Individualizing The Informed Consent Process for Whole Genome Sequencing:

A Patient Directed Approach

by

Katherine Hunt

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Graduate Supervisory Committee:

J. Benjamin Hurlbut, Co-Chair
Jason Robert, Co-Chair
Donald Northfelt
Karin Ellison
Gary Marchant
Jane Maienschein

ARIZONA STATE UNIVERSITY

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ABSTRACT

Whole genome sequencing (WGS) and whole exome sequencing (WES) are two comprehensive genomic tests which use next-generation sequencing technology to sequence most of the 3.2 billion base pairs in a human genome (WGS) or many of the estimated 22,000 protein-coding genes in the genome (WES). The promises offered from WGS/WES are: to identify suspected yet unidentified genetic diseases, to characterize the genomic mutations in a tumor to identify targeted therapeutic agents and, to predict future diseases with the hope of promoting disease prevention strategies and/or offering early treatment. Promises notwithstanding, sequencing a human genome presents several interrelated challenges: how to adequately analyze, interpret, store, reanalyze and apply an unprecedented amount of genomic data (with uncertain clinical utility) to patient care? In addition, genomic data has the potential to become integral for improving the medical care of an individual and their family, years after a genome is sequenced. Current informed consent protocols do not adequately address the unique challenges and complexities inherent to the process of WGS/WES.

This dissertation constructs a novel informed consent process for individuals considering WGS/WES, capable of fulfilling both legal and ethical requirements of medical consent while addressing the intricacies of WGS/WES, ultimately resulting in a more effective consenting experience. To better understand components of an effective consenting experience, the first part of this dissertation traces the historical origin of the informed consent process to identify the motivations, rationales and institutional commitments that sustain our current consenting protocols for genetic testing. After understanding the underlying commitments that shape our current informed consent

protocols, I discuss the effectiveness of the informed consent process from an ethical and legal standpoint. I illustrate how WGS/WES introduces new complexities to the informed consent process and assess whether informed consent protocols proposed for WGS/WES address these complexities. The last section of this dissertation describes a novel informed consent process for WGS/WES, constructed from the original ethical intent of informed consent, analysis of existing informed consent protocols, and my own observations as a genetic counselor for what constitutes an effective consenting experience.

DEDICATION

I dedicate this dissertation to my parents, David and Judith Hunt.

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CHAPTER 1

INTRODUCTION

Bill Miller is a 28-year-old science reporter working on an article about the implications of whole genome/exome sequencing on the Affordable Care Act. He works at *The Washington Post*, and has been with the newspaper for about a year. He owes over $75,000 in student debt incurred while earning his master's degree in journalism from Northwestern University. He recently married his college girlfriend, Melinda. Melinda is 25 years old and works part-time as a freelance photographer. She brings $25,000 in student debt to the marriage. The couple has been married for eight months. They are considering starting a family in a little over a year so that they can take some time to pay off their student debts.

Through his research on whole genome/exome sequencing, Bill becomes intrigued with the technology and the implications of this technology on personal health care. His fascination reaches the point where he decides that he must learn about his genetic make-up and he persuades his editor to extend the deadline for his article to allow him to write about his own experience undergoing whole genome sequencing as part of his article. Bill even persuades Melinda to undergo sequencing as well, not as part of his article for the newspaper, but simply because he knows that she is concerned about her own health risks based on her family history, and he believes the sequencing would provide her with information and possible reassurance for future health risks. In addition, he argues they would learn information about any possible risks for genetic conditions that might affect their future offspring.

Genome sequencing is a new technology designed to analyze most of a human genome in order to identify genetic alterations. A human genome is the complete set of DNA inside our cells. DNA is made up of four bases: adenine (A), thymine (T), guanine (G), and cytosine (C) (Strachan & Read, 1999). These bases are paired together on the DNA molecule. The process of sequencing an entire genome involves scanning and identifying the exact order of the approximate 3.2 billion base pairs in a human genome (Nussbaum, McInnes, & Willard, 2001). Whole genome sequencing (WGS) sequences the entire genome (all the bases) and whole exome sequencing (WES) sequences the genes that express proteins (known as exons). A gene is a section of DNA bases. A human genome contains approximately 22,000 genes (E. Green, 2013).

WGS and WES were introduced into clinical medicine around the year 2010 (Lifton, 2010) (Ashley et al., 2010) and sequencing was initially used to help medical oncologists identify more targeted chemotherapy agents for patients with advanced cancers that no longer respond to traditional chemotherapy drugs (Diamandis, White, & Yousef, 2010). The process of WGS and WES in oncology care involves sequencing a tumor genome and comparing the DNA sequence of the tumor to the corresponding DNA sequence of the individual's hereditary genome, to better understand the genetic changes that cause a cancer to continue growing despite multiple treatments (Plon, 2011). Whole genome sequencing is also used in clinical medicine to assist physicians with obtaining a better understanding of a complex disease which is likely hereditary, but for which single-gene testing has been unable to identify the underlying genetic mutation (Lupski et al., 2010). At this time, only a small percentage of healthy individuals seek out WGS/WES to learn about possible disease susceptibilities.

