology or genetics doctoral program.

compliance; (2) what type of research results fall under the scope of the CLIA regulations; (3) how confirmation testing could be used for results not generated in a clinical lab; (4) how samples could be collected to maintain CLIA Chain of custody; (5) model consent language to inform the participant if additional samples may need to be collected for confirmation testing; and (6) flexibility to allow institutions to make exceptions to the CLIA requirement in extenuating circumstances. The CLIA guidance does not necessarily need to be in a CLIA-focused policy; I recommend that all institutions provide a policy or guidance focused on the return of results and include a section in the document providing CLIA points to consider.

Of the 73 documents analyzed for this study, a few stand out as paradigmatically good examples that other institutions could model their documents after. In particular, the University of Washington's *Zipline Supplement on Participant Results Sharing* was thorough in walking investigators through the details of a proper return of results plan, which included: (1) what results would be disclosed and why; (2) who the recipients of the information are; (3) how the information will be disclosed; and (4) things to think about for the informed consent process. This document addresses CLIA throughout but mainly in the context of criteria for data to be returned. I would improve the form by including CLIA confirmation cost and CLIA chain of custody for rare or hard to recollect samples.

Another informative document was the Massachusetts General Hospital Genetics Research Advisory Panel GAP report. This document provided a lot of background and information on the CLIA regulations' applicability to research testing, along with guidelines for investigators. There were detailed discussions on the pros and cons of returning results, and providing participants with the option to receive results. The only drawback of this document is that it is a report that was rather long and included topics other than just returning results and CLIA. I recommend taking

the valuable information in the report and making a return of results-specific guidance document with the information.

Finally, for informed consent templates, I recommend the Columbia University Consent Form Builder template. While the template is extremely long – 46 pages – it breaks down model consent text by topic and guides investigators about including the various recommended text. The document is thorough and covers all of the components of returning genetic research results to study participants, including addressing the costs of CLIA confirmation and the possibility of additional sample collections.

Conclusion

The present study addressed whether and how U.S. Institutional Review Boards (IRBs) address the return of individual research results and compliance with the Clinical Laboratory Improvements Amendments (CLIA) regulations.

In Chapter 1, I introduced the project and my driving questions. In Chapter 2, I reviewed the complex web of federal regulations that govern human subjects protections and the return of research results. I described in Chapter 3 how the prospect of returning research results became hotly debated within the research community. Chapter 4 outlined my study design and the mixed qualitative methods I used to collect, code, and analyze the data. Chapter 5 presents my study findings, including (1) coding categories used to identify key texts in the IRB documents; (2) themes around the practice of returning individual-level research results; (3) Institutions' stance on compliance with the CLIA regulations for the return of findings; (4) how IRBs addressed the key research ethics principles with regards to returning results; and (5) a comparison of my findings with previously published work on IRB documents and the return of results. Finally, in Chapter 6, I discussed the findings and

made recommendations for improved guidance on addressing CLIA compliance in IRB guidance documents.

The study results provide evidence that the majority of U.S. biomedical institutions require or recommend compliance with CLIA stipulations when investigators intend to return individual research results to study participants. However, the study data indicates there is heterogeneity and variation in the quality of the guidance provided. Only 36.67% (n=11) of institutions provided more than a few sentences informing investigators that results should be confirmed or verified in a CLIA-certified laboratory.

To better serve their research community and the broader public prospectively involved in their research studies, I recommend that institutions provide investigators with transparent guidance on (1) the institution's position regarding CLIA compliance when individual results are meant to be returned; and (2) points to consider when designing a study with the potential to generate returnable primary, secondary, or incidental findings. I am not suggesting that Institutional Review Boards (IRBs) fulfill the role of CLIA compliance enforcer. Rather, I think the IRB is an excellent avenue to provide education and at least raise the question of the quality of the data investigators wish to return to study participants.

Future research should expand this study to U.S. institutions across the NIH funding spectrum, not simply in the top NIH-funded organizations, to ensure the knowledge gained from this study is representative of biomedical IRBs in general. Additionally, future research should include a survey of institutional officials and/or human research protection representatives to understand any differences between an institution's policies and supporting documents and their actual practices. For example, although an institution may require compliance with the CLIA regulations, do they ever approve the return of non-CLIA-certified research data due to

extenuating circumstances? Another prospect is to look at the current state of IRB policies and procedures now that the 2018 Final Rule has been implemented (as of January 2019). The Final Rule did ask investigators to address the return of results in the informed consent form for federally funded research. Have institutions that were silent on the return of results now included it in their guidance documents? Finally, future research should broaden the scope of the content analysis to include all aspects of returning research results and not just compliance with the CLIA regulations. This type of research can help IRBs identify gaps in their guidance to investigators conducting research that may generate returnable data.

As the present study makes clear, it is only by having institutions carefully consider the ethical and legal requirements of CLIA-compliance in the context of the return of individual research results, and addressing these issues in guidance documents for investigators, that we can properly protect those human subjects who volunteer to advance clinically relevant research.

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APPENDICES

APPENDIX A

INSTITUTIONS INCLUDED IN THE STUDY BY 2017 NIH FUNDING RANK

Fund Rank [a]	Institution	State	2017 NIH Funding	Type [b]
1	Johns Hopkins University	MD	$651,844,903	D-M
2	University of California, San Francisco	CA	$593,909,890	D-M
3	University of Michigan	MI	$521,788,658	D-M
4	University of Pennsylvania	PA	$493,869,965	D-M
5	University of Pittsburgh at Pittsburgh	PA	$485,268,079	D-M
6	Stanford University	CA	$465,856,075	D-M
7	University of Washington	WA	$443,367,966	D-M
8	Duke University	NC	$440,306,575	D-M
9	Washington University	MO	$435,637,200	D-M
10	Yale University	CT	$425,247,606	D-M
11	University of California San Diego	CA	$424,405,801	D-M
12	University of North Carolina Chapel Hill	NC	$419,977,336	D-M
13	Columbia University Health Sciences	NY	$402,667,654	D-M
14	University of California Los Angeles	CA	$401,246,794	D-M
15	Massachusetts General Hospital	MA	$394,465,880	ND-H
16	Brigham and Women's Hospital [c]	MA	$390,450,002	
17	Emory University	GA	$324,991,446	D-M
18	Icahn School of Medicine at Mount Sinai	NY	$317,816,778	D-M
19	University of Wisconsin-Madison	WI	$298,100,400	D-M
20	Fred Hutchinson Cancer Research Center	WA	$284,704,566	ND-R
21	Vanderbilt University Medical Center	TN	$259,711,413	ND-H
22	Northwestern University at Chicago	IL	$259,084,419	D-M
23	University of Southern California	CA	$258,125,982	D-M
24	Mayo Clinic Rochester	MN	$256,129,281	D-M
25	University of Minnesota	MN	$245,922,132	D-M
26	University of Alabama at Birmingham	AL	$244,213,416	D-M
48	Indiana University	IN	$146,733,443	D-M
51	University of Virginia	VA	$139,400,908	D-M
56	University of California Berkeley	CA	$126,789,875	D-M
63	University of California Irvine	CA	$116,517,198	D-M
802	University of Colorado, Colorado Springs	CO	$1,350,077	D-NM

[a] NIH Funding Rank in 2017

[b] Type of Institution: D = degree granting, ND = non-degree granting, M = medical school, H = teaching hospital, R = research institute, NM = non-medical school

[c] Massachusetts General Hospital and Brigham and Women's Hospital use the same IRB through Partners Healthcare (now called Mass General Brigham). Therefore, I did

not include Brigham and Women's Hospital in my analysis and added the 26th institution in the funding rank to my sample set.

APPENDIX B

DOCUMENT INFORMATION PRESENTED ALPHABETICALLY BY INSTITUTION

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
Columbia University	Genetic Testing Flowchart	no date	Guidance	https://web.archive.org/web/20191223092415/https://research.columbia.edu/sites/default/files/content/HRPO/GeneticTestingICresultsconfirmationrequirementflowchart.pdf
Columbia University	Policy on Research Involving Genetic Testing	3/1/17	Policy	https://web.archive.org/web/20180621194927/https://research.columbia.edu/sites/default/files/content/HRPO/GeneticTestingPolicyrevised3117.pdf
Columbia University	Consent Form Builder	8/16/16	Template	https://web.archive.org/web/20210207220705/https://research.columbia.edu/sites/default/files/content/HRPO/GeneticConsentTemplate070816final.pdf
Columbia University	Consent Cover Sheet Genetic	1/25/16	Template	https://web.archive.org/web/20180621210824/https://research.columbia.edu/sites/default/files/content/HRPO/WESWGSCFSummarycoversheetFINAL.pdf
Columbia University	Consent Form Genetic Research	8/8/16	Template	https://web.archive.org/web/20181221050123/https://research.columbia.edu/sites/default/files/content/HRPO/RASCALConsentformbuilderSample%2005.16.2018clean.doc
Duke University	Consent Language	10/13/17	Template	https://web.archive.org/web/20160308231148/https://irb.duhs.duke.edu/printpdf/2813
Emory University	Emory IRB Biomedical Protocol Outline for Investigator-Initiated Studies	6/8/15	Template	https://web.archive.org/web/20180414163533/http://www.irb.emory.edu/documents/Protocol%20Guidelines-Biomedical.docx

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
Emory University	Emory IRB Guidelines for Databases, Registries, and Specimen Repositories	10/5/16	Guidance	https://web.archive.org/web/20180414163540/http://www.irb.emory.edu/documents/Example_Registry_Repository_Template.docx
Emory University	Genetic Information Informed Consent Information PowerPoint	9/8/16	Other	https://web.archive.org/web/20180414161543/http://www.irb.emory.edu/documents/Genetic_Testing_IC_slides.pdf
Emory University	IRB Policies and Procedures	1/10/18	Policy	https://web.archive.org/web/20180414153355/http://www.irb.emory.edu/documents/PoliciesandProcedures.pdf
Emory University	Modular Consent Language	5/25/18	Template	https://web.archive.org/web/20181014174639/http://irb.emory.edu/documents/modular-consent-language.docx
Fred Hutchinson Cancer Research Center	Model Consent Clinical Research [d]	12/22/17	Template	https://archive.org/download/20-fhcrc-consent-model-consent-clinical-research-122217/20%20-%20FHCRC%20-%20Consent%20-%20Model%20Consent%20Clinical%20Research%20122217.pdf
ICHAN School of Medicine at Mount Sinai	Research Involving Genetic Testing Under NYS Law	1/1/15	Guidance	https://web.archive.org/web/20180801170901/https://icahn.mssm.edu/files/ISMMS/Assets/Research/PPHS/GUIDANCE%20ON%20RESEARCH%20INVOLVING%20GENETIC%20TESTING%20UNDER%20NYS%20LAW.pdf
Indiana University	Use and Collection of Biospecimens	no date	Guidance	https://web.archive.org/web/20180614171725/https:/research.iu.edu/compliance/human-subjects/guidance/areas/biospecimens.html
Indiana University	Indiana University Informed Consent Statement for Research (Biomedical)	3/29/18	Template	https://web.archive.org/web/20181214172758/https://research.iu.edu/doc/compliance/human-subjects/iu-informed-consent-document-template-biomedical.docx

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
Indiana University	Indiana University Study Information Sheet for Research (Expedited)	3/29/18	Template	https://web.archive.org/web/20180614172521/https://research.iu.edu/doc/compliance/human-subjects/iu-hso-sis-expedited-template.docx
Indiana University	Indiana University Informed Consent Statement for Future Research use of Information and Biospecimens	3/29/18	Template	https://web.archive.org/web/20180614172443/https://research.iu.edu/doc/compliance/human-subjects/iu-informed-consent-document-template-future-research.docx
Johns Hopkins University	Clinical Genetic Research	12/1/03	Guidance	https://web.archive.org/web/20171020185623/http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/clinical_genetics_research.html
Johns Hopkins University	HIPAA Quest. & Answers Relating to Research	2/1/15	Guidance	https://web.archive.org/web/20171020185623/http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/access_to_study_records
Johns Hopkins University	Participants' Access to Study Records	1/20/05	Guidance	https://web.archive.org/web/20170903125858/http://www.hopkinsmedicine.org/institutional_review_board/hipaa_research/faq_research.html
Johns Hopkins University	Organization Policy on Research Lab Testing	8/1/13	Policy	https://web.archive.org/web/20171024054940/http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/101_2.html
Massachusetts General Hospital	Guidelines for Genetic Research	no date	Guidance	https://web.archive.org/web/20210208020101/https://www.massgeneralbrigham.org/sites/default/files/2020-06/Guidelines-for-Genetic-Research.pdf

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
Massachusetts General Hospital	Returning Individual Results and Incidental Findings to Participants in Genetic Research Points to Consider	4/23/14	Guidance	https://web.archive.org/web/20210208020309/https://www.massgeneralbrigham.org/sites/default/files/2020-06/Points-to-consider-RORR-Final-Guidance.pdf
Massachusetts General Hospital	Genetics Research Advisory Panel GAP Report	No date [a]	Other	https://web.archive.org/web/20210208020207/https://www.massgeneralbrigham.org/sites/default/files/2020-06/gap-dec22.doc
Mayo Clinic Rochester	Human Specimen Research Repositories	8/29/17	Policy	https://web.archive.org/web/20210508020303/https://www.mayo.edu/research/documents/44-human-specimen-research-repositoriespdf/doc-10027908
Mayo Clinic Rochester	Informed Consent and the Research Subject Policy	9/18/17	Policy	https://web.archive.org/web/20190112033225/https://www.mayo.edu/research/documents/28-informed-consent-the-research-subjectpdf/doc-10027563
Mayo Clinic Rochester	Return of Research Laboratory Test Results Procedure	1/24/18	Procedure	https://web.archive.org/web/20190112033023/https://www.mayo.edu/research/documents/51-return-of-research-laboratory-test-results-procedure/doc-20421354
Northwestern University at Chicago	Genetic Biobanking Studies	11/22/18	Guidance	https://web.archive.org/web/20190702154734/https://irb.northwestern.edu/sites/irb/files/documents/HRP-442%20-%20CHECKLIST%20-%20Genetic%20Biobanking%20Studies_11222018.docx
Northwestern University at Chicago	Biomedical Protocol	11/22/18	Template	https://archive.org/download/22-northwestern-protocol-template-biomedical-protocol-112218/22%20-%20NORTHWESTERN%20-%20Protocol%20Template%20-%20Biomedical%20Protocol%20112218.pdf

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
Stanford University	Consent template	11/20/17	Template	https://web.archive.org/web/20171211013131/http://humansubjects.stanford.edu/consents/SUSampCons.doc
Stanford University	VA Template Consent Form	11/27/17	Template	https://web.archive.org/web/20171211013129/http://humansubjects.stanford.edu/consents/VASampCons.doc
University of Alabama at Birmingham	Additional Elements That May Be Included in the Consent Form	5/8/13	Guidance	https://archive.org/download/26-uab-consent-guidance-additional-elements-that-may-be-included-in-the-consent-form-050813/26%20-%20UAB%20-%20Consent%20Guidance%20-%20Additional%20Elements%20That%20May%20Be%20Included%20in%20the%20Consent%20Form%20050813.pdf
University of Alabama at Birmingham	Sample Consent Form	2/11/17	Template	https://archive.org/download/26-uab-consent-sample-consent-form-020117/26%20-%20UAB%20-%20Consent%20-%20Sample%20Consent%20Form%20020117.pdf
University of California Berkley	Clinical Laboratory Testing in Human Subjects Research	07/2015	Guidance	https://web.archive.org/web/20210208025749/https://cphs.berkeley.edu/clia.pdf
University of California Berkley	Genetic/Genomic Research	08/17	Guidance	https://web.archive.org/web/20170520140541/http://cphs.berkeley.edu/genetic_genomic.pdf
University of California Berkley	Informed Consent Genetic Checklist for Genetic/Genomic Testing	8/1/17	Template	https://web.archive.org/web/20150909224451/http://cphs.berkeley.edu/CPHS_informed_consent_dna.pdf
University of California Irvine	Collection of Genetic Specimens and Genetic Testing Studies Checklist	no date	Template	https://web.archive.org/web/20160426002323/http://www.research.uci.edu/forms/docs/irb-appendices/appendixN.doc

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
University of California Irvine	IRB Primer: Incidental and Secondary Findings [b]	4/16/14	Other	https://web.archive.org/web/20160426003503/https://www.research.uci.edu/compliance/human-research-protections/irb-members/IRB%20Primer%20-%20Incidental%20and%20Secondary%20Findings.pdf
University of California Irvine	Protocol Narrative for Expedited and Full Committee Biomedical/Clinical Research	no date	Template	https://web.archive.org/web/20200520080510/https://www.research.uci.edu/forms/docs/irb-forms/protocol-narrative-bio-expedited-full-committee.doc
University of California Los Angeles	Guidance and Procedure Genetics Research	4/14/09	Guidance	https://web.archive.org/web/20180225155222/https://ora.research.ucla.edu/OHRPP/Documents/Policy/8/Genetics_Research.pdf
University of California San Diego	Returning Research and/or Incidental Findings	2/26/18	Guidance	https://web.archive.org/web/20180225052939/https://irb.ucsd.edu/Returning-findings.pdf
University of California San Diego	Registry/Repository/ Banking Use of Data/Specimens	3/2/17	Policy	https://web.archive.org/web/20180225052318/https://irb.ucsd.edu/3.16.pdf
University of California San Francisco	Research Using Human Biological Specimens	3/7/16	Guidance	https://web.archive.org/web/20180713021334/https://irb.ucsf.edu/print/871
University of California San Francisco	CLIA Compliance and Lab Test Results	11/17/15	Guidance	https://web.archive.org/web/20180713015733/http://irb.ucsf.edu/clia-compliance-and-lab-test-results

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
University of Colorado, Colorado Springs	Researcher Manual for IRB Submission	02/2018	Guidance	https://archive.org/download/uccs-researcher-manual-for-irb-submission-feb-2018/UCCS%20-%20Researcher%20Manual%20for%20IRB%20Submission%20Feb%202018.pdf
University of Colorado, Colorado Springs	Human Research Protection Program (HRPP) Standard Operation Procedures (SOP) for the Institutional Review Board (IRB)	1/31/18	Policy	https://archive.org/download/uccs-hrpp-sops-for-irb-013118/UCCS%20%20-%20HRPP%20SOPS%20for%20IRB%20013118.pdf
University of Colorado, Colorado Springs	List of Additional Standard Language Statements for the Consent Form	1/8/18	Template	https://archive.org/download/uccs-irb-sample-additional-language-consent-010818/UCCS%20-%20IRB%20Sample%20Additional%20Language%20Consent%20010818.pdf
University of Michigan	Genetic DNA Research Studies [c]	7/18/07	Guidance	https://web.archive.org/web/20200209031858/https://az.research.umich.edu/medschool/guidance/irbmed-guidance-irb-reviewers-and-medical-school-investigators-regarding
University of Michigan	Operations Manual	6/12/18	Procedure	https://web.archive.org/web/20180615183812/http://research-compliance.umich.edu/operations-manual-laws-regulations-and-standards
University of Minnesota	Biomedical Consent Form [d]	7/1/18	Template	https://archive.org/download/25-um-protocol-medical-template-protocol-with-instructions-011918/25%20-%20UM%20-%20Protocol%20-%20MEDICAL%20TEMPLATE%20PROTOCOL%20-%20WITH%20INSTRUCTIONS%20011918.docx

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
University of Minnesota	Medical Template Protocol (HRP-590) - with instructions	1/19/18	Template	https://archive.org/download/25-um-consent-biomedical-consent-form-070118/25%20-%20UM%20-%20Consent%20-Biomedical%20Consent%20Form%20070118.pdf
University of North Carolina Chapel Hill	Office of Human Research Ethics/IRB Standard Operating Procedures	6/2/17	Procedure	https://web.archive.org/web/20180125032004/https://research.unc.edu/files/2017/05/SOP-June-2-2017-bookmarked-and-TOC-links.pdf
University of Pennsylvania	GINA Template consent Language	5/31/16	Template	https://web.archive.org/web/20190611150402/https://irb.upenn.edu/sites/default/files/GINA%20Template%20Language.docx
University of Pennsylvania	Protocol Template for Interventional Clinical Trial Protocol	5/31/16	Template	https://web.archive.org/web/20190611150851/https://irb.upenn.edu/sites/default/files/ProtocolTemplate_%20ClinicalTrial_final_201502.docx
University of Southern California	All Policies and Procedures	2018	Policy	https://archive.org/download/23-usc-policies-all-2018/23%20-%20USC%20-%20Policies%20-%20All%202018.pdf
University of Southern California	USC HSIRB Informed Consent Template and Instructions	3/6/17	Template	https://archive.org/download/23-usc-template-consent-template-investigator-initiated/23%20-%20USC%20-%20Template%20-%20Consent%20Template%20Investigator%20Initiated.pdf
University of Virginia	IRB-HSR Research Guidance	10/3/12	Guidance	https://archive.org/download/51-uni-virginia-guidance-investigator-guide-100312/51%20-%20UNI%20VIRGINIA%20-%20Guidance%20-%20Investigator%20Guide%20100312.pdf

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
University of Washington	Genomic-Data-Sharing	2/5/18	Guidance	https://archive.org/download/uni-of-washington-genomic-data-sharing/Uni%20of%20Washington%20-%20Genomic-Data-Sharing.pdf
University of Washington	Zipline Supplement Participant Results Sharing	8/26/16	Template	https://archive.org/download/uni-of-washington-zipline-supplement-participant-results-sharing/Uni%20of%20Washington%20-%20Zipline%20Supplement%20Participant%20Results%20Sharing.pdf
University of Washington	SOP Lab Certification (CLIA)	2/28/14	Procedure	https://archive.org/download/uni-of-washington-university-of-washington-lab-certification-sop/Uni%20of%20Washington%20-%20%20University%20of%20Washington%20Lab%20Certification%20sop.pdf
University of Washington	Consent Template Form Identifiable Specimens	8/26/16	Template	https://archive.org/download/uni-of-washington-template-consent-form-identifiable-specimens/Uni%20of%20Washington%20-%20TEMPLATE-Consent-Form-Identifiable-Specimens.pdf
University of Washington	Template Consent Form Non-Identifiable Specimens	6/31/14	Template	https://archive.org/download/uni-of-washington-template-consent-form-non-identifiable-specimens/Uni%20of%20Washington%20-%20TEMPLATE-Consent-Form-Non-Identifiable-Specimens.pdf
University of Washington	Template Consent Form Standard [d]	11/30/18	Template	https://archive.org/download/uni-of-washington-template-consent-form-standard/Uni%20of%20Washington%20-%20TEMPLATE-Consent-Form-Standard.pdf

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
University of Wisconsin Madison	Clinically Relevant Information and Reporting Guidance	8/4/11	Guidance	https://web.archive.org/web/20150912000607/https://kb.wisc.edu/hsirbs/page.php?id=19553
University of Wisconsin Madison	Genetic Testing or Analysis	11/30/18	Guidance	https://web.archive.org/web/20210210011212/https://www.help.wisc.edu/19770
University of Wisconsin Madison	New Information Reporting Guidance	1/16/18	Guidance	https://web.archive.org/web/20210210011005/https://www.help.wisc.edu/26915
Vanderbilt University Medical Center	Incidental Findings (IFs)	no date	Guidance	https://archive.org/details/21-vanderbilt-guidance-incidental-findings-ifs-no-date
Vanderbilt University Medical Center	When to disclose the findings to the research participant	no date	Guidance	https://archive.org/download/21-vanderbilt-guidance-when-to-disclose-the-findings-to-the-research-participant-no-date/21%20-%20VANDERBILT%20-%20Guidance%20-%20When%20to%20disclose%20the%20findings%20to%20the%20research%20participant%20no%20date.pdf
Washington University	Guidelines for reviewing studies involving genetic research	12/6/11	Guidance	https://web.archive.org/web/20181222131242/https://hrpo.wustl.edu/wp-content/uploads/2015/04/2015-04-03-Guidelines-for-reviewing-studies-involving-genetic-research-revised-12_06_2011-2.pdf
Yale University	Sharing Incidental Study Findings with Participants	2/13/13	Guidance	https://web.archive.org/web/20180225020503/https://your.yale.edu/sites/default/files/720gd1sharingstudyfindingsfinal.pdf

Institution	Document Name	Doc. Date	Doc. Type	Archived Document Internet Address
Yale University	Incidental Findings with Possible Health and Safety Significance for Research Participants	12/11/17	Policy	https://web.archive.org/web/20180225021330/https://your.yale.edu/sites/default/files/irb_policy_720_incidentalfindingswithpossiblehealthandsafetysignificanceforresearchparticipants.pdf
Yale University	Use of Genetic Tests and Investigational Genetic Tests in Human Research	1/19/13	Procedure	https://web.archive.org/web/20170325211551/https://your.yale.edu/sites/default/files/400pr3_genetictestingfinal.pdf
Yale University	Consent template	3/21/16	Template	https://web.archive.org/web/20210206204817/https://your.yale.edu/sites/default/files/200fr1hicconsentformtemplate-3-21-16.doc

[a] Document date is unclear. The advisory panel met in 2000 and the report lists "October 02 Version" in the footer. It is not clear if 02 is the year or the version. Additionally, the document states that the April 14, 2003 HIPAA guidelines were incorporated into the document.

[b] This document was written by the Presidential Commission for the Study of Bioethical Issues (2014) and was posted in its entirety as a resource for the University of California Irvine research community.

[c] This guidance was a webpage in the University's IRBMED guidance repository. At the top of the webpage, it stated "January 2015: This 2007 guidance is under revision. Certain passages may not reflect current IRBMED views and recommendations." As of June 1, 2021, this is "guidance under revision" language is still posted.

[d] Document appears to have incorporated the 2018 Final Rule changes which included the return of results.

APPENDIX C

CODING SCHEME FOR OVERALL CONTENT ANALYSIS

Category	Code	Definition	Example
Data Quality	Accuracy	The quality of being near the true value	If the test is investigational in nature, a statement that the efficacy, accuracy or diagnostic value of the test itself is unknown or being investigated, and that a test result may not be an indication that the individual is predisposed to or may have the specific disease or condition targeted by the test (Yale University, 2013b, p. 4).
Data Quality	CLIA	Clinical Laboratory Improvement Amendments of 1988. Federal regulations that regulate clinical laboratory testing	Only tests ordered by a physician and conducted in a CLIA certified lab may be shared (University of California Irvine, n.d.-b, p. 14).
Data Quality	Clinical Laboratory	A laboratory where tests are done on clinical specimens in order to get information about the health of a patient as pertaining to the diagnosis, treatment, and prevention of disease.	If the investigators return genetic test results to you, it may be because they think you could have a health risk and want to recommend that the test should be re-done by a certified clinical laboratory to check the results (University of Minnesota, 2018, p. 14).
Data Quality	Clinically	Relating to a clinical test or intervention	If the research intervention is not approved for use clinically, the findings should not be disclosed to the participant. This should clearly be outlined in the consent form (Vanderbilt University Medical Center, n.d.).

Category	Code	Definition	Example
Data Quality	Confirmation	The action of establishing the truth or correctness	Such a procedure would allow confirmation of true positives but does not address the potential for false negatives (ICHAN School of Medicine at Mount Sinai, 2015, p. 3).
Data Quality	Reliability	The quality of being dependable	Study doctors will review with you the level of reliability about the genetic information obtained as a result of your participation (Massachusetts General Hospital, n.d., p. 34).
Data Quality	Validity	The extent to which a test accurately measures what it is supposed to measure	Describe your rationale for considering the findings to analytically valid and reliable (University of Washington, 2016, p. 3).
Giving Back	Other for Giving Back	Other words that imply giving back data	How, if at all, the genetic information will be transmitted to the subject and whether the subject will be given the options to know, or not to know, the results of the genetic analysis, and how that decision will be recorded (Emory University, 2018a, p. 352).
Giving Back	Disclosure	The act of making something evident	How will the investigator determine what findings merit disclosure to the participant? (Washington University, 2011, p. 2)
Giving Back	Return	Give back	Are you likely to return, or do you definitely plan to return, any intentional research findings to individual subjects? (University of Washington, 2016, p. 2)

Category	Code	Definition	Example
Giving Back	Report	Impart knowledge of some fact	Under the current interpretation of these requirements, the Organization will not permit researchers to disclose or report results of research tests when such tests have been performed in laboratories that have not been CLIA-certified and do not have a state laboratory license. (Johns Hopkins University, 2013, para. 1)
Giving Back	Communicate	Transmit Information	If the protocol contemplates that a portion or all of the samples will be matched up with identifying information to communicate the results of the tests to the individuals who provided the samples, then the provisions of New York's Civil Rights Law §79-1 that apply to clinical genetic testing apply to the research (ICHAN School of Medicine at Mount Sinai, 2015, p. 2).
Giving Back	Inform	Give facts or information	If there is no plan to inform participants of research findings, this should be stated in the consent (Washington University, 2011, p. 2).
Giving Back	Provide	Make available for use	Who will provide the information to the participant, and will an opportunity for genetic counseling, if appropriate, provided? (Washington University, 2011, p. 2)
Giving Back	Be Given	To supply something to someone	You and your doctor will be given the results of this genetic testing (University of Southern California, 2017, p. 8).

Category	Code	Definition	Example
Giving Back	Share	Give a portion of something to another	Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician) (University of California Irvine, n.d.-b, p. 14).
Findings	Incidental Findings	Results that are outside the original purpose for which a test or procedure was conducted	The possibility that a research study may uncover information of potential health and safety significance or other incidental findings should be anticipated in all research studies that have the potential to generate these findings (Yale University, 2013a, p. 1).
Findings	Secondary Findings	Genetic test results that provide information about variants in a gene unrelated to the primary purpose for the testing; OR additional result actively sought by the practitioner	The absence of a reportable secondary finding does not mean that you have no disease-causing genetic changes, so if you have symptoms or features of a genetic disease in the future, clinical genetic testing should be considered (Columbia University, 2016b, p. 5).
Findings	Results	The outcome of the research	Whether, how, and under what circumstance results from research studies using the specimens would be communicated to the subjects and, where relevant, to their family members (University of North Carolina Chapel Hill, 2017, p. 18).

Category	Code	Definition	Example
Findings	Research Findings	Something that is discovered in research	Labs that are providing research findings for medical use (e.g., affected patients will be recommended for surgery, drug therapy or the research result will be used to guide other aspects of medical management) should be encouraged to obtain CLIA certification for the test (University of Michigan, 2002, p. 3).
Findings	Clinically Relevant	Having clinical significance in the health and well-being of a person	Could other clinically relevant information be uncovered by the study (i.e., Incidental Findings)? Will disclosure of this added information occur? (University of Southern California, 2018, p. 1)
Genomic	Genetic(s)	Relating to genes or heredity	Genetic research involves the analysis of any of the following: DNA, RNA, chromosomes, proteins, or certain metabolites which might act as or identify markers associated with a known or suspected predisposition to disease or behavior (University of Wisconsin Madison, 2018a, p. 1).
Genomic	Sequencing	The process of determining the nucleic acid sequence	We may use the specimens collected as a part of this study for whole genome sequencing, which involves mapping all of your DNA (Indiana University, 2018, p. 8).
Individual-level	Individual Results	Results for a particular person	Individual results will not be shared with subjects (University of California Irvine, n.d.-b, p. 14).

Category	Code	Definition	Example
Individual-level	"Other" for Individual	Other words that imply the individual level results	Indicate if this information will represent only that which pertains to each subject or if it will be aggregate data from all study subjects (University of Virginia, 2012, p. 128).
Individual-level	Participant Specific	A particular study participant	Specify that there are no plans to return participant-specific information to any participant or reported to any third party besides those that conduct reviews as required by regulatory agencies (Massachusetts General Hospital, n.d., p. 24).
Individual-level	Patient Specific	A particular patient	Laboratories performing testing on human specimens and reporting patient-specific results must be certified under the provisions of the Clinical Laboratory Improvement Amendments of 1998 (CLIA). (University of California San Francisco, 2016, p. 6)

APPENDIX D

CONCEPT MATRIX OF CODES PRESENT BY DOCUMENT

See Supplemental File: Tab 1 of the Excel Spreadsheet

APPENDIX E

CODING CATEGORIES BY DOCUMENT

See Supplemental File: Tab 2 of the Excel Spreadsheet

APPENDIX F

CODING CATEGORIES BY INSTITUTION

See Supplemental File: Tab 3 of the Excel Spreadsheet

APPENDIX G

POLICY TYPE FOR THE TOPICS OF RETURN OF RESULTS, CLIA, AND GENETICS/GENOMICS BY DOCUMENT

See Supplemental File: Tab 4 of the Excel Spreadsheet

APPENDIX H

ASSIGNED CODE WITH RESPECT TO HOW A DOCUMENT ADDRESSED COMPLIANCE WITH THE CLIA REGULATIONS

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
Johns Hopkins University	1	Clinical Genetic Research	Guidance	Required: Full Stop
Johns Hopkins University	2	HIPAA Quest. & Answers Relating to Research	Guidance	Vague
Johns Hopkins University	3	Participants' Access to Study Records	Guidance	Required: Exception
Johns Hopkins University	4	Organization Policy on Research Lab Testing	Policy	Required: Full Stop
University of California San Francisco	5	Research Using Human Biological Specimens	Guidance	Required: Full Stop
University of California San Francisco	6	CLIA Compliance and Lab Test Results	Guidance	Required: Exception
University of Michigan	7	Genetic DNA Research Studies	Guidance	Recommended
University of Michigan	8	Operations Manual	Procedure	CLIA Silent: Full Stop
University of Pennsylvania	9	GINA Template consent Language	Template	CLIA Silent: Full Stop
University of Pennsylvania	10	Protocol Template for Interventional Clinical Trial Protocol	Template	CLIA Silent: Full Stop
University of Pittsburgh at Pittsburgh		No Documents		
Stanford University	11	Consent template	Template	CLIA Silent: Full Stop
Stanford University	12	VA Template Consent Form	Template	Required: Full Stop

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
University of Washington	13	Genomic-Data-Sharing	Guidance	CLIA Silent: Full Stop
University of Washington	14	Zipline Supplement Participant Results Sharing	Template	Required: PI Determines
University of Washington	15	SOP Lab Certification (CLIA)	Procedure	Required: PI Determines
University of Washington	16	Consent Template Form Identifiable-Specimens	Template	CLIA Silent: Full Stop
University of Washington	17	Template Consent Form Non-Identifiable Specimens	Template	CLIA Silent: Full Stop
University of Washington	18	Template Consent Form Standard	Template	CLIA Silent: Full Stop
Duke University	19	Consent Language	Template	Recommended
Washington University	20	Guidelines for reviewing studies involving genetic research revised	Guidance	CLIA Silent: Data Quality
Yale University	21	Sharing Incidental Study Findings with Participants	Guidance	Not Required
Yale University	22	Incidental Findings with Possible Health and Safety Significance for Research Participants	Policy	Recommended
Yale University	23	Use of Genetic Tests and Investigational Genetic Tests in Human Research	Procedure	Not Required
Yale University	24	Consent Template	Template	CLIA Silent: Full Stop

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
University of California San Diego	25	Returning Research and/or Incidental Findings	Guidance	Recommended
University of California San Diego	26	Registry/Repository/Banking Use of Data/Specimens	Policy	CLIA Silent: Data Quality
University of North Carolina Chapel Hill	27	IRB SOPs	Procedure	CLIA Silent: Full Stop
Columbia University	28	Genetic Testing Flowchart	Guidance	Required: Full Stop
Columbia University	29	Policy on Research Involving Genetic Testing	Policy	Required: Full Stop
Columbia University	30	Consent Form Builder	Template	Required: Full Stop
Columbia University	31	Consent Cover Sheet Genetic	Template	CLIA Silent: Full Stop
Columbia University	32	Consent form Genetic Research	Template	Required: Full Stop
University of California Los Angeles	33	Guidance and Procedure Genetics Research	Guidance	Required: Full Stop
Massachusetts General Hospital	34	Guidelines for Genetic Research	Guidance	CLIA Silent: Full Stop
Massachusetts General Hospital	35	Returning Individual Results and Incidental Findings to Participants in Genetic Research	Guidance	Required: Exception
Massachusetts General Hospital	36	Genetics Research Advisory Panel GAP Report	Other	Required: Qualified
Emory University	37	Emory IRB Biomedical Protocol Outline for Investigator-Initiated Studies	Template	CLIA Silent: Full Stop

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
Emory University	38	Emory IRB Guidelines for Databases, Registries, and Specimen Repositories	Guidance	Recommended
Emory University	39	Genetic Information Informed Consent Information PowerPoint	Other	Ambiguous/Unclear
Emory University	40	Policy - IRB P&Ps	Policy	CLIA Silent: Full Stop
Emory University	41	Modular Consent Language	Template	Required: Exception
ICHAN School of Medicine at Mount Sinai	42	Research Involving Genetic Testing Under NYS Law	Guidance	Required: Full Stop
University of Wisconsin Madison	43	Clinically Relevant Information and Reporting Guidance	Guidance	Required: Exception
University of Wisconsin Madison	44	Genetic Testing or Analysis	Guidance	CLIA Silent: Data Quality
University of Wisconsin Madison	45	New Information Reporting Guidance	Guidance	Required: Exception
Fred Hutchinson Cancer Research Center	46	Model Consent Clinical Research	Template	CLIA Silent: Full Stop
Vanderbilt University Medical Center	47	Incidental Findings (IFs)	Guidance	CLIA Silent: Data Quality
Vanderbilt University Medical Center	48	When to disclose the findings to the research participant	Guidance	Required: Full Stop
Northwestern University at Chicago	49	Genetic Biobanking Studies	Guidance	Ambiguous/Unclear

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
Northwestern University at Chicago	50	Biomedical Protocol	Template	CLIA Silent: Full Stop
University of Southern California	51	All Policies and Procedures	Policy	CLIA Silent: Data Quality
University of Southern California	52	Consent Template Investigator Initiated	Template	Required: Full Stop
Mayo Clinic Rochester	53	Human Specimen Research Repositories	Policy	CLIA Silent: Full Stop
Mayo Clinic Rochester	54	Informed Consent and the Research Subject Policy	Policy	CLIA Silent: Full Stop
Mayo Clinic Rochester	55	Return of Results	Procedure	Required: Exception
University of Minnesota	56	Biomedical Consent Form	Template	CLIA Silent: Data Quality
University of Minnesota	57	Medical Template Protocol - with instructions	Template	Required: Full Stop
University of Alabama at Birmingham	58	Additional Elements That May Be Included in the Consent Form	Guidance	CLIA Silent: Data Quality
University of Alabama at Birmingham	59	Sample Template Form	Template	CLIA Silent: Full Stop
Indiana University	60	Biospecimen Use and Collection of Biospecimens	Guidance	CLIA Silent: Full Stop
Indiana University	61	Consent Biomedical	Template	CLIA Silent: Full Stop
Indiana University	62	Consent Expedited	Template	CLIA Silent: Full Stop

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
Indiana University	63	Consent Future Research	Template	CLIA Silent: Full Stop
University of Virginia	64	Investigator Guide	Guidance	Required: Full Stop
University of California Berkley	65	Clinical Laboratory Testing in Human Subjects Research	Guidance	Required: Qualified
University of California Berkley	66	Genetic Genomic Research	Guidance	Required: Qualified
University of California Berkley	67	Informed Consent Genetic checklist	Guidance	CLIA Silent: Full Stop
University of California Irvine	68	Collection of Genetic Specimens & Genetic Testing Studies	Template	Required: Qualified
University of California Irvine	69	Incidental and Secondary Findings	Other	CLIA Silent: Data Quality
University of California Irvine	70	Template - protocol narrative	Template	Required: Full Stop
University of Colorado Colorado Springs	71	Researcher Manual for IRB Submission	Guidance	Required: Qualified
University of Colorado Colorado Springs	72	Procedure Lab Certification (CLIA)	Procedure	Required: PI Determines
University of Colorado Colorado Springs	73	IRB Sample Additional Language Consent	Template	Required: Qualified

APPENDIX I

ASSIGNED CODE WITH RESPECT TO HOW AN INSTITUTION ADDRESSED COMPLIANCE WITH THE CLIA REGULATIONS

Institution	Assigned Code
Columbia University Health Sciences	Required: Full Stop
Duke University	Recommended
Emory University	Required: Exception
Fred Hutchinson Cancer Research Center	CLIA Silent: Full Stop
Icahn School of Medicine at Mount Sinai	Required: Full Stop
Indiana University	CLIA Silent: Full Stop
Johns Hopkins University	Required: Full Stop
Massachusetts General Hospital	Required: Exception
Mayo Clinic Rochester	Required: Exception
Northwestern University at Chicago	Ambiguous/Unclear
Stanford University	Ambiguous/Unclear
University of Alabama at Birmingham	CLIA Silent: Data Quality
University of California Berkeley	Required: Qualified
University of California Irvine	Required: Full Stop
University of California Los Angeles	Required: Full Stop
University of California San Diego	Recommended
University of California, San Francisco	Required: Exception
University of Colorado, Colorado Springs	Required: PI Determines
University of Michigan	Recommended
University of Minnesota	Required: Full Stop
University of North Carolina Chapel Hill	CLIA Silent: Full Stop
University of Pennsylvania	CLIA Silent: Full Stop
University of Pittsburgh at Pittsburgh	CLIA Silent: Full Stop
University of Southern California	Required: Full Stop
University of Virginia	Required: Full Stop
University of Washington	Required: PI Determines
University of Wisconsin-Madison	Required: Exception
Vanderbilt University Medical Center	Required: Full Stop
Washington University	CLIA Silent: Data Quality
Yale University	Recommended

APPENDIX J

ASSIGNED CODE WITH RESPECT TO HOW A DOCUMENT ADDRESSED THE COST OF CLIA-CONFIRMATION OF RESEARCH RESULTS

Institution	Doc. Num.	Document Name	Document Type	Assigned Code
University of California San Francisco	6	CLIA Compliance and Lab Test Results	Guidance	Confirmation Cost: Vague
Washington University	20	Guidelines for reviewing studies involving genetic research revised	Guidance	Confirmation Cost: Not Specific
University of California San Diego	25	Returning Research and/or Incidental Findings	Guidance	Confirmation Cost: Vague
Columbia University	30	Consent Form Builder	Template	Confirmation Cost: Not Participant
Columbia University	32	Consent form Genetic Research	Template	Confirmation Cost: Not Participant
Massachusetts General Hospital	35	Returning Individual Results and Incidental Findings to Participants in Genetic Research	Guidance	Confirmation Cost: Not Specific
Emory University	41	Modular Consent Language	Template	Confirmation Cost: Participant
University of Minnesota	56	Biomedical Consent Form	Template	Confirmation Cost: Participant

Note: All documents not listed were assigned the code Confirmation Cost: Silent.