### CONTENT ANALYSIS OF CONSENT FORMS FOR CLINICAL WHOLE EXOME SEQUENCING

### A THESIS IN Bioinformatics

Presented to the Faculty of the University of Missouri-Kansas City in partial fulfillment of the requirements for the degree

MASTER OF SCIENCE

by SARA A. FOWLER

M.S., Avila University, 2008 B.A., Ottawa University, 1999

> Kansas City, Missouri 2016

# © 2016 SARA ANN FOWLER ALL RIGHTS RESERVED

## CONTENT ANALYSIS OF CONSENT FORMS FOR CLINICAL WHOLE EXOME SEQUENCING

Sara Ann Fowler, M.S., Candidate for the Master of Science Degree
University of Missouri-Kansas City, 2016

### **ABSTRACT**

As genomic sequencing becomes increasingly incorporated into clinical care, the patient informed consent process must successfully manage many ethical challenges, including whether to seek secondary findings and which results will be returned to the patient. The goal of the current study was to explore variation among existing informed consent forms for clinical whole exome sequencing (WES) in order to identify the level of consistency with the recommendations from the Presidential Commission for the Study of Bioethical Issues and the American College of Medical Genetics and Genomics (ACMG) regarding informed consent for clinical genomescale sequencing.

Recommendations of the Presidential Commission for the Study of Bioethical Issues and ACMG were organized into a framework of 18 key points for analysis. In addition, 5 other points relevant to informed consent were identified from a preliminary review of the sampled forms and review of the literature. These were

assessed separately from the Bioethics Commission and ACMG list. Using these frameworks, content analysis was conducted on a sample of 18 informed consent forms for clinical WES downloaded from laboratory websites.

For each of the individual Bioethics Commission and ACMG recommended consent items, the frequency of inclusion ranged from 11% to 100%. Among all forms in the sample, the average adherence to the complete list of 18 Bioethics and ACMG recommendations was 74.4%. For each of the 5 additionally identified items, the frequency of inclusion ranged from 5.6% to 50%.

We observed considerable variability in the content of informed consent forms among the sample of 18 laboratories. This analysis can be useful to laboratories that provide clinical WES to create informed consent forms that they are in alignment with recommendations from the Bioethics Commission and ACMG. The development of a more standardized informed consent process could improve communication between clinicians and patients, increase understanding of genetic testing, and allow for increased data sharing.

#### **APPROVAL PAGE**

The faculty listed below, appointed by the Dean of the School of Medicine, have examined a thesis titled "Content Analysis of Consent Forms for Clinical Whole Exome Sequencing," presented by Sara A. Fowler, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

### **Supervisory Committee**

Mark A. Hoffman, Ph.D., Committee Chair Department of Biomedical and Health Informatics

Jenifer E. Allsworth, Ph.D.

Department of Biomedical and Health Informatics
Department of Obstetrics and Gynecology

Carol J. Saunders, Ph.D, FACMG
Department of Pathology and Laboratory Medicine
Children's Mercy Center for Pediatric Genomic Medicine

### **CONTENTS**

ABSTRACT	iii
LIST OF TABLES	vii
LIST OF ILLUSTRATIONS	ix
ACKNOWLEDGEMENTS	x
Chapter	
1. INTRODUCTION	1
2. REVIEW OF LITERATURE	5
Recommendations of the Presidential Commission for the Study of Bioethical Issues	6
Recommendations of the American College of Medical Genetics and Genomics	7
Informed Consent Procedures for Clinical Genomic Sequencing Vary	8
Ethical Considerations for the Provision of Secondary Findings to Children	10
Ethical Considerations for Secondary Findings and the Patient's Relatives	11
Legal Considerations	13
Need for Guides for Standard Practices for Secondary Findings	14
3. METHODOLOGY	16
Data Collection	16
Document Description and Case Definition	17
Data Analysis Process	17
4. RESULTS	24

	21
Other Recommendations for Informed Consent	. 34
5. DISCUSSION	.39
Implications for Informed Consent	.45
Study Limitations	.46
Further Study	.47
Conclusion	.47
Appendix	
A. RECOMMENDATIONS OF THE PRESIDENTIAL COMMISSION     FOR THE STUDY OF BIOETHICAL ISSUES:     Informed Consent: Privacy and Progress in     Whole Genome Sequencing	.49
B. RECOMMENDATIONS OF THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES: Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-consumer Contexts	.51
C. AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS POLICY STATEMENT: Points to Consider for Informed Consent for Genome/Exome Sequencing	. 52
D. AMERICAN COLLEGE OF MEDICAL GENETICS AND     GENOMICS POLICY STATEMENT:     Updated Recommendations Regarding Analysis and     Reporting of Secondary Findings in Clinical     Genome-scale Sequencing	.54
REFERENCES	.56
VITA	.60

### LIST OF TABLES

Table		Page
1.	Type of Laboratory among Laboratories Providing Clinical Whole Exome Sequencing	17
2.	Bioethics Commission and ACMG Recommended Key Points and Common Themes	19
3.	Recommended Key Points for Informed Consent Derived from Review of the Literature and Preliminary Scan of Sample Forms	21
4.	Content Analysis Coding Matrix	22
5.	Examples of Content Identified as Addressing Bioethics Commission and ACMG Recommendations	26
6.	Examples of Content Identified as Addressing Other Recommended Content of Informed Consent Forms	36

### LIST OF ILLUSTRATIONS

Illustr	ation	Page
1.	Number of Bioethics and ACMG Recommendations per Laboratory by Laboratory Type	24
2.	Average Adherence to the Complete List of Bioethics Commission and ACMG Recommendations	25
3.	Adherence to Individual Bioethics and ACMG Recommendations for 18 Laboratories	30
4.	Adherence to Individual Bioethics and ACMG Recommendations by Laboratory Type	32
5.	Number of Other Recommendations per Laboratory by Laboratory Type	34
6.	Frequency of Other Recommendations for Informed Consent for 18 Laboratories	35
7.	Adherence to Other Recommendations for Informed Consent by Laboratory Type	37

#### **ACKNOWLEDGEMENTS**

I would like to express my sincere appreciation and give special thanks for the support of my thesis committee. My committee chair, Dr. Mark Hoffman, opened up the world of genomics to me, gently pushed me out of my comfort zone, and held high expectations for my success. I am grateful for his mentorship, time, encouragement, and generosity. My advisor, Dr. Jenifer Allsworth, has been immeasurably patient as she instructed and counseled me throughout my time in the program. I have succeeded due to the safe space she provided for me to regain my confidence and start taking steps on a new life path. Dr. Carol Saunders extended herself graciously, offering expertise, feedback, and valuable time. Her participation strengthened my project and expanded my knowledge and understanding of the fascinating field of genomic medicine. I am fortunate to have had such a high caliber team supporting me to complete this master's thesis.

#### **CHAPTER 1**

#### INTRODUCTION

Genomic analysis, including whole genome sequencing (WGS), whole exome sequencing (WES), and direct-to-consumer genetic testing (DTC), is becoming more useful and accessible to both physicians and individuals. Genomic sequencing can be considered in a variety of clinical contexts, including the diagnosis of rare diseases, the individualization of treatment (particularly in cancer), and pharmacogenomics (Botkin et al., 2015; Green et al., 2013). Medical professionals are using genomic testing for patients experiencing a "diagnostic odyssey," cases with numerous unsuccessful attempts to establish a definite diagnosis (Tacik et al., 2015). WGS and WES are useful methods for identifying complex hereditary disorders that can be difficult to diagnose clinically because of unusual presentations or rare occurrence (Lohmann & Klein, 2014; Tacik et al., 2015). The general public can also obtain personal genomic information, including disease predisposition and ancestry information, from companies that offer testing services. However, it is important to understand that genetic testing is not a simple tool but a complex practice (Buchbinder & Timmermans, 2011).

WGS is a procedure to determine the order in which the bases are arranged within an individual's DNA. The goal is to identify, annotate, and interpret variants in the sample by comparing it to a known reference sequence. WES consists of analyzing all of a genome's coding exons, representing approximately 1% of the genome (Lohmann & Klein, 2014). WES is particularly useful for patients who have genetic disorders with profound and heterogeneous phenotypes and atypical and

incomplete presentations (Tacik et al., 2015). It is becoming more cost-effective and as a result more extensively applied (Tacik et al., 2015).

As genomic sequencing becomes increasingly incorporated into clinical care, ethical challenges about the appropriate management of incidental findings are a growing concern (Crawford, Foulds, Fenwick, Hallowell, & Lucassen, 2013; Hull & Berkman, 2014; Wolf, 2015). "Incidental findings" refer to unexpected results that are unrelated to the indication for a particular test (Green et al., 2013; Roche & Berg, 2015). "Secondary findings" is the term now recommended by the Presidential Commission for the Study of Bioethical Issues (2013) and adopted by the American College of Medical Genetics and Genomics (ACMG; 2015) for test results that are not the primary object of study but that are deliberately sought because they may have potential health importance for an individual and their biological relatives (ACMG, 2015; Bioethics Commission, 2013; Crawford et al., 2013; Hull & Berkman, 2014; Roche & Berg, 2015; Weiner, 2014; Wolf, 2015). Important ethical issues posed by secondary findings include the role of patients in informed consent, whether clinicians will be expected to actively seek secondary findings, whether secondary findings for adult-onset disorders should be disclosed to children, and obligations of patients and physicians to disclose secondary findings to family members of patients (Hull & Berkman, 2014; McGuire & Gibbs, 2006; Wolf, 2015).

The ACMG suggests an ethical duty to actively seek secondary findings in large-scale genetic sequencing any time it is used in the clinical setting, advising that clinically actionable secondary findings for 56 specific genes must be disclosed to patients regardless of the patient's age (Green et al, 2013; Hull & Berkman, 2014;

Weiner, 2014). As the field of genomic medicine continues to evolve and more patients have the opportunity to undergo genomic testing, the clinical and ethical issues associated with the reporting of secondary findings will need ongoing evaluation (Hegde et al., 2015).

General safeguards need to be put in place for informed consent for clinical genomic sequencing (McGuire & Gibbs, 2006). One suggested approach is to have a stratified informed consent process, which could help patients determine what type of results they would like to receive (e.g., with reproductive or life planning implications) and with whom they want their data shared (Egalite, Groisman, & Godard, 2014; McGuire & Gibbs, 2006; Weiner, 2014). There is also the corresponding "right *not* to know", as patients could wish to not be informed of secondary findings (Egalite et al., 2014; Hull & Berkman, 2014; Weiner, 2014). The ACMG (2013) recommends that patients should have an opportunity to "opt out" of the analysis of medically actionable genes when undergoing clinical genome-scale sequencing. Consent and disclosure practices also need to take potential familial implications into account (Crawford et al., 2013; Hull & Berkman, 2014).

Clinicians would benefit from guidelines on returning secondary findings and the development of infrastructure to support that process (Klitzman et al., 2013). The 2013 Presidential Commission for the Study of Bioethical Issues recommended the creation of evidence-based practice guidelines and additional empirical research on return of results (Weiner, 2014). The development of a framework for reporting secondary findings will be an essential part of standardizing the informed consent process, improving communication between clinicians and patients, and increasing

understanding of genetic testing. Therefore, an empirical study of informed consent for clinical WES was conducted to evaluate the representation of recommendations of the Bioethics Commission and ACMG.

#### **CHAPTER 2**

#### **REVIEW OF LITERATURE**

Identification of incidental findings is not a new problem in medicine.

Laboratory values or diagnostic imaging findings that require clinical action are commonly discovered incidentally (Berg et al., 2015; Hegde et al., 2015). Some may cause concern but are not actionable. Decisions regarding the return of medical incidental findings reflect consideration of the patient's right to know, beneficence, a duty to warn, the clinical relevance of findings, and the potential for false-positive or negative results (Hegde et al., 2015; Hull & Berkman, 2014; Klitzman et al., 2013). As with diagnostic imaging incidental findings, the reporting of genomic secondary findings should seek to maximize the benefits (increasing the likelihood of true positive results) and minimize the harms (decreasing the likelihood of false positive results) (Green et al., 2013).

The implications of secondary findings for the patient and first-degree relatives are varied. A secondary finding may provide relief to patients and families if it is negative for an altered gene associated with a high risk or certainty of hereditary disease (American College of Obstetricians and Gynecologists (ACOG), 2008; American College of Preventive Medicine (ACPM), 2010). However, a secondary finding with positive results indicating a high risk or certainty of hereditary disease may bring emotional burdens including feeling angry, depressed, anxious or guilty (ACOG, 2008; ACPM, 2010; Botkin et al., 2015). Consequences can also include family discord or social stigmatization (ACOG, 2008; ACPM, 2010; Botkin et al., 2015). Family members may be faced with difficult reproductive choices for a finding

of carrier status for a disorder inherited in an autosomal recessive manner (ACOG, 2008). The findings also cannot determine for the patient or their relatives the timing or severity of symptoms of a disorder (ACPM, 2010).

Large-scale genomic sequencing is rapidly being integrated into clinical practice (Green et al., 2013; Bioethics Commission, 2012). When WGS/WES is used, the likelihood of identifying secondary findings increases significantly (Bioethics Commission, 2013; Hegde et al., 2015). The current estimation for the likelihood of finding a medically actionable secondary finding as a result of WES is 1-3% (Botkin et al., 2015). In order to minimize the likelihood of discovering secondary findings, the American Society of Human Genetics (ASHG) recommends targeted tests or selective sequence analysis when the clinical challenge can be addressed through such an approach (Botkin et al., 2015).

### Recommendations of the Presidential Commission for the Study of Bioethical Issues

The Presidential Commission for the Study of Bioethical Issues (referred to as the Bioethics Commission throughout this report) has issued guidance for clinicians regarding the integration of WGS into clinical care (Bioethics Commission, 2012; Bioethics Commission, 2013). These recommendations are grounded in the principles of respect for persons, specifically "public beneficence, responsible stewardship, intellectual freedom and responsibility, democratic deliberation, and justice and fairness" (Bioethics Commission, 2012, p. 3). The Bioethics Commission recognized that a robust informed consent process is necessary for ethical clinical care. Given the complexities of WGS, this process is more difficult than for common

diagnostic tests. According to the Bioethics Commission (2013), the consent process for genome-scale sequencing should include:

...information about what whole genome sequencing is; how data will be analyzed, stored, and shared; the types of results the patients and participants can expect to receive, if relevant; and the likelihood that the implications of some of these results might currently be unknown, but could be discovered in the future (p.7).

The Bioethics Commission (2013) acknowledged that context-specific differences allow for variance between consent models. The process should effectively inform individuals without undermining their ability to make voluntary choices, but there is no imperative to use one kind of consent model (Bioethics Commission, 2012). However, as large amounts of patient data are being collected into the infrastructure that supports precision-medicine, known as the "learning healthcare system," standardized systems can facilitate health information exchange so that data can be more easily aggregated and studied (Aronson & Rehm, 2015; Bioethics Commission, 2012; Reinke, 2015).

### Recommendations of the American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG; 2013) has created a set of recommendations for the situation in which a physician orders genome-scale sequencing for a clinical indication, based on available evidence of clinical validity and utility. Acknowledging a lack of sufficient data about benefits, risks, and costs of disclosing secondary findings, the ACMG recommendations are based upon clinical consensus among its members (Green et al., 2013). The ACMG

recommends that for any evaluation of clinical genome sequencing, a minimum list of 56 genes be examined and the pathogenic and likely pathogenic variants reported to the ordering clinician. Regarding the informed consent process, the ACMG (2013) recommends addressing issues including interpretive uncertainty, privacy, and possible impact on other family members. The ACMG (2013) recommends the development of an appropriate metric to guide the reporting of secondary findings (Berg et al., 2015; Green et al., 2013).

### Informed Consent Procedures for Clinical Genomic Sequencing Vary

Earlier studies of consent forms among sites engaged in genomic sequencing research found discrepancies and omissions in the descriptions of potential findings, types of results to be returned or not, and the role of patient preferences (McGuire & Gibbs, 2006; Roche & Berg, 2015). McGuire and Gibbs (2006) found that the consent process for most genomic sequencing research simply stated that genetic analysis would be performed, without specifically explaining the analysis or with whom results would be shared. Roche and Berg (2015) described the content of consent forms that were created based on hypothetical situations rather than empirical data and concluded the management of secondary findings revolved around perceived differences in responsibilities of practitioners and preferences of participants (Roche & Berg, 2015).

Providing a patient with informed consent requires a balance between information overload and uninformed consent (Rigter et al., 2013). There are many attributes that may be significant to a patient's informed decision to learn secondary findings, including lifetime risk, treatability, seriousness, and cost (Roche & Berg,

2015). Procedures for providing informed consent vary in whether patients are given an opt-in, opt-out, or stratified option for receiving secondary findings. With an "optin" option, the default procedure of the laboratory is not to seek secondary findings and patients actively choose to receive secondary findings; if they opt-in, results will be returned. With an "opt-out" option, the default procedure of the laboratory is to seek and report secondary findings, and patients actively choose *not* to receive these results; if they opt-out, results will *not* be returned. With a stratified consent process, the laboratory does not have a default procedure, allowing patients who receive clinical genomic sequencing options about what genes will be reported, what secondary findings may be returned, and with whom they want their data shared (McGuire & Gibbs, 2006).

There is conflicting guidance about whether to seek and how to manage secondary findings (Gutmann, 2013). The management of secondary findings and the extent to which laboratories are obliged to seek and disclose an expanding list of genetic results of varying significance pose important ethical challenges (Hull & Berkman, 2014). While variants are ubiquitous in the genome, the presence of known pathogenic variants must be actively sought from among the vast number of unknown or non-pathogenic genomic variants in order to be identifiable and reportable (Roche & Berg, 2015). Most secondary findings have limited medical actionability, thereby leading to a lack of consensus regarding their routine disclosure (Roche & Berg, 2015). The ACMG recommends required reporting of mutations found in 56 genes on the "minimum list," regardless of the indication for which the clinical sequencing was ordered (Green et al., 2013). In contrast, guidance

from both the ASHG and the Bioethics Commission finds no ethical duty for clinicians to search for genetic results that are not relevant to the clinical indication for sequencing (Botkin et al., 2015; Weiner, 2014).

### Ethical Considerations for the Provision of Secondary Findings to Children

The standards for clinical genomic sequencing recognize a distinction between providing secondary findings to adults versus children and adolescents (Green et al., 2013). One important dilemma is that federal privacy laws are inconsistent in defining the age of consent (Bioethics Commission, 2012). A second consideration is that scientific advancements during a child's lifetime can compound the current unknown risks raised by genome-scale sequencing (Bioethics Commission, 2012). Third, sequencing data obtained from a minor could be widely shared before they reach an age to self-determine data sharing limits, thereby diminishing their autonomy (Bioethics Commission, 2012).

Clinical practice guidelines generally recommend that only information that is clearly actionable in childhood be disclosed and that the decision to learn about adult-onset conditions be delayed until the age of majority out of respect for the child's developing autonomy (Hull & Berkman, 2013; Roche & Berg, 2015). In 1995, the ACMG and ASHG issued a joint recommendation that in the absence of medical benefits to the child, testing should be deferred until adulthood, particularly for adult-onset conditions or for carrier status for reproductive decision making (Botkin et al., 2015). However, the ACMG recently changed this longstanding guidance with the reasoning that the potential benefit to the future health of the child outweighs ethical concerns of discovering secondary findings for treatable adult-onset conditions. The

ACMG also reasoned that the disclosure of a secondary finding of cancer risk for the child may indicate high-risk of cancer for the parent, and the child is protected if the parent is informed. The ACMG now recommends that seeking and reporting secondary findings not be limited by the age of the person being sequenced (Green et al., 2013). The ASHG recommends the return of results to parents only if the secondary findings have clinical utility for the child (Botkin et al., 2015). It is also recommended that parents be allowed to decline to receive secondary findings in advance of genomic testing, but if a secondary finding with urgent and serious implications for the child's health is found, the clinician is advised to communicate those findings to parents regardless of their preference not to know (Botkin et al., 2015). Additionally, the ASHG recommends that genomic testing in children should include a long-term communication plan for all results (Botkin et al., 2015).

### **Ethical Considerations for Secondary Findings** and the Patient's Relatives

Information about genetic variants has health implications for the patient's family, since first-degree biological relatives share 50 percent of their genes (Bioethics Commission, 2013; Egalite et al., 2014; Wolf, 2015). Genetic studies targeting specific genes in an affected patient may reveal genetic variants relevant to the patient's immediate family (Egalite et al., 2014). In this situation, the clinician is confronted with conflicting duties to protect the patient's privacy and to warn biological relatives of shared risk (Rigter et al., 2013; Wolf, 2015). Decisions depend on the specific context of a given case.

Genomic sequencing may reveal that a patient's first-degree biological relative has, is at risk for, or is a carrier of a specific disease (Bioethics Commission,

2013; Egalite et al., 2014; Wolf, 2015). Like other medical information, physicians have stringent responsibilities to protect the privacy of a patient's genetic data as a matter of law, ethics and institutional policy, but professional guidance varies (Ross et al, 2013; Wolf, 2015). The Health Insurance Portability and Accountability Act (HIPAA) protects the privacy of health information, including a patient's genetic information, for 50 years after an individual's death (McGuire & Gibbs, 2006; Wolf, 2015). The ASHG acknowledges that physicians have a privilege, but not an obligation, to warn relatives of possible genetic risks in cases where the patient fails to voluntarily disclose to relatives; serious and foreseeable harm is highly likely to occur; at-risk relatives are identifiable; and, the disease is preventable, treatable, or early monitoring will reduce the risk of dying from the related condition (Wolf, 2015). In contrast, the Institute of Medicine advises that genetic risk information should be withheld so as to avoid family disruption (ACOG, 2014; Buchbinder & Timmermans, 2011). Moreover, the American Medical Association has argued that physicians have an obligation to pay almost unlimited respect to a patient's confidentiality (ACOG, 2014).

A relatively common incidental consequence of genomic testing is the detection of misattributed parentage, with estimated rates of 1–10% from various studies (Botkin et al., 2015; Ross et al., 2013). Recommendations for the disclosure of misattributed parentage are diverse and unsettled (Botkin et al., 2015). Arguments in favor of disclosure of paternity findings center on the patient's right to know, avoiding paternalism, and the duty of physicians to be truthful (Botkin et al., 2015). Arguments opposing disclosure conclude that because of the potential for harm to

individuals and the family, misattributed parentage should not be disclosed to either the mother or the father (Botkin et al., 2015). Pretest counseling should alert parents or guardians to this possibility (Ross et al., 2013).

### **Legal Considerations**

An important possible consequence of genomic sequencing is how the results might affect future insurance coverage (ACOG, 2014; Apold & Downie, 2011; OHRP, 2009). The Genetic Information Nondiscrimination Act (GINA) (2008) provides federal protection from genetic discrimination in employment and health insurance, but not long-term care, disability, or life insurance, potentially leaving patients unable to obtain this insurance after genomic sequencing (Hegde et al., 2015; OHRP, 2009). The Office for Human Research Protections (OHRP) recommends that the informed consent process provide information describing the protections provided by GINA (OHRP, 2009).

Patent law and controversies over intellectual property in biotechnology and pharmaceutical industries, and particularly over patenting genes, have affected the provision of genomic sequencing results to patients (Sherkow & Greely, 2015).

Myriad Genetics, Inc. aggressively enforced patent rights to the *BRCA1* and *BRCA2* genes, bringing litigation against clinicians performing *BRCA1*- and *BRCA2*-based cancer risk assessments (Sherkow & Greely, 2015). The U.S. Supreme Court case of *Association for Molecular Pathology v. Myriad Genetics, Inc.* broke the company's patent-based monopoly on *BRCA1* and *BRCA2* testing in the United States (Sherkow & Greely, 2015). "Gene patents may be officially dead in the United States, but could live on, at least weakly, in other countries" (Sherkow & Greely,

2015, p. 175). Concerns over intellectual property rights may be reflected in informed consent procedures for which results will be provided to patients undergoing genomic sequencing tests.

### **Need for Guides for Standard Practices for Secondary Findings**

The development of an appropriate framework to guide the identification and disclosure of secondary findings is needed (Berg et al., 2015; Green et al., 2013; Gutmann, 2013). Guidance is sought on what information should be discussed preceding the test, whether clinicians will be expected to actively look for secondary findings, options for patients to choose broad data return or to opt-out, which results are mandatory to disclose regardless of patient choice, and consequences for children and relatives (Hull & Berkman, 2014; Rigter et al., 2013; Weiner, 2014).

Practice guidelines must acknowledge the complexity of genomic data (Weiner, 2014).

Prior research provides frameworks to consider for the development of informed consent guidelines for identifying and reporting secondary findings. Berg et al. (2013) proposed a system that assigns genes to bins according to features such as clinical actionability, clinical validity, potential to cause harm, and reproductive implications. Building on this work, Berg et al. (2015) established five core characteristics of clinical actionability: severity, likelihood, efficacy of intervention, burden of intervention, and knowledge base about the gene, condition, and intervention. These characteristics are scored on a continuum, not as a binary state (Berg et al., 2015). Another possible framework approach is to define categories by the nature of the condition, differentiating between early and late-onset diseases, the

level of risk, burden of the disease, and options for treatment or prevention (Rigter et al., 2013).

Given the inconsistency in guidance for the identification and disclosure of secondary findings, a standard framework that will allow for evidence-based decisions about benefits and risks of reporting secondary findings needs to be developed (Green et al., 2013; Weiner, 2014). Common practices need to be put in place to encourage understanding of and trust in clinical genomic sequencing (McGuire & Gibbs, 2006). The development of standard practices for informed consent and return of secondary findings will permit empirical study of the benefits and challenges associated with clinical genomic sequencing, and facilitate evidence-based recommendations to patients during pre-test informed consent and post-test counseling (Berg et al., 2013; Green et al., 2013; McGuire & Gibbs, 2006).

In order to evaluate the penetrance of the Bioethics Commission's and ACMG's recommendations for informed consent for clinical WES, an empirical study of informed consent models for clinical WES was undertaken. We hypothesized that variability would be found in models of informed consent for clinical WES, and for seeking and reporting of secondary findings, as well as the extent to which recommendations from the Bioethics Commission and ACMG are incorporated into the process of informed consent. The study objectives are aligned with the emergence of precision medicine and the learning healthcare system that supports it, through improved informed decision making for the identification and reporting of secondary findings and creation of a standard framework to guide informed consent (Aronson & Rehm, 2015; Reinke, 2015; Wiley et al., 2016).

### **CHAPTER 3**

### **METHODOLOGY**

To test the hypothesis that variability would be found in models of informed consent for clinical WES, consent forms were evaluated using a content analysis matrix. The objective of the analysis was to identify the extent to which patient consent is guided by recommendations from the Bioethics Commission and the ACMG.

#### **Data Collection**

We collected a purposeful convenience sample of informed consent forms for clinical WES. We identified laboratories that conduct clinical WES from the National Center for Biotechnology Information's Genetic Testing Registry

(http://www.ncbi.nlm.nih.gov/gtr/), Gene Tests (https://www.genetests.org/), and NextGxDx (https://www.nextgxdx.com). Each of these sites was searched for Clinical Laboratory Improvement Amendment (CLIA) certified laboratories in the United States that provide clinical WES. Laboratories that provide tests for specific genes or conditions and those that conduct WES only for research purposes were excluded.

Between January and February 2016, we identified 25 laboratories registered with the sites listed above as providing clinical WES. We accessed each website and found two of these laboratories provided WES only for research, not clinical, purposes. We were able to download informed consent forms from 18 of the remaining 23 organizations (78%).

### **Document Description and Case Definition**

We found a range of documents and addendums for provision of informed consent, including: 'Patient Consent Form', 'Consent Form, Proband Only', 'Consent Form, Family Trio', 'Test Requisition Form', 'Expanded Secondary Findings Request Form', 'Raw Sequence Data Consent Form', and 'Authorization for Participation in a Research Protocol'. Given the variation in forms, the combination of documents from each organization was organized to comprise a unit of analysis as they would be presented to a patient (i.e. primary consent template with addendums).

Our final sample was comprised of 18 cases combining 29 different informed consent forms and addendums. The informed consent units were categorized by institution type as commercial laboratories (n=8), or academic laboratories affiliated with a hospital or university (n=10) (Table 1).

Table 1

Type of Laboratory among Laboratories Providing Clinical Whole Exome Sequencing

Laboratory Type	N	%
Commercial	8	44.4
Academic	10	55.6
Total	18	100

### **Data Analysis Process**

We applied content analysis to the units of consent in order to identify and describe characteristics of the documents that align with recommendations from the Bioethics Commission and ACMG. The first step was to create a content analysis matrix to evaluate the sample of informed consent forms. Recommendations from

two Bioethics Commission reports pertaining to informed consent, *Privacy and progress in whole genome sequencing* (2012), and *Anticipate and communicate:* Ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts (2013), and two ACMG policy statements, *ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing* (Green et al., 2013), and *Points to consider for informed consent for genome/exome sequencing* (2013), were analyzed (Appendices A-D). Key points that should be included in informed consent for WES were identified. These key points were organized by common themes (Table 2).

Table 2

Bioethics Commission and ACMG Recommended Ke	ey Points and Common Themes
--	-----------------------------

Recommendation	Key Points	Common Theme
Privacy & Practice, 2	Briefly describe whole genome sequencing and analysis	Description of WES
Privacy & Practice, 2	State how the data will be used in the present study	Purpose of WES
Privacy & Practice, 2	Define benefits and potential risks	Benefits and risks of
ACMG	Potential benefits and risks of exome sequencing	WES
Privacy & Practice, 2	There might be unknown future risks	Uncertainty of
ACMG	Limitations of testing	results
ACMG	Policies regarding re-contact of referring physician as new	Follow-up if results
<u></u>	knowledge is gained about significance of particular results	are updated
Privacy & Practice, 3	To whom the findings will be communicated	Results returned to
		whom
Privacy & Practice, 2	What data and information, if any, might be returned to the	Describe results
	individual	returned to proband
Privacy & Practice, 3	The scope of communicated findings	
Anticipate & Communicate, 1	What findings will be returned	
Anticipate & Communicate, 6	The scope of findings that will be communicated	
ACMG	Expected outcomes of testing	
Anticipate & Communicate, 1	What findings will not be returned	Results excluded
ACMG	Types of results that will not be returned	from report
Privacy & Progress, 3	Incidental findings are likely to be discovered	Define incidental/
Anticipate & Communicate, 1	Incidental and secondary findings that are likely to arise or be	secondary findings
	sought from the tests and procedures conducted	
Anticipate & Communicate, 6	Incidental and secondary findings are a possible, or likely, result of	
	the tests or procedures being conducted	
ACMG	Likelihood and type of incidental results that may be generated	
Privacy & Progress, 3	Whether these findings will be communicated	Options for ACMG
Anticipate & Communicate, 1	Plan for disclosing and managing incidental and secondary	minimum list
	findings	

Recommendation	Key Points	Common Theme
ACMG	Incidental/secondary findings may have high clinical significance	
	for which interventions exist to prevent or ameliorate disease	
	severity	
Anticipate & Communicate, 6	Respect a patient's preference not to know about incidental or	
	secondary findings to the extent consistent with a clinician's	
	fiduciary duty	
Anticipate & Communicate, 6	Steps to be taken upon discovery of incidental findings	Return secondary
ACMG	Potential implications for family members	findings for minors
Anticipate & Communicate, 6	Steps to be taken upon discovery of incidental findings	Disclose secondary
ACMG	Potential implications for family members	findings to relatives
Privacy & Practice, 1	How these data might be used in the future	Request to use
Privacy & Practice, 2	How the data might be used in the future, i.e. for research	sample for research
	purposes	
Privacy & Practice, 2	Extent to which the individual will have control over future data use	
Privacy & Practice, 1	How these data might be used in the future	Sample may be
ACMG	Whether individually identifiable results may be provided to	shared in databases
	databases	
ACMG	Permitted to opt-out of disclosing individually identifiable results to	
	databases	
Privacy & Practice, 1	Who has access to whole genome sequences and other data	Who has access to
	generated in the course of clinical sequencing	sequence data
ACMG	Before initiating exome sequencing, counseling should be	Opportunity for
	performed by a genetic counselor	genetic counseling
ACMG	The clinician should also provide posttest counseling	
ACMG	Information derived: carrier status	Disclose carrier
		status for recessive
		disorders
ACMG	Information derived: ancestry	Risk discovery of
		misattributed
		parentage

During the review of the literature and preliminary scanning of consent documents, other key points for consent were identified in addition to those recommended by the Bioethics Commission and ACMG. These items were included in the coding framework as separate items for analysis (Table 3).

Table 3

Recommended Key Points for Informed Consent Derived from Review of the Literature and Preliminary Scan of Sample Forms

**Key Points** 

Return raw data file

Transfer results to other health care provider

Samples from NY destroyed in 60 days

Risk: Insurance discrimination/Genetic Information Nondiscrimination Act (GINA)

Some genetic information is proprietary

The key points of all recommended consent guidance were structured into a matrix for evaluating and coding the content of each sample unit (Table 4).

Table 4

Content Analysis Coding Matrix

Bioethics & ACMG	Recommendation Key Points
1.	Description of WES
2.	Purpose for WES
3. 4. 5. 6.	Benefits and risks of WES
4.	Uncertainty of results
5.	Follow-up if results are updated
	Results returned to whom
7.	Describe results returned to proband
8.	Results excluded from report
9.	Define incidental/secondary findings
10.	Options for ACMG minimum list
11.	Return secondary findings for minors
12.	Disclose secondary findings to relatives
13.	Disclose carrier status for recessive disorders
14.	Sample may be shared in databases
15.	Request to use sample for research
16.	Who has access to sequence data
17.	Opportunity for genetic counseling
18.	Risk discovery of misattributed parentage
<u>Other</u>	
1.	Transfer results to other health care provider
2.	Return raw data file
2. 3. 4.	Samples from NY destroyed in 60 days
4.	Risk: insurance discrimination/GINA
5.	Some genetic information is proprietary

During the second step, the cases were analyzed using the coding matrix. Each of the 29 documents was read and language addressing each theme was highlighted and coded. This step was then repeated twice for all documents as a confirmation check that the matrix was applied consistently and accurately. Each form was reviewed three times.

Descriptive statistics were used to describe the overall sample and differences between types of institution. The nonparametric statistical method of

Fisher's Exact test was used to compare the significance of differences of frequency of each key point between the two categories of institutions.

### **CHAPTER 4**

### **RESULTS**

### **Recommendations of Bioethics Commission and ACMG**

We found recommendations of the Bioethics Commission and ACMG present in all cases, to varying degrees. The frequency of inclusion of the 18 Bioethics and ACMG recommendations ranged from 11 to 17 items (Figure 1). The median frequency of inclusion of these 18 recommendations was 14 items.

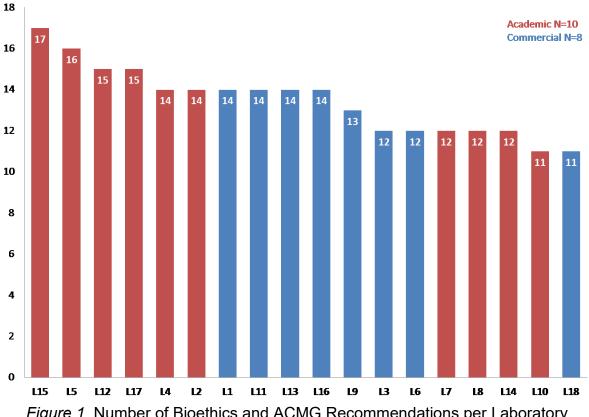


Figure 1. Number of Bioethics and ACMG Recommendations per Laboratory by Laboratory Type

Among all forms in the sample, the average adherence to the complete list of 18 Bioethics and ACMG recommendations was 74.4%, with academic laboratories

averaging 76.7% completeness and commercial laboratories averaging 72.2% completeness (Figure 2).

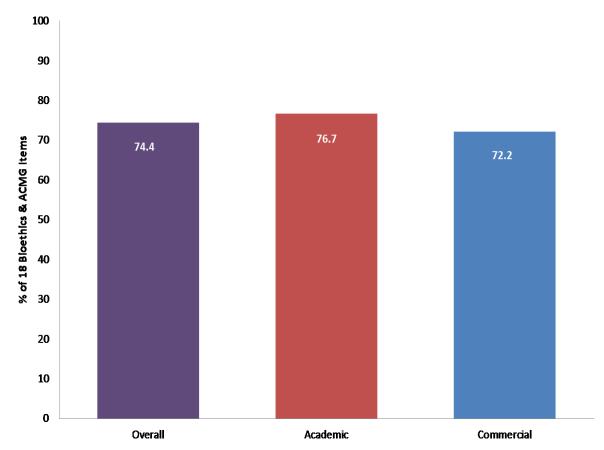


Figure 2. Average Adherence to the Complete List of Bioethics Commission and ACMG Recommendations

Examples of content language identified for each of the key points of the Bioethics Commission and ACMG recommendations are presented in Table 5.

Table.5

Examples of Content Identification	Example Consent Form Content
1. Description of WES	[The test] attempts to evaluate the protein-coding regions of the human genome, which represents approximately 20,000 genes. These regions of DNA are referred to as 'exome'. The exome accounts for approximately 2% of the genome and comprises the majority of DNA variations that cause human disease. Exome sequencing is a useful and powerful tool for diagnostic applications and has been utilized to identify mutations in disorders that are both genetically and phenotypically heterogeneous and to identify mutations in genes associated with Mendelian disorders.
2. Purpose for WES	The purpose of WES is to identify genetic cause(s) of the patient's health issues.
3. Benefits and risks of WES	Benefits: identify a cause for your health condition or symptoms, assist you and your healthcare provider in choosing the best treatment for you, determine recurrence risk of disease in your family, identify predisposition to disease  Risks: information might reveal: genetic risks for diseases that may develop later in life, disease unrelated to the primary reason for ordering the test, disorders that do not have current treatment, other unexpected familial relationships
4. Uncertainty of results	Although there are some entire genes that we may not be able to capture and sequence in a particular patient, in general we expect that there may be small portions of different genes that are not amenable to evaluation.  Information about the human genome is not yet complete. It is possible that we will not recognize the cause of a child's disease even though we may identify the presence of the variant in the DNA. This is because the functions of many genes are completely unknown at this time.  I have been informed that the sensitivity of the [test] is not 100% and that the cause of the disease in my child may not be identified by this analysis.
5. Follow-up if results are updated	By signing this consent, you give [the laboratory] permission to retain the genetic information generated by this test and to contact your physician if [the laboratory] learns new information about the genetic variants detected by this test that affects your reported test results. [The laboratory] will make reasonable efforts to contact your physician in these instances. It is the responsibility of the patient to maintain current contact information with

26

,		Recommendation	Example Consent Form Content
			the healthcare provider so that the patient may be advised of any changes to their test results.
27	6.	Results returned to whom	The results of this test will be kept confidential and will be released only to the physician(s) ordering the test or other persons authorized by you, in writing, unless otherwise required by federal and state law.
	7.	Describe results returned to proband	[The laboratory] will report on genetic variants that have been reported to be pathogenic, predicted to be pathogenic, possibly pathogenic as well as unclassified variants in established genes for the clinical features/suspected condition indicated for the patient. In addition, truncating pathogenic variants and variants that have been previously reported to be pathogenic or possibly pathogenic in genes hypothesized to be related to the cause of the patient's phenotype will also be reported.
	8.	Results excluded from report	The report will not contain information on variants associated with drug metabolism, common variants associated with modest changes in the risk of common diseases, or variants in genes that have not yet been linked to diseases in humans.
	9.	Define incidental/secondary findings	The test may find genetic changes that tell us that you/your child are at risk for diseases other than your/your child's condition, such as cancer risk. These changes are often called "incidental" or secondary findings.
	10	Options for ACMG minimum list	The ACMG have published guidelines for the reporting of these types of medically actionable or incidental findings (PMID: 23788249). These guidelines include a list of genes, which may be updated periodically, that have been determined to be considered medically actionable and therefore laboratories should seek and report pathogenic variants in these genes. In accordance with an update to this policy statement, there is the option to opt out of receiving pathogenic variants information if identified in the genes listed in ACMG policy statement. It will not be reported on either the focused or the expanded report.
	11	Return secondary findings for minors	Incidental findings that cause a childhood onset disorder where medical intervention can prevent or decrease the effect of a disease will always be included in the laboratory report.
	12	Disclosure secondary findings to relatives	This test could reveal information about the health of your relatives, such as their chance of developing certain disorders. Such information could be unexpected, or it could explain a medical condition in your family. If the test finds a genetic change that may be important to your family's health, you/your child's healthcare provider will ask you to tell your family members about it.

Recommendation	Example Consent Form Content
13. Disclose carrier status	Carrier status for autosomal recessive conditions (e.g., Cystic Fibrosis). A recessive
for recessive disorders	condition is one in which two pathogenic variants in the same gene are required in order to show symptoms of the disease (one variant is inherited from each parent). Someone who
	has only one pathogenic variant does not show symptoms and is called a carrier. However,
	if we find a pathogenic variant in a recessive gene that is related to the patient's phenotype,
	we will report it as a diagnostic finding. You can choose whether or not you want us to report carrier status in genes that are not related to the patient's phenotype. The [test] is not
	designed to be a comprehensive carrier test.
14. Sample may be shared in databases	The data used to generate the final report while performing [the test] will be saved for at least two (2) years after testing is completed and the report is issued to your medical professional, your child's medical professional or the medical professional for the patient for
	whom you are legal guardian, as applicable, who ordered this test. In addition, if you give your permission below, [the laboratory] may retain de-identified sequence, variants, and
	clinical information in the databases that [the laboratory] uses to generate test results, and deposit such de-identified information in appropriate public databases e.g. ClinVar, with the
	goal of improving diagnosis for future families and parents.
<ol><li>15. Request to use sample for research</li></ol>	There may be research studies that you may be eligible for and may be of interest to you. If the "yes"/contact option is chosen please complete the additional information requested.
	Please note that if neither box is checked the laboratory will default to the "no"/no contact option.
	Yes, [the laboratory] may share my contact information with researchers who have IRB
	approved research study for which I may be eligible for participation. There is no obligation
	to participate if contacted. No information, other than the contact information below, will be provided to the researcher.
	No, I do not wish to be contacted regarding participation in research studies.
16 Who has access to	Your genomic sequencing report will list medically important genetic changes that were
sequence data	found by the genomic sequencing test. This report containing your test results as well as
	any updates to those results will become part of your child's permanent electronic medical
	record and be made available to any healthcare provider treating you now or in the future.  The laboratory will not initially deposit your complete genetic sequence into your medical
	record. However, it is possible that this policy will change in the future in which case your

Recommendation	Example Consent Form Content
	complete genetic sequence may be incorporated into your permanent medical records.
17. Opportunity for genetic counseling	Given the complexity of the [test], genetic counseling and informed consent by a trained medical geneticist or genetic counselor is required prior to and after undergoing this testing. Informed consent is a process that provides education about genetics, and the options, benefits, limitations, and consequences of genetic testing. Genetic counseling provides the patient with informed consent prior to the decision to undergo testing and with the opportunity to review the results of the test in detail.
18.Risk discovery of misattributed parentage	There is a risk that you may learn other genetic information about you or your family members that is not related to any specific medical concern(s). Learning about this information might cause anxiety and psychological stress. As an example, this test may reveal non-paternity and non-maternity (where the father or mother is not the biological parent) or other unexpected familial relationships.

The adherence to each of the individual Bioethics Commission and ACMG recommendations ranged from 11.1% to 100% (Figure 3).

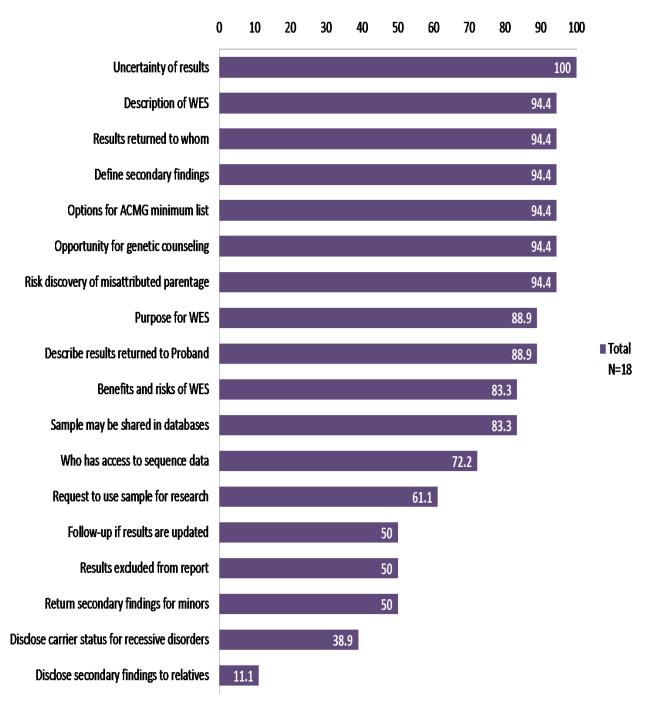


Figure 3. Adherence to Individual Bioethics and ACMG Recommendations for 18 Laboratories

All of the informed consent forms disclosed that the results may be uncertain due to limitations of the test, such as DNA changes that are not detected with WES and/or limited understanding of detected changes in some gene sequences. Nearly all consent forms (94.4%) included a description of WES, stated to whom results would be returned, defined secondary findings, explained options for receiving results for the ACMG minimum list, discussed opportunities for pre- and/or posttest genetic counseling, and disclosed the risk of discovering misattributed parentage. Approximately 90% of sampled forms explained the purpose for WES and described the results to be included in the report. The benefits and risks of WES were explained in 83% of consent forms, and the same frequency disclosed that the laboratory may use the de-identified data for sharing with national DNA databases. Seventy-two percent of forms stated who may have access to the sequence data. Approximately 60% included a request to use the sample for research purposes. One-half of all forms discussed the possibility for follow-up communication if a new interpretation of results is learned, described results to be excluded from the report, or explained the approach to returning secondary findings for minors. Nearly 40% offered search and disclosure of results for carrier status for recessive disorders. Only 11% of consent forms included the recommendation that relevant secondary findings should be disclosed to relatives.

We distinguished between two types of institutions: 1) laboratories affiliated with a hospital or university, referred to as "academic" laboratories, and 2) laboratories without such affiliation, referred to as "commercial" laboratories throughout this report. For academic laboratories, the adherence to each of the

individual Bioethics and ACMG recommendations ranged from 20% to 100% (Figure 4). Among commercial laboratories, the adherence to individual recommendations ranged from 0% to 100%. Differences between the two types of laboratories for each of the Bioethics and ACMG recommendations were measured using Fisher's Exact test. One statistically significant difference was found.

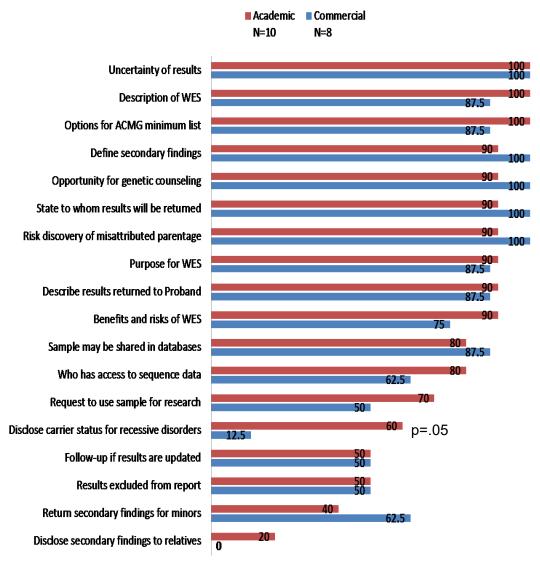


Figure 4. Adherence to Individual Bioethics and ACMG Recommendations by Laboratory Type

All laboratories, both academic and commercial, disclosed that there would be uncertainty of results due to limitations of WES. Approximately 90% of both academic and commercial laboratories explained the purpose of the WES and described the results that would be contained in the report. One-half of both laboratory types discussed the possibility for follow-up communication in light of new information about results, and described results that would be excluded from the report.

Every academic laboratory described WES and provided options for seeking and reporting the ACMG minimum list, compared to 87.5% of commercial laboratories. Ninety percent of academic laboratories specifically described benefits and risks of WES compared to 75% of commercial laboratories. Eighty percent of academic laboratories described who would have access to the sequence data compared to 62.5% of commercial laboratories. Seventy percent of consent forms from academic laboratories requested to use the remaining sample for research purposes compared to one-half of commercial laboratories. The search and disclosure of carrier status for recessive disorders was offered by 60% of academic laboratories but only 12.5% of commercial laboratories, a statistically significant difference (p=.05). Twenty percent of the academic laboratories recommended that relevant secondary findings should be disclosed to relatives but none of the commercial laboratories included this recommendation.

Every commercial laboratory and 90% of academic laboratories defined secondary findings, discussed opportunities for pre- and/or posttest genetic counseling, stated to whom results would be returned, and disclosed the risk of

discovering misattributed parentage. Nearly 88% of commercial laboratories explained that the de-identified data may be shared in DNA databases while 80% of academic laboratories did so. Nearly 63% of commercial laboratories described the policy for returning secondary findings to minors, compared to 40% of academic laboratories.

## Other Recommendations for Informed Consent

We examined guidance pertaining to additional recommendations for informed consent identified from the review of literature and preliminary examination of forms. The frequency of inclusion of these 5 other recommendations ranged from 0 to 4 items (Figure 5). The median frequency of inclusion of these 5 other recommendations was 1.5 items.

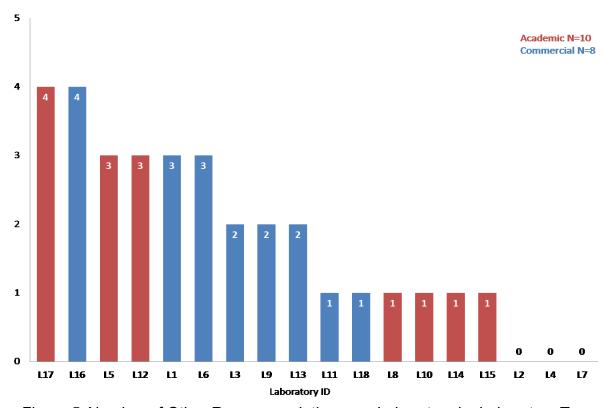


Figure 5. Number of Other Recommendations per Laboratory by Laboratory Type

One-half of informed consent forms included provisions for WES results to be transferred to another health care provider in addition to the ordering clinician (Figure 6). Forty-four percent of consent forms provided for return of the raw data file to the clinician. The Genetic Information Nondiscrimination Act (GINA) and/or the risk of insurance discrimination were explained in 44% of consent forms. The New York state statute requiring that samples be destroyed within 60 days of testing was acknowledged in 39% of forms. One consent model (6%) informed patients that there may be proprietary data that could not be included in the analysis.

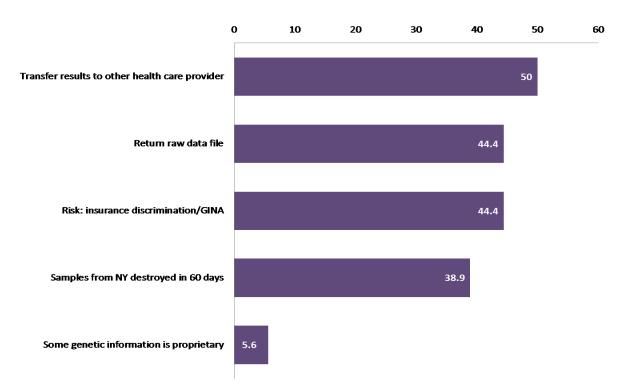


Figure 6. Frequency of Other Recommendations for Informed Consent for 18 Laboratories

Example language pertaining to these other key points for informed consent is presented in Table 6.

Table 6

Examples of Content Identified as Addressing Other Recommended Content of Informed Consent Form	ns
---	----

	<u> </u>
Recommendation	Example Consent Form Content
Transfer results to other	I also authorize [the laboratory] to disclose the test results to the ordering physician and any
health care provider	other provider I designate.
Return raw data file	The raw data generated from the sequencing may be released to the ordering healthcare
	provider with your consent.
	I authorize the release of raw data to my/my child's healthcare provider and understand that
	any interpretation of the variations identified outside the context of the laboratory report is at
	my/my child's provider's discretion.
Samples from NY	Samples with New York state origin will be destroyed at the end of testing or no more than 60
destroyed in 60 days	days after the sample was taken, unless a longer period of retention is expressly authorized.
Risk: Insurance	The Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits health insurance
discrimination/GINA	plans and employers from some discrimination based on genetic information, including the
	results of genetic testing. However, such genetic testing may result in life insurance, disability
	insurance, and/or long-term care insurance discrimination that is not prohibited by law.
Some genetic information	Certain people and companies have been granted patent rights on certain genes. This gives
may be proprietary	those people and companies the right to prevent others from using those patented genes for
	certain purposes. As a result, [the laboratory] may not be able to analyze or report variants in
	patented gene, even if they are relevant to the disorder in your family.
	Transfer results to other health care provider Return raw data file  Samples from NY destroyed in 60 days Risk: Insurance discrimination/GINA  Some genetic information

Differences between the two types of laboratories in the adherence to the other recommendations for informed consent were examined (Figure 7).

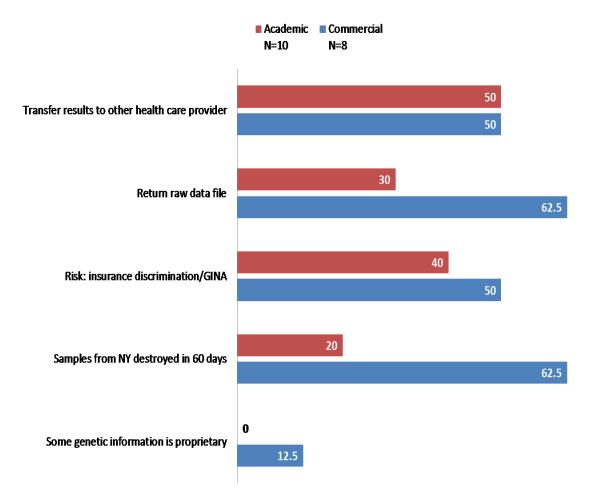


Figure 7. Adherence to Other Recommendations for Informed Consent by Laboratory Type

One-half of consent forms from both types of laboratories provided for the patient to have results transferred to another health care provider. The return of the raw sequence data file was allowed by 62.5% of commercial laboratories but only 30% of academic laboratories. One-half of commercial laboratories and 40% of academic laboratories described GINA and/or the possibility of insurance

discrimination as a possible risk. The New York state statute requiring samples to be destroyed within 60 days of testing was explained in 62.5% of commercial laboratory consent forms but only 20% of academic laboratories. The possibility of proprietary genetic information was included in one commercial laboratory's consent form; none of the academic laboratories included this information.

### **CHAPTER 5**

### DISCUSSION

Our results indicate a range of inclusion of the recommendations of the Bioethics Commission and ACMG for informed consent of clinical WES. The current study is, to the best of our knowledge, the first to systematically examine informed consent forms in order to assess the representation of these recommendations. The results confirmed our hypothesis that variability would be found in models of informed consent for clinical WES.

The informed consent process is grounded on the ethical principles of respect for persons, beneficence, non-maleficence, and autonomy (Bioethics Commission, 2012; Escobedo, Guerrero, Lujan, Ramirez, & Serrano, 2007; Kole & Feister, 2013; OHRP, 1993). An informed consent process that respects the autonomy of patients involves providing adequate information so that patients understand the procedure and are able to choose the care that is best for them, with regard to their personal values (Bioethics Commission, 2012; Escobedo et al., 2007; Kole & Feister, 2013). Clinical practice guidelines such as those from the Bioethics Commission and ACMG can be helpful in establishing standards, but guidelines do not mandate standard of care; adherence is voluntary (Bioethics Commission, 2013). Therefore, it is worthwhile to understand how these theoretic ideals are being integrated (or not) into real practice so that awareness of the issue and conformance to guidance for informed consent of the evolving use of genomic medicine may be encouraged.

We found that nearly all laboratories in the sample addressed one-half of the identified 18 Bioethics Commission and ACMG recommendations. Informed consent

forms were generally consistent in describing how and why WES is conducted, defining secondary findings and options for receiving these results, describing what results would be reported, and explaining that genetic counseling was recommended before and after testing. These issues are central to allowing patients to make an educated choice to have the clinical WES test, and are reflective of the imperative ethical principle of respect for persons. These findings demonstrate that laboratories are integrating many of the Bioethics Commission and ACMG recommendations into their informed consent process.

In addition to respect for persons and beneficence, the Bioethics Commission (2013) found the ethical principles of justice and fairness, intellectual freedom and responsibility, as well as virtues such as honesty, courage, and humility, to be particularly applicable to the ethical assessment of secondary findings. Policy and ethics professionals are actively debating specific criteria that can be used to determine when it is ethically permissible or obligatory for clinicians to disclose (or not disclose) secondary findings to patients (Bioethics Commission, 2013; Green et al., 2013). A fundamental aspect of this problem is the variation among patients about the choice of disclosure of secondary findings. Information that causes anxiety for one recipient could empower another recipient in making health-related decisions (Bioethics Commission, 2013). The shift from discrete genetic tests toward large-scale genetic sequencing such as clinical WES increases the likelihood that physicians and patients will confront these issues (Bioethics Commission, 2013; Crawford et al., 2013). Our results seem to reflect this unsettled debate.

We found one-half to 90% of the laboratories sampled did not address the Bioethics Commission and ACMG recommendations for informed consent related to secondary findings. Fifty percent of consent forms did not discuss the return of secondary findings for minors, 61% did not address disclosure of carrier status for recessive disorders, and nearly 90% did not plainly recommend that patients should disclose relevant secondary findings to relatives. Laboratories that do address the ethical dilemmas of disclosing secondary findings for children and relatives demonstrate a pioneering approach to informed consent that is not yet well-established. While the approach of most laboratories to provide non-specific, general information about these issues is not unethical, and does respect the patient's freedom and responsibility to make a choice without "paternalistic" guidance, it also could infringe on principles of justice and fairness to patients who are not equipped to manage these difficult choices and would benefit from unambiguous advice.

The understanding of results from genome-scale sequencing will change as genomic technologies continue to develop and mature (Bioethics Commission, 2012). Indeed, disclosure of the uncertainty of results for WES was the only recommendation item that was included in every consent form, regardless of laboratory type. A consent issue related to the uncertainty of results is the need to follow up with patients as new knowledge becomes available. However, an explanation that the laboratory may re-analyze the data after a certain period of time and could re-contact the ordering clinician if a new interpretation of results is learned was included in just one-half of consent forms from both types of laboratories. This discrepancy deserves further attention in future professional guidance. As genome-

scale sequencing becomes more ubiquitous, laboratories will need to understand their responsibility to apprise patients of new information, and patients will need to understand whether or not they are responsible to seek updated results.

One basic component of informed consent that is well-established and less controversial is the disclosure of benefits and risks (Bioethics Commission, 2012). However, all consent forms did not include a specific section to explain benefits and risks of the procedure. This means that psychological risks such as the patient feeling frustrated, angry, disappointed, or depressed related to the results of genetic testing was omitted. But it does not mean that risks were not explained. For example, instead of explicitly describing risks in a dedicated section of the form, some forms included possible risks such as the discovery of misattributed parentage in the section describing what results would be returned to the patient. By formatting the consent information in this way, laboratories may misguide patients that there are no risks, or place more responsibility on the patient to comprehend that a risk is possible when it is not specifically stated. This is an aspect of informed consent that could be improved with an explicit section with standard language describing risks such as psychological distress, possible discovery of misattributed parentage, and another often overlooked risk, potential insurance discrimination.

According to the OHRP, consent processes should reflect the protections provided by the Genetic Information Nondiscrimination Act (GINA) in the descriptions of risks and protection of confidentiality of the data. GINA's protections prohibit discrimination in employment and health insurance coverage, but do not extend to life, disability, or long-term care insurance (Apold & Downie, 2011; OHRP,

2009). Discovery and disclosure of secondary findings brings the potential of the loss of insurability (Apold & Downie, 2011; Simon et al. 2011). Our study found that 56% of laboratories did not include information about GINA and/or the risk of insurance discrimination. This omission is a potentially serious oversight as it could have severe financial and/or health care repercussions for the patient and/or family members who receive secondary findings.

Patients undergoing genome-scale testing may be experiencing a diagnostic odyssey, attempting to establish a definite diagnosis for a rare disease or complex condition. At the same time, the yield of clinical WES is limited and current ability to interpret the data is evolving. Consequently, patients may want to explore other clinical opinions of the information and data received from the test. In the context of genome-scale sequencing there is a difference between the return of "information" and "data". Information refers to analyzed data interpreted by experts, whereas "raw data" refers to the unanalyzed sequence data (Bioethics Commission, 2012). Laboratories that permit the transfer of information and/or return of raw data to patients can help the patient undergoing a diagnostic odyssey by simplifying access to test information and data that may facilitate diagnostic insight from other clinicians. In our study, one-half of laboratories included a provision for the transfer of results to another health-care provider. Forty-four percent offered to return the raw data to the patient, but this allowance differed between types of laboratories. Approximately 63% of consent forms from commercial laboratories permitted the patient to request the raw data file, but only 30% of academic laboratories did so. Professional guidance committees such as the Bioethics Commission and ACMG

may want to consider providing advice to professionals for including transfer of genetic information and data to patients so that standards for these practices may become established and patients receive maximum benefit from the procedure.

There are legal issues associated with genetic testing that are reflected in our analysis of informed consent forms. One example is the New York state law requiring that biological samples be destroyed within 60 days of the testing process unless the patient consents to a longer period of storage (NY Department of Health, 2011). This statute was referred to in 39% of the overall sample, but there was considerable difference between types of laboratories. Approximately 63% of commercial laboratories cited that the sample would be destroyed in 60 days and requested approval to store the sample for a longer period of time, whereas only 20% of academic laboratories included this rule. This discrepancy may reflect the service area of the laboratory. While this issue only applies to samples from New York, it is possible that more states will enact specific legislation for genetic testing and the informed consent process will need to be attentive and responsive to changing legal requirements.

Another legal matter pertains to protections for intellectual property and patent laws. As explained by Sherkow & Greely (2015), the US Supreme Court's recent decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* established that methods of conducting genetic risk-assessment are not eligible for patent claims (Sherkow & Greely, 2015). However, patents on the use of specific genes for gene therapy continue to be possible and as specific gene therapy technologies become commercially available, patent protection for them could come

to be significant (Sherkow & Greely, 2015). One consent form in our sample, from a commercial laboratory, did include language disclosing the possibility of proprietary data which could not be used in the analysis of results. This was a notable exception among the sample of consent forms. It is unknown whether this is an artifact of the litigation brought by Myriad, Inc. or an innovation that may become more widely disseminated into the process of informed consent.

# **Implications for Informed Consent**

"Informed consent is a process, not just a form" (OHRP, 1993, p. 1). The informed consent process provides a principal opportunity for communication between clinicians and patients (Bioethics Commission, 2013). Good clinical care includes providing patients with sufficient information to make educated decisions about the treatment they receive. This can be challenging for genome-scale tests (Crawford et al., 2013). Traditional approaches to informed consent may not be compatible with the specific contexts of genomic testing (Simon et al, 2011).

Our study demonstrates that patients receive different information for the consent of clinical WES depending on which laboratory conducts the procedure. In order to improve the quality and consistency of communication between clinicians and patients, practitioners should collaborate to improve the process of informed consent by developing clear and consistent guidelines for consent forms (Bioethics Commission, 2012, 2013). The recommendations of the Bioethics Commission, ACMG, and exemplars from practitioners provide a framework for this task. Our study results may be used as a template for informed consent that addresses 18 recommendations from the Bioethics Commission and ACMG and 5 additional

elements of consent. The examples of informed consent content displayed in Tables 5 and 6 serve as a template for a standard model of informed consent. A common set of consent elements will help to serve the ethical principle of respect for persons. In addition, development of standardized systems and infrastructure to enable health information exchange so that data can be aggregated and studied is advocated to support the emerging practice of personalized medicine and the learning healthcare system (Aronson & Rehm; Bioethics Commission, 2012; Reinke, 2015; Wiley et al., 2016).

# **Study Limitations**

The study had a limited scope, including only informed consent forms for clinical WES that were available for download. Additional laboratories were identified as providing clinical WES that did not post their informed consent forms online. The scope of inclusion of Bioethics Commission and ACMG recommendations for ACMG may be different among laboratories that restrict access to their informed consent forms. The generalizability of the findings of this study is restricted to publicly available consent forms. The small sample size limited the statistical power to detect meaningful differences.

The study identified laboratories that conduct clinical WES by searching online genetic test registries. Registration in databases such as the National Center for Biotechnology Information's Gene Test Registry is voluntary, thus the sampling of laboratories reflects only those that choose to submit information to such databases. It is unknown how many laboratories actually conduct the clinical WES procedure.

The study sample may be biased toward larger laboratories and exclude small or private organizations that do not participate in genetic test registration databases.

Another limitation is that the content analysis was conducted by a single evaluator. While steps were taken to improve the validity and reliability of the ratings by repeating the assessment of forms three times, the analysis lacks inter-rater reliability. It is possible that the interpretation of consent language could be different by another analyst. In order to make transparent the content analysis criteria used by the investigator, the results include examples of content that were identified as addressing each recommendation item.

# **Further Study**

Further study of informed consent forms used for clinical WES is needed.

Future studies that include consent forms from laboratories that do not provide online access to their forms and/or are not listed in genetic test registries is needed to better evaluate the spectrum of informed consent procedures. The analysis of informed consent guidance would also be augmented by surveys of clinicians and patients to learn opinions and preferences for the recommendations of the Bioethics Commission, ACMG, and other elements of informed consent.

### Conclusion

We observed considerable variability in the content of informed consent forms among the sample of 18 laboratories. This analysis can be useful to laboratories that provide clinical WES to improve informed consent forms so that they are in alignment with recommendations from the Bioethics Commission and ACMG. The development of a more standardized informed consent process could improve

communication between clinicians and patients, increase understanding of genetic testing, and allow for increased data sharing.

APPENDIX A

RECOMMENDATIONS OF THE PRESIDENTIAL COMMISSION

FOR THE STUDY OF BIOETHICAL ISSUES:

Informed Consent: Privacy and Progress in

Whole Genome Sequencing

**Recommendation 3.1** 

Researchers and clinicians should evaluate and adopt robust and workable

consent processes that allow research participants, patients, and others to

understand who has access to their whole genome sequences and other data

generated in the course of research, clinical, or commercial sequencing, and to

know how these data might be used in the future. Consent processes should

ascertain participant or patient preferences at the time the samples are obtained.

Recommendation 3.2

The federal Office for Human Research Protections or a designated central

organizing federal agency should establish clear and consistent guidelines for

informed consent forms for research conducted by those under the purview of the

Common Rule that involves whole genome seguencing. Informed consent forms

should: 1) briefly describe whole genome sequencing and analysis; 2) state how the

data will be used in the present study, and state, to the extent feasible, how the data

might be used in the future; 3) explain the extent to which the individual will have

control over future data use; 4) define benefits, potential risks, and state that there

might be unknown future risks; and 5) state what data and information, if any, might

be returned to the individual.

49

## **Recommendation 3.3**

Researchers, clinicians, and commercial whole genome sequencing entities must make individuals aware that incidental findings are likely to be discovered in the course of whole genome sequencing. The consent process should convey whether these findings will be communicated, the scope of communicated findings, and to whom the findings will be communicated.

# **Recommendation 3.4**

Funders of whole genome sequencing research should support studies to evaluate proposed frameworks for offering return of incidental findings and other research results derived from whole genome sequencing. Funders should also investigate the related preferences and expectations of the individuals contributing samples and data to genomic research and undergoing whole genome sequencing in clinical care, research, or commercial contexts.

### APPENDIX B

RECOMMENDATIONS OF THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES: Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-consumer Contexts

# **Recommendation 1**

Clinicians, researchers, and direct-to-consumer providers should describe to potential recipients incidental and secondary findings that are likely to arise or be sought from the tests and procedures conducted. Practitioners should inform potential recipients about their plan for disclosing and managing incidental and secondary findings, including what findings will and will not be returned.

## Recommendation 6

Clinicians should make patients aware that incidental and secondary findings are a possible, or likely, result of the tests or procedures being conducted. Clinicians should engage in shared decision making with patients about the scope of findings that will be communicated and the steps to be taken upon discovery of incidental findings. Clinicians should respect a patient's preference not to know about incidental or secondary findings to the extent consistent with a clinician's fiduciary duty.

### APPENDIX C

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS POLICY STATEMENT:
Points to Consider for Informed Consent for

Genome/Exome Sequencing

- Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient.
- Incidental/secondary findings revealed in either children or adults may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. Patients should be informed of this possibility as a part of the informed consent process.
- 3. Pretest counseling should include a discussion of the expected outcomes of testing, the likelihood and type of incidental results that may be generate, and the types of results that will or will not be returned. Patients should know if and what types of incidental findings may be returned to their referring physician by the laboratory performing the test.
- 4. Patients should be counseled regarding the potential benefits and risks of GS/ES, the limitations of such testing, potential implications for family members, and alternatives to such testing.
- 5. GS/ES is not recommended before the legal age of majority except for:
  - a. Phenotype-driven clinical diagnostic uses;
  - b. Circumstances in which early monitoring or interventions are available and effective; or
  - c. Institutional review-board-approved research.

- 6. As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing.
- Patients should be informed as to whether individually identifiable results may be provided to databases, and they should be permitted to opt out of such disclosure.
- Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results.

## APPENDIX D

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS POLICY STATEMENT:
Updated Recommendations Regarding Analysis and Reporting of Secondary Findings in Clinical Genome-scale Sequencing

- When clinical genome-scale (e.g., whole-exome sequencing, whole-genome sequencing) sequencing is performed, written informed consent should be obtained by a qualified genetics health-care professional describing the nature of the test and addressing points such as interpretive uncertainty, privacy, possible impact on other family members, and the inevitable generation of data not immediately relevant to the clinical indication for sequencing. At the time of testing, the patient should be made aware that, regardless of the specific indication for testing, laboratories will routinely analyze the sequence of a set of genes deemed to be highly medically actionable so as to detect pathogenic variants that may predispose to a severe but preventable outcome.
- Patients should be informed during the consent process that, if desired, they may
  opt out of such analysis. However, they should also be made aware at that time
  of the ramifications of doing so.
- In accordance with the recent recommendations of the Presidential Commission
  for the Study of Bioethical Issues, as well as a lack of clear consensus in the
  ACMG membership survey administered in January 2014, the board
  recommends that the same policy should be adhered to in children as in adults;
  i.e., analysis of a set of selected genes to identify pathogenic variants associated

- with severe but preventable disease should be routinely performed. Parents should have the option during the consent process to opt out of such analysis.
- At this time, given the practical concerns and inherent difficulty of counseling patients about the features of each disorder and every gene on an ever-changing list, it is not feasible for patients to be offered the option of choosing a subset of medically actionable genes for analysis. Thus, the decision regarding routine analysis should apply to the entire set of genes deemed actionable by the ACMG.

### REFERENCES

- American College of Medical Genetics and Genomics, Board of Directors (ACMG). (2013). Points to consider for informed consent for genome/ exome sequencing. *Genetics in Medicine*, *15*(9), 748-749
- American College of Medical Genetics and Genomics, Board of Directors (ACMG). (2015). ACMG policy statement: Updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genetics in Medicine*, *17*(1), 68-69
- American College of Obstetricians and Gynecologists (ACOG). (2008, reaffirmed 2014). Ethical issues in genetic testing. *ACOG Committee Opinion, 410,* 1-8.
- American College of Preventive Medicine (ACPM). (2010). Genetic testing: A resource from the American College of Preventive Medicine. P. 1-49.
- Aronson, S.J., & Rehm, H.L. (2015). Building the foundation for genomics in precision medicine. *Nature*, *526*, 336-342
- Apold, V. S., & Downie, J. (2011). Bad news about bad news: The disclosure of risks to insurability in research consent processes. *Accountability in Research*, 18, 31-44
- Berg, J. S., Adams, M., Nassar, N., Bizon, C., Lee, K., Schmitt, C. P., et al. (2013). An informatics approach to analyzing the incidentalome. *Genetics in Medicine*, *15*(1), 36-44
- Berg, J. S., Foreman, A. K., O'Daniel, J. M., Booker, J. K., Boshe, L., Carey, T., et al. (2015). A semi-quantitative metric for evaluating clinical actionability of incidental or secondary findings from genome-scale sequencing. *Genetics in Medicine*, 1-8.
- Botkin, J. R., Belmont, J. W., Berg, J. S., Berkman, B. E., Bombard, Y., Holm, I. A., et al. (2015). Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *The American Journal of Human Genetics* 97, 6-21.
- Buchbinder, M., & Timmermans, S. (2011). Newborn screening and maternal diagnosis: Rethinking family benefit. *Social Science & Medicine, 73,* 1014-1018
- Crawford, G., Foulds, N., Fenwick, A., Hallowell, N., & Lucassen, A. (2013). Genetic medicine and incidental findings: It is more complicated than deciding whether to disclose or not. *Genetics in Medicine*, *15*(11), 896-899

- Egalite, N., Groisman, I. J., & Godard, B. (2014). Genetic counseling practice in next generation sequencing research: Implications for the ethical oversight of the informed consent process. *Journal of Genetic Counseling*, 23, 661-670.
- Escobedo, J., Guerrero, J., Lujan, G., Ramirez, A., & Serrano, D. (2007). Ethical issues with informed consent. *Bio-Ethics*, *1*, 1-8
- Federal Policy for the Protection of Human Subjects (Common Rule). http://www.hhs.gov/ohrp/humansubjects/commonrule/ accessed 12/1/2015
- Gene Tests. https://www.genetests.org/ accessed 1/10/2016
- Green, R. C., Berg, J. S., Grody, W. W., Kalia, S. S., Korf, B. R., Martin, C. L., et al. (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine*, *15*(7), 565-574
- Gutmann, A. (2013). The Bioethics Commission on incidental findings. *Science*, *342*, 1321-1323
- Hegde, M., Bale, S., Bayrak-Toydemir, P., Gibson, J., Bone-Jeng, L. J., Joseph, L., et al. (2015). Reporting incidental findings in genomic scale clinical sequencing—a clinical laboratory perspective. *The Journal of Molecular Diagnostics*, *17*(2), 107-116.
- Hull, S. C., & Berkman, B. E. (2014). Grappling with genomic incidental findings in the clinical realm. *CHEST*, 145(2), 226-230.
- Klitzman, R., Appelbaum, P. S., Fyer, A., Martinez, J., Buquez, B., Wynn, J., et al. (2013). Researchers' views on return of incidental genomic research results: qualitative and quantitative findings. *Genetics in Medicine*, *15*(11), 1-10
- Kole, J., & Feister, A. (2013) Incidental findings and the need for a revised informed consent process. *American Journal of Roentgenology*, 201,1064-1068
- Lohmann, K., & Klein, C. (2014). Next generation sequencing and the future of genetic diagnosis. *Neurotherapeutics*, 11, 699-707
- McGuire, A. L., & Gibbs, R. A. (2006). No longer de-identified. *Science*, 312, 370-371
- National Center for Biotechnology Information. Genetic Testing Registry (GTR). http://www.ncbi.nlm.nih.gov/gtr/ accessed 12/10/15

- New York State Department of Health. Genetic testing and screening in the age of genomic medicine.

  https://www.health.ny.gov/regulations/task\_force/reports\_publications/screeni
  - ng.htm accessed 2/20/2016
- Next Gx Dx. https://www.nextgxdx.com/ accessed 2/10/2016
- Office for Human Research Protections. (2009). Guidance on the Genetic Information Nondiscrimination Act: Implications for investigators and institutional review boards. <a href="http://www.hhs.gov/ohrp/policy/gina.pdf">http://www.hhs.gov/ohrp/policy/gina.pdf</a> accessed 1/7/2016
- Presidential Commission for the Study of Bioethical Issues. Washington, DC:
  Presidential Commission for the Study of Bioethical Issues; 2012. Anticipate
  and Communicate: Ethical Management of Incidental and Secondary
  Findings in the Clinical, Research, and Direct-to-Consumer Contexts.
  (October 2012 Report of the Presidential Commission for the Study of
  Bioethical Issues.
  <a href="http://bioethics.gov/sites/default/files/PrivacyProgress508\_1.pdf">http://bioethics.gov/sites/default/files/PrivacyProgress508\_1.pdf</a> Accessed
  1/7/2016.
- Presidential Commission for the Study of Bioethical Issues. Washington, DC:
  Presidential Commission for the Study of Bioethical Issues; 2013. Anticipate
  and Communicate: Ethical Management of Incidental and Secondary
  Findings in the Clinical, Research, and Direct-to-Consumer Contexts.

  (December 2013 Report of the Presidential Commission for the Study of
  Bioethical Issues.

  <a href="http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate">http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate</a> PCSBI 0
  .pdf. Accessed 1/7/2016.
- Reinke, T. (2015). Transforming health care delivery into a learning health care system. *Physician Leadership Journal, November/December,* 12-17
- Rigter, T., Henneman, L., Kristoffersson, U., Hall, A., Yntema, H.G., Borry, P., et al. (2013). Reflecting on earlier experiences with unsolicited findings: Points to consider for next-generation sequencing and informed consent in diagnostics. *Human Mutation*, *34*(10), 1322-1328.
- Roche, M. I., & Berg, J. S. (2015). Incidental findings with genomic testing: Implications for genetic counseling practice. *Current Genetic Medicine Reports*, *3*, 166-176
- Ross, L. F., Saal, H. M., David, K. L., Anderson, R. R., the American Academy of Pediatrics, & American College of Medical Genetics and Genomics. (2013). Technical report: Ethical and policy issues in genetic testing and screening of children. *Genetics in Medicine*, 15(3), 234-241.

- Sherkow, J. S., & Greely, H. T. (2015). The history of patenting genetic material. Annual Review of Genetics, 49, 161-178
- Simon, C. M., Williams, J. K., Shinkunas, L., Brandt, D., Daack-Hirsch, S., & Driessnack, M. (2011). Informed consent and genomic incidental findings: IRB chair perspectives. *Journal of Empirical Research on Human Research Ethics*, *6*(4), 53–67
- Tacik, P., Guthrie, K. J., Strongosky, A. J., Broderick, D. F., Riegert-Johnson, D. L., Tang, S., et al. (2015). Whole-exome sequencing as a diagnostic tool in a family with episodic Ataxia Type I. *Mayo Clinic Proceedings*, *90*(3), 366-371
- The Genetic Information Nondiscrimination Act (GINA) (2008).

  <a href="http://ghr.nlm.nih.gov/spotlight=thegeneticinformationnondiscriminationactgina">http://ghr.nlm.nih.gov/spotlight=thegeneticinformationnondiscriminationactgina</a>

  accessed 11/29/2015
- US Department of Health and Human Services, Office for Human Research Protections (OHRP). (2009). What is informed consent and when, why, and how must it be obtained? <a href="http://www.hhs.gov/ohrp/policy/faq/informed-consent/what-is-informed-consent.html">http://www.hhs.gov/ohrp/policy/faq/informed-consent.html</a> accessed 12/5/2015
- US Department of Health and Human Services, Office for Human Research Protections (OHRP). (1993). Tips on informed consent. http://www.hhs.gov/ohrp/policy/ictips.html accessed 1/17/2016
- Weiner, C. (2014). Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research and direct-to-consumer contexts (December 2013 Report of the Presidential Commission for the Study of Bioethical Issues). *American Journal of Epidemiology, 180*(6), 562-564
- Wiley, L.K., Tarczy-Hornoch, P., Denny, J.C., Freimuth, R.R., Overby, C.L., Shah, N., et al. (2016). Harnessing next-generation informatics for personalizing medicine: A report from AMIA's 2014 health policy invitational meeting. *American Medical Informatics Association*, 23, 413-419
- Wolf, S.M. (2015). The new world of genomic testing, families and privacy. *Minnesota Medicine,* June, 32-34

## VITA

Sara Ann Fowler was born December 11, 1967, in Kansas City, Missouri. She was educated in local public and parochial schools and graduated from St. Teresa's Academy in 1985. She attended Ottawa University where she received the Honor of Distinction in 1999. Her degree was a Bachelor of Arts in Psychology.

After working for 5 years as a Research Assistant for an independent evaluator of federal-, state-, and philanthropically-funded education programs, Ms. Fowler began a master's program in general psychology at Avila University. She was awarded the Master of Science degree in Psychology in May, 2008. While at Avila, she held a Graduate Assistant position with the Vice-Provost of Academic Affairs.

In 2008, Ms. Fowler assumed a position managing the assessment of institutional learning outcomes and process for self-study to support university accreditation at Rockhurst University. In 2010, Ms. Fowler began employment at the Ewing Marion Kauffman Foundation where she assisted in founding a public charter school, managed a multi-million dollar grant portfolio, and served as interim director of a college scholarship program.

Ms. Fowler began work on her second master's degree in Fall of 2014. Upon completion of her degree requirements, Ms. Fowler plans to continue her career in research and to pursue opportunities in clinical research and translational medicine.

Ms. Fowler is a member of the American Psychological Association.