After Melinda agrees to undergo genomic sequencing, Bill contacts a clinical laboratory to inquire about their whole-genome sequencing services. He finds a company that offers a preventative genome analysis for adults, designed to identify specific disorders commonly screened for in newborn and carrier testing as well as a predisposition test evaluating risk factors for a number of known and well described hereditary conditions. The company agrees to sequence the couple's DNA and produce a report for each of them. The fee for the sequencing one individual is $9,500, but the cost was reduced for Bill and Melinda because the company knew they would gain some publicity from the story. *The Washington Post* paid for the balance of the total fee. The genomic testing protocol requires that a licensed physician discuss the consequences of genomic testing with interested individuals and order a sample collection kit so the blood sample can be collected at a physician's office. A physician signature is required on the test requisition form and results are released only to the ordering physician.

Bill contacts his brother-in-law (his sister's husband) who is a plastic surgeon, and asks if he would order the test for both him and Melinda. His brother-in-law agrees and arranges to have the sample collection kits sent to his office. Bill and Melinda go to the office together to have their blood drawn and sign a three-page consent form. Bill carefully reads the consent form but feels that the form did not contain any new information. Because of the research he has done for his article about the implications of undergoing WGS, he believes he is prepared to learn about his genomic make-up. Melinda accompanied Bill somewhat reluctantly to the office and signs the form without reading it completely because she was late meeting a potential client.

Bill and Melinda's results were delayed by two months (results are typically available in 90 days) due to issues with processing the samples in the laboratory, but after about five months, Bill receives a phone call from his brother-in-law's office that the results are back. The receptionist in his brother-in-law's office emails Bill a copy of both his and Melinda's results. The couple decides to look at the information together on a Sunday afternoon when they are both home and know they would not be interrupted.

The process of sequencing a human genome takes more than three months on average to complete because, instead of searching for only one genetic alteration in one gene (known as single gene testing), WGS and WES search for thousands of possible alterations amongst the 3.2 billion base pairs in a genome. Researchers who are working to understand the implications of the process predict individuals will carry between 20,000-40,000 possible structural variants in one genome (Chen et al., 2012) (The 1000 Genomes Project Consortium, 2010). What is important to understand about these 20,000-40,000 variants is that many of them are not always related to a disease, but instead may be part of the normal variations found between all people: Other variants are themselves not enough to cause a particular disease, but are only one of multiple variants necessary for the disease to occur. In addition, some variants require environmental insults to trigger the cascade of events that lead to the beginning of a disease process (Mueller & Young, 2001) (Cirulli & Goldstein, 2010). At this time, the implications for possible disease risks are not well understood for many variants identified through genome sequencing, but researchers believe that someday many, if not all of these variants will be better understood (E. Green & Guyer, 2011).

In the meantime, the dilemma for laboratories performing genomic sequencing is whether to report uncertain variants uncovered in sequencing a genome, and if so, which variants should be reported: those with a possible association for increased risks for a particular disease or only the variants with a known risk for a particular disease? The variants, which have been confirmed to have a known link to a described hereditary disease, I will refer to throughout the remainder of this document as deleterious mutations. Because many variants, with an unknown disease association, may be associated with a disease at some point in the future, how will an individual who was found to carry the variant before it was fully understood, be re-contacted with the updated information and if they are re-contacted, who is responsible for re-contacting the individual? The other question to ask: should the individual be re-contacted at all?

Beyond the issue of identifying thousands of variants with unknown associated disease risk factors is the fact that there are currently over 4,000 described hereditary conditions (McKusick, 2013). When an individual elects to undergo WGS or WES, it is not known how many variants or deleterious mutations and corresponding genetic conditions each person will be identified with at the conclusion of the sequencing process. Several major academic centers have reported their experiences with sequencing over several hundred individuals and predict that on average, most individuals will carry at least one hundred deleterious mutations (Ormond, Wheeler, Hudgins, Klein, & Butte, 2010). Without a specific clinical indication of a possible hereditary condition based on medical history or family history suggestive of a hereditary condition, it is unknown which of the 4,000 hereditary disorders each individual undergoing sequencing will be diagnosed with at the completion of genome sequencing.

Because Bill and Melinda submitted their samples as a couple, the laboratory created a report combining the first set of results. The first set of results is categorized as carrier testing and report mutations for any autosomal recessive conditions they might pass along to their offspring. The term autosomal recessive refers to the fact that an individual who is a carrier of the disease is typically not going to be affected with symptoms of the condition, but if their partner is a carrier of the same disease, their children have a 25% chance to be affected (Nussbaum et al., 2001). Melinda was found to be heterozygous (defined as carrying only one mutation) for three different genetic conditions: Tay-sachs disease, Gaucher's disease and cystic fibrosis. Tay-sachs disease and Gaucher's disease are both genetic conditions more commonly diagnosed in the Ashkenazi Jewish population (Mueller & Young, 2001). Melinda was raised Catholic and her family always believed that her ancestors were from France and England. Sharing the fact that her family might have Jewish heritage would be difficult for Melinda, given her family's strong Catholic faith. Melinda is torn about whether she should reveal this information to her parents fearing the information will cause family tension.

Bill also tested positive for a mutation for cystic fibrosis. Because Melinda and Bill both carry one mutation for the same condition, they learn that with every future pregnancy, there is a 25% chance they will have a child born with cystic fibrosis. Carriers of a CF mutation are also predicted to have between a 2% to a 23% chance to develop symptoms of chronic pancreatitis. Pancreatitis is inflammation in the pancreas and symptoms of chronic pancreatitis include upper abdominal pain, indigestion, and weight loss (Behrman & Fowler, 2007).

The next set of results was compiled separately from the carrier screening results and summarizes their individual genome sequencing findings. Melinda tested positive for a mutation for familial amyloidosis, a multi-system adult-onset, autosomal dominant disorder. The symptoms of amyloidosis differ according to the specific mutation identified in a family but typically include carpal tunnel syndrome, neuropathy, gastrointestinal issues (alternating bouts of constipation with diarrhea) and progressive heart failure (Sekijima, Yoshida, & Tokuda, 2012). The only viable treatment option for some patients with familial amyloidosis is a liver transplant, but not all forms of this genetic disease will respond to a liver transplant (Sekijima et al., 2012). Melinda's father died young, at age 52. In the years before his death, he suffered a variety of health issues and complained of pain and numbness in his extremities, lost over 25 pounds and ultimately died from heart failure. While the cause of his symptoms were never determined, Melinda now suspects that her father died from amyloidosis as his symptoms match the description of this condition. She becomes concerned she is destined to suffer the same fate as her father.

Melinda's genomic analysis also included pharmacogenomics results. Pharmacogenetic testing predicts individual variation in drug response based on specific genomic markers (Mills, Voora, Peyser, & Haga, 2013). Melinda's pharmacogenomics analysis reveals she carries a variant in the genes that control the production of the CYP2D6 enzymes. CYP2D6 enzymes are responsible for metabolizing approximately 25% of all medications, including many of the common antidepressant medications (Hicks et al., 2013). Melinda's specific variant leads to an over production of enzyme resulting in a rapid breakdown of the medications metabolized by the CYP2D6 enzymes.

Therefore she is predicted to respond poorly to normal doses of medications metabolized by these enzymes. This information is very useful to Melinda because she has tried several different types of antidepressants over the last several years, none of which were effective in treating her depression.

Melinda has a strong family history of cardiovascular disease and was hoping to learn about her genetic risk factors for heart disease. The report from the laboratory stated her risk for cardiovascular disease was no greater than the general population risk. Melinda did not find this information very helpful because she was unclear what a person's general population risk is and how this risk relates to her strong family history of heart disease. Melinda is uncertain whether the laboratory knew about her family history of heart disease and thought that perhaps without her family history information, her genetic test results would not be accurate. She feels frustrated that she did not have a better understanding of how the genomic test determined her disease risks. Specifically, she did not understand what type of health information genome sequencing could provide versus what type of information it could not provide? She began to question the accuracy of her results as well as the validity of the company.

Bill's individual genome results report he is positive for variants known as SNPs (single nucleotide polymorphisms) that might increase his background risk for prostate cancer. Bill's father and his maternal grandfather were diagnosed with prostate cancer later in life. The type of genetic variants Bill was found to carry were identified through genome wide association studies (GWAS). GWAS look at common variants associated with hundreds of diseases and traits. When a specific variant is found to occur repetitively in hundreds to thousands of individuals with the same disease, then it is more

likely to be associated with that disease. There is great skepticism amongst genetic researchers about the validity of the association of SNPs to common diseases, as most scientists believe that the SNPs are not enough by themselves to cause a disease, because environmental exposures also significantly contribute to the manifestation of a disease (Offit, 2008). Recent findings suggest that less commonly identified rare variants are more likely to be linked to common diseases providing conflicting information on the role SNPs play in complex disease processes (Cirulli & Goldstein, 2010). Because the findings from genome-wide-association studies are continuously being revalidated, the laboratory commented in their report that the information regarding Bill's prostate cancer SNPs will be updated in the future and it is Bill's responsibility to contact his physician to learn about any changes to the data available about the risk factors from carrying this variant.

Bill was hoping to learn whether he was at an increased risk for a hereditary neurological condition known as Huntington's disease. He became worried about being affected with this condition while writing an article about the financial burden of incurable diseases for *The Washington Post*. His research for this article included spending several days with a woman who was taking care of her husband in the late stages of Huntington's disease. Bill learned first hand what a devastating disease this was, with profound psychological, neurological and physical symptoms. Even more shocking to him was the fact that the average age of onset of symptoms was between 35 and 44 years, with an average lifespan of only fifteen years once the symptoms of the disease begin (Warby, Graham, & Hayden, 2010). Bill also witnessed the tremendous financial and emotional toll of this disease on the entire family, and learned about the

tragic fate of this gentleman's two children, who were also found to carry the same genetic mutation for Huntington's disease. Both children were predicted to experience the same symptoms as their father. Bill's genomic report did not include information about Huntington's disease, yet he was concerned enough about his potential risk for this disease that he planned to contact the company and ask if they were certain he does not carry the mutation for Huntington's disease.

While WGS and WES are capable of sequencing many of the known important genes in our genomes and capable of identifying many of the known mutations for a large majority of hereditary diseases currently defined, neither test is capable of identifying ***all*** the known mutations and therefore identifying all the genetic diseases currently described (Ormond et al., 2010). Most laboratories offering WGS and WES report they are able to sequence approximately 97% of the genes with known functions (exons) in our genome. The ability to find a variant and/or mutation in the exons is estimated to be 90% (Bick, Chao, Cho, & Cohen, 2013). In other words, not all of the exons in a genome can be sequenced and approximately 10% of the time, the sequencing technology will not be able to identify a specific variant and/or mutation present within the exons. There are areas of the genome where WGS and WES cannot identify known mutations for well described hereditary conditions: there are also many unknown hereditary conditions for which WGS and WES will not be able to identify the causative mutation, since the disorder and corresponding genetic mutation for the disorder have not been well defined at this point (Feero, Guttmacher, & Collins, 2008).

The same week the couple received their results Melinda learned that she was 12 weeks pregnant. Because Melinda is a freelance photographer she does not carry any

health insurance. After the couple got married, Bill had intended to add Melinda to his insurance policy at work, but never got around to it. Bill has no life insurance policy yet. Given his young age and the fact he and Melinda had no children, he figured he had more time to look into his options for life insurance policies. Bill is now wondering if their genome results will make it difficult for Melinda to obtain health insurance and whether his genomic test results must be reported on a life insurance application and if so, how this will affect his premiums? Melinda and Bill need to quickly figure out how to obtain health insurance for Melinda so she can establish care with an obstetrician.

After reviewing their results together, Melinda becomes very emotional and is angry with Bill for talking her into participating in one of his projects for work. The joy she hoped to experience during her first pregnancy is overshadowed by her fear that the baby she is carrying could be affected with cystic fibrosis and potentially, also affected with the same condition she tested positive for, familial amyloidosis. She searches frantically online for doctors' offices where she can discuss prenatal testing options. She wants to determine if her baby will be born with either of these conditions. After reading about the various options for prenatal diagnosis, she quickly becomes distraught again when she learns that prenatal testing could result in the loss of her pregnancy. Melinda and Bill do not know whom to contact to ask for help with the overwhelming amount of information about their individual genomes that was suddenly thrust upon them, in the midst of learning about Melinda's pregnancy.

Could Bill and Melinda have been better prepared for their genomic information? How could this scenario played out differently? Should it have played out any differently? Were Bill and Melinda harmed in any way? If so, who is at fault for not

providing more information to Bill and Melinda about the consequences of their sequencing? Should the blame to be placed on Bill's brother-in-law for not fulfilling his legal and ethical obligations as a physician to ensure Bill and Melinda were properly informed? Was it the laboratory's responsibility to better inform the couple about what to expect and ensure the couple was more prepared for the information before undergoing sequencing? Should the onus be placed on Bill for not taking the time to better understand some of the consequences of whole genome sequencing? Bill is a science reporter, who has been researching the technology of genome sequencing and therefore, one could assume that he would have understood the potential implications for undergoing genome sequencing including better understanding the consequences of learning about disease they may or may not exhibit symptoms for in the future. He should have conceivably understood the potential for health insurance discrimination after genetic testing as well as the possibility that life insurance or long-term care insurance would also be affected by a positive genetic test result.

Perhaps it would be unfair to fault this couple for not understanding the possible emotional responses they experienced when reviewing their results, if neither one fully comprehended what kind of information the test would reveal. Who could or should be responsible for informing the couple on how to prepare themselves psychologically and financially, for the type of genomic information they could expect from genome sequencing? Do the Millers have a strong enough legal argument to successfully file a lawsuit against the laboratory for failure to warn them about the financial and psychological harm that resulted from undergoing whole genome sequencing?

How can medical providers adequately prepare individuals for all the possible type of results available after undergoing WGS or WES, as well as discuss the possible medical, psychological, and psychosocial implications of learning information about an unknown number of genetic risk factors?

The traditional practice of informed consent is the point in clinical care when individuals are informed of all the possible implications from undergoing a specific test, diagnostic procedure or medical treatment. Informed consent is obtained before the recommended test, procedure or treatment is ordered or initiated. Along with providing information about a specific test to individuals during the consent process, the consent process was designed to allow time for individuals to ask questions or request additional clarification about the information provided to them, to be sure they fully comprehend the implications to their own health, and in the case of genomic testing, the implications to family members. The third component of the traditional informed consent process is for the individual to be given an opportunity to decline the test recommended by their physician. Although informed consent is an institutional requirement at all hospitals and medical clinics across the United States, and a requirement for all medical research studies in the world, the process itself may not fulfill the underlying ethical obligations it was designed to achieve.

Informed consent practices in medical research and clinical care evolved from the same ethical principle of autonomy; and one intent of informed consent is to fulfill ethical obligations of fully informing, respecting and engaging individuals in medical decisions about their own health, and the decision to participate in a clinical trial. The implementation of informed consent into clinical care and medical research, historically

occurred at the same time, but the practices of informed consent differ due to underlying differences in the legal objectives between the two consent protocols. The legal emphasis of informed consent practices in clinical care is to inform individuals of the underlying risks, benefits and limitations of a recommended test/procedure/treatment. The legal emphasis of informed consent practices in medical research is to ensure research participants know they are "research subjects". Chapter two describes the divergence of these two practices and explores the similar reason both practices do not always fulfill the underlying ethical obligations. The complexities of undergoing genome sequencing have challenged the informed consent practices and in chapter four I discuss how this technology blurs the distinction between clinical informed consent and research informed consent practices.

There is considerable focus at this time in medicine (both in clinical care and medical research) on how to obtain informed consent for WGS/WES. The informed consent process for WGS/WES is burdened by the vast amount of potential genomic information generated from sequencing, as well as the large degree of uncertainty surrounding the potential medical implications of the results from WGS/WES. The informed consent process is also burdened by unknown utility for how or whether genomic information should be used in the medical care of individuals undergoing sequencing; and unknown implications for the relatives of individuals undergoing sequencing. These are the issues researchers and clinicians are discussing while working to create informed consent protocols for individuals seeking WGS/WES (van El et al., 2013). The fact that current informed consent protocols do not fulfill the ethical

obligations of the informed consent process is an issue that is not being considered in the design of new informed consent protocols for WGS/WES.

As a genetic counselor, I have been privileged to work with individuals and families, like Bill and Melinda, who are considering genetic and genomic testing. My experiences in the field of genetics for over 18 years inspired me to pursue further research and study in the area of medical informed consent to find ways to improve upon the informed consent process. I have witnessed the failures of informed consent in medical care through many of my interactions with individuals undergoing genetic and genomic testing and these experiences motivate me to deepen my understanding of the intent of informed consent in an effort to develop methods to improve informed consent practices, especially now, as the field of medical genetics is grappling with the complexities of whole genome and whole exome sequencing.

The goal of this dissertation is to describe the rationale and ongoing motivations for sustaining traditional models of informed consent for genetic testing; to analyze the effectiveness of these traditional models and the applicability of the traditional models to WGS/WES, in order to better understand how to create a more effective informed consent process for individuals considering WGS/WES. This dissertation culminates with a novel proposal of an informed consent process for WGS/WES designed to fulfill the ethical obligations of informed consent and respond to the complexities of WGS/WES, resulting in a more effective consenting experience for individuals undergoing WGS/WES and the medical professionals obtaining consent.

The original contribution achieved from this project is to provide the medical professionals and scientists who are currently enmeshed in the process of sorting through

the complexities of how to adequately consent individuals considering WGS/WES a new perspective for how to think about the informed consent process. It is my hope that by thinking about informed consent differently, a new approach towards the informed consent process can be achieved for WGS/WES, which will result in a more effective informed consent process for both patients and the medical providers who are consenting individuals. A secondary contribution achieved from this project is to present a novel method for obtaining informed consent for WGS/WES which both improves upon existing informed consent protocols and provides opportunities to integrate the technology of WGS/WES into our current health care model.

This dissertation begins with an ethnographic review of the practices and effectiveness of informed consent in clinical medicine and informed consent practices for genetic testing. The next chapter (chapter two) begins with a historical review of the legal rulings and the corresponding ethical obligations that provide the rational for informed consent mandates in medical research and clinical care. The historical review of the legal incorporation of informed consent into clinical care is drawn from the accounts of the legal proceedings published in textbooks and journal articles. The review of the ethical evolution of informed consent is drawn from accounts in bioethics textbooks and journal articles describing the failure of medical research studies to protect and respect the rights of medical research subjects. In chapter two I describe the motivations for creating informed consent practices in medicine, to better understand the fundamental intent of informed consent from both a practical and ethical standpoint.

The subsequent chapter (chapter three) continues the exploration of the rationale for informed consent practices in medical care as it relates specifically to genetic testing.

To illustrate the evolution of informed consent practices, I review components of genetic testing protocols (defined in professional genetics literature) to demonstrate the ways genetic testing challenged existing informed consent protocols and restructured these early informed consent practices. After establishing the foundation for the rationale, integration and perpetuation of informed consent practices for genetic testing, chapter three concludes with a description of the effectiveness and ineffectiveness of the traditional informed consent practices for genetic testing; the examples of effective and ineffective informed consent practices for genetic testing are drawn from journal articles, textbooks and clinical experiences working as a genetic counselor. I provide my own analysis of informed consent practices for genetic testing by comparing these current informed consent protocols to the original intent and ethical motivations for creating informed consent protocols described in chapter two; and explore the reasons current informed consent protocols for genetic testing are not effective at fulfilling the ethical obligations of informed consent.

Building upon the fundamentals of the rationale and effectiveness or ineffectiveness, of current informed consent practices for genetic testing, I introduce the technology of genome sequencing in chapter four and describe the ways in which WGS/WES produce a more complex set of consequences to the individual undergoing sequencing, and new challenges to the traditional informed consent process. After reviewing the complexities of the technology, I describe current proposals identified in the literature and obtained from clinical practices, for how to tackle the informed consent challenges of WGS/WES. I conclude this chapter with a discussion about why existing informed consent protocols for genetic testing and the new proposals for how to obtain

informed consent for WGS/WES are not effective at fulfilling the goals of informed consent or addressing the challenges of this technology.

The second half of this dissertation describes novel solutions for how to respond to the complexities of WGS/WES and improve upon existing informed consent protocols. The solutions presented in chapters five and six are drawn from the historical summary of the original ethical obligation of informed consent practices in medical care (described in chapter two) and the analysis in chapter three on which components of traditional informed consent protocols are effective at achieving the ethical goals of informed consent. In chapter five, I outline the solutions for how to more effectively fulfill the ethical and legal obligations of informed consent. These solutions are describe in four principles drawn from the original intent of informed consent (both from a legal and ethical perspective), and based on my own clinical experiences for what constitutes an effective consenting experience for individuals undergoing WGS/WES. The ways in which these four principles have the potential to create an informed consent process that is more effective than current informed consent protocols are explored at the conclusion of chapters five and seven.

Chapter six describes each step of a novel informed consent process for WGS/WES, which is shaped by the four principles discussed in chapter five. The first objective of chapter six is to demonstrate the process of a novel informed consent protocol for WGS/WES by providing examples of how an individual would be consented, including explicit descriptions of each step of the informed consent process. The second objective is to explain how this novel informed consent process is more

effective at fulfilling the ethical and practical obligations of informed consent while also capable of addressing the complexities of WGS/WES.

Chapter seven presents a model for how to incorporate informed consent into the multiple systems of WGS/WES. The systems of WGS/WES include, the individual undergoing sequencing, physician(s), the sequencing laboratory, the ancillary medical services within the health system (health insurance companies, electronic medical record systems, and pharmacies), the individuals' family and other support networks (friends and online support groups) and medical research studies. In chapter seven, I describe how the consent process discussed in chapter six can be integrated into the systems of WGS/WES; and I review how the consenting process provides a framework for how to integrate genomic data reported from WGS/WES, into the larger medical model.

This dissertation concludes in chapter eight with a summary of the evolution of informed consent protocols, from the original implementation of informed consent into medical care, to the incorporation of genetic testing informed consent protocols, and new ways in which WGS/WES is challenging us to find a better approach for fulfilling the ethical obligation required from the consenting process. I review how the challenges of WGS/WES provide opportunities for researchers and medical practitioners to better understand why we have been consenting the way we have and whether this is the best way possible, or whether there might be alternative, more fulfilling ways in which to achieve an even better outcome from the informed consent process.

CHAPTER 2

CLINICAL AND RESEARCH MEDICAL INFORMED CONSENT

Informed consent was implemented into clinical medicine to protect patient rights and promote patient autonomy. In the clinical setting, informed consent is designed to move decisions regarding medical procedures and tests away from a paternalistic approach of medical decision making into a shared decision making model between the patient and their physician. The content of an informed consent conversation is based on legal requirements and is standardized to include a discussion of: the risks, benefits and limitations of a recommended treatment as well as alternative options and consequences of not pursuing a recommended treatment (Plaut, 1989).

The rationale for incorporating informed consent practices into the medical model is grounded in the philosophical argument of what "must" be done. The legal interpretation of informed consent is characterized by a "rule-based method" of providing information without undue coercion or influence (Goldstein, 2010). In this sense, informed consent is achieved by following rules and requirements that satisfy a specific institution's practice of health care (Behrman & Fowler, 2007). The combined rulings from two pivotal legal cases from the early and mid 1900s shaped the five principles that embody the current doctrine of informed consent in medical care; disclosure of: 1. the diagnosis and the nature of the patient's condition; 2. the nature and objectives of a recommended medical course of action; 3. the expected outcome and probability of success; 4. the attendant risks and benefits; and 5. all alternative procedures, and their respective risks and benefits, including the risks of not consenting to the recommended medical course of action (Sharpe, 1994). The four exceptions to standard informed

consent are: 1. emergency; 2. waiver, 3. incompetence and, 4. therapeutic privilege (Plaut, 1989).

Unlike the rule-based, legal interpretation of informed consent stating what "must" be done, the ethical grounding of informed consent is based on what "ought" to be done (Goldstein, 2010). The core ethical principle of autonomy embodies the principle of voluntary consent. Individual autonomy is defined by two core conditions: 1. freedom from controlling influences and 2. the capacity to make intentional choices (Hamilton & Bowers, 2003). The ethical applications of informed consent have primarily been linked to medical research. In medical research, informed consent evolved from an ethical concern over the abuse of human subjects enrolled in medical trials. The ethical principles justifying the rationale for proper utilization of informed consent in a research study evolved in parallel to the legal ruling resulting in the implementation of informed consent into clinical medicine. While there are similarities in the rationale and justification for legal and ethical interpretations of informed consent, the embodiment of the two approaches for informed consent have been accurately characterized by bioethicists Ruth Faden and Tom Beauchamp as two "common, entrenched, and starkly different meanings of 'informed consent'" (Faden & Beauchamp, 1986). These two interpretations of informed consent will be explored fully in this chapter and serve to set the backdrop for understanding the rational and ongoing motivations for sustaining traditional models of informed consent for genetic and genomic testing.

The first reported legal case, which predicated the eventual inception of informed consent as a legal requirement in medical care, *was Scloendorff v Society of New York in 1914* (*Schloendorff v. Society of New York Hospital*, 1914). The ruling in this case was in

favor of a patient who sued her surgeon for removing a tumor despite her wish not to have the surgery performed (Hamilton & Bowers, 2003). The judge for this case provided this argument for his decision: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages" (*Schloendorff v. Society of New York Hospital*, 1914).This case provides the first example of considering patient rights in health care decisions and thereby introduces concepts of self-determination and rationale decision-making into medical care (Hamilton & Bowers, 2003).

Informed consent became a requirement in medical research studies before the legal incorporation of informed consent into clinical care. Informed consent in medical research occurred in response to the atrocities revealed from the Nazi experiments during World War II and was supported by the rise of the human rights movement. The Nuremberg Trials in 1946 signify the first discussion about ethical treatment of research subjects in medical trials (Rothman, 2003). The Nuremberg Trials were the legal proceedings brought against the medical professionals and scientists conducting unethical medical experiments on prisoners in the concentration camps in World War II. The direct outcome of these trials was the creation of the Nuremberg Code in 1947. The Nuremberg Code is known as the first accepted code of ethics in medical research (Mascalzoni, Hicks, Pramstaller, & Wjst, 2008). The Nuremberg Code lists ten moral imperatives for conducting research studies; the first principle states, "The voluntary consent of the human subject is absolutely essential" (Rothman, 2003). On the heels of the publication of the Nuremberg Code, the National Institutes of Health (NIH) created a human subjects

review board known as Clinical Research Committees (CRC) in 1953. CRCs represent the first formal committee review process for evaluating the ethical components of medical studies. The format and role of CRCs became the model for today's Institutional Review Boards (IRB) (Stark, 2012).

Before the legal mandate of informed consent was implemented in clinical care, patients were expected to follow their physicians' advice without questioning. This was known as a paternalistic model of medical care. An example of the paternalistic model of medical care was the common practice for a physician to keep the knowledge that his patient had cancer from the patient, to protect the patient from psychological distress associated with the knowledge of their condition (Gefenas, Cekanauskaite, Tuzaite, Dranseika, & Characiejus, 2011). Physicians practicing medicine in the early 1900s were revered as the "medical expert" capable of unilaterally recommending a treatment plan to save or prolong the life of the patient; a paternalistic model of patient care was accepted in part because patients in the early 1900s respected physicians' expertise. Physicians practicing medicine in this era of medicine also believed patients were unable to reason when it came to medical matters (Stark, 2012). Edward Shorter wrote about the relationships between patients and physicians in his book, *Bedside Manners*, and describes physicians who practiced medicine between 1880 and the late 1940s as healers, who possessed inspirational qualities, capable of healing patients by offering explanations for why a patient was ill. According to Shorter, doctors in this era were friendly, attentive, humane and treated their patients respectfully (Shorter, 1985).

The landmark case resulting in the actual incorporation of the doctrine of informed consent as a legal requirement in medical care is *(Salgo v. Leland Stanford etc.*

Board of Trustees, 1957). In this case, the plaintiff, Mr. Salgo testified that his physician did not properly inform him about the potential risks from a surgery, which ultimately left him paralyzed. The court ruled that the surgeon was negligent as he had a duty to disclose all facts and possible risks resulting from the surgery. Only when the patient has all the facts can he make a fully informed decision (Hamilton & Bowers, 2003). The *Salgo* case resulted in the first legal requirement of informed consent into the medical care model in 1957. Since the California court introduced informed consent as a legal requirement, at least twenty-three states have adopted similar informed consent statutes (Andrews, 2001).

Around the same time the *Salgo* case ruled in favor of patient rights in medical decision-making and informed consent practices become mandated into clinical practice, patients in this country were beginning to lose confidence in their doctors as healers. Shorter explains that with the development of the first sulfa drug, sulfanilamide, in the 1930s, doctors began to practice medicine based on the medications that were available to treat ailments. The availability of novel, miraculous in some cases, new medications gave physicians a new sense of empowerment. Enamored with their ability to cure some diseases, physicians no longer practiced medicine the same way and the focus shifted from talking to patients about their illnesses, to prescribing medications (Shorter, 1985).

As patients and doctors grew apart from lack of communication, patients lost trust in their physician's ability to heal. "By the end of the 1960s, doctors noticed they were dealing with a new kind of patient, one unwilling to accept doctor as priest, or medicine as series of holy rites" (Shorter, 1985). Shorter's account of the changing dynamic between doctor as healer and patient as skeptic, coincides with the initial legal

proceedings brought against physicians in 1957, resulting in our current informed consent mandates. Informed consent practices implemented into medical care reflect patients' dissatisfaction with the lack of communication between doctors and patient about medical treatment plans and options for treatment. Echoing the same theme as Edward Shorter, physician and law professor Jay Katz wrote about the lack of conversations between physicians and their patients; Dr. Katz is well known for his quote; 'hospital rooms before the 1970s have been portrayed as silent worlds' (Stark, 2012).

The lack of communication between physician scientists and research subjects was demonstrated in medical research studies throughout the 1960s and 1970s. In 1964, an article was published in the journal *Science,* describing the research violations of a study conducted at New York's Jewish Chronic Disease Hospital. This widely cited study describes lack of informed consent practices when two physicians admitted that they injected 22 patients (some who were diagnosed with cancer and some who did not have cancer) with cancer cells, without obtaining consent from the patients (Langer, 1964). The same year this research trial was exposed for its ethical violations, the World Medical Association updated the Nuremberg Code with a set of recommendations for medical research practices that was less restrictive for the contemporary medical researcher who knew "right from wrong" (Mascalzoni et al., 2008).

The 1960s proved to be a disappointing time in medical research, as Dr. Henry Beecher revealed abuses within the medial profession in 1966. Dr. Beecher is known as the physician who bravely published an essay in *The New England Journal of Medicine,* describing 22 examples of "unethical research" carried out by his colleagues at renowned universities (Beecher, 1966). Feeling the pressures from these abuses, the government

acted again; in 1966, Surgeon General Stewart, announced to the research community, that hospitals, universities and other research institutions needed to establish human subjects review boards if they wanted to receive federal funding (Stark, 2012).

Also in 1966, the premiere research institute in the United States, the National Institutes of Health, began to encourage researchers to obtain a signed form from research participants as evidence of consent (Stark, 2012). Researchers however, were very resistant to follow this mandate arguing that they had other ways to document consent, such as making notes in the medical charts. They fought to employ their professional discretion for determining what constitutes evidence that study participants knew they were participating in a research study. Despite the fact researchers claimed to know what was best practice for informed consent, it was well known that conversations between researchers and research subject were ephemeral during the 1950s and 1960s (Stark, 2012).

A second horrific example of the failure of informed consent in medical research occurred in 1972 when researchers failed to protect the autonomy of research participants in the infamous Tuskegee Syphilis Study. In this study, researchers were observing African-American men diagnosed with syphilis without offering or even discussing the availability of a treatment for syphilis once it became available. The purpose of the study was to document the "natural course of the disease," but the men were never made aware of the fact they were participating in a study and further, they were never told that treatment for their condition was available at the time they were being observed (Faden & Beauchamp, 1986). The study aim was prioritized over the rights of the study participants. This case illustrates additional failure of the moral imperatives from the

Nuremberg Code and the role of the Clinical Research Committees charged with overseeing the ethical components of research studies.

As the medical research community was struggling to uphold the moral principles they were required to embody, the informed consent mandate in clinical care was undergoing its own challenges. The initial mandate requiring informed consent from the *Salgo* case created the legal principle of informed consent, but left room for physicians to use their own "discretion" for how much information about risk from a procedure, is necessary to disclose to their patients (Hamilton & Bowers, 2003). Therefore, further legal cases resulted in additional requirements for informed consent protocols. The case that settled the issue for how much information regarding risks related to medical procedures is necessary to reveal in the consent process was *Canterbury v. Spence, 1972 (Canterbury v. Spence, 1972).* The court again ruled in favor of a patient who became paralyzed after a laminectomy because the physician was negligent for failing to properly inform the patient on all possible risks which could result from his surgery. The outcome of this case signified a shift from an emphasis on the physician's professional judgment about the extent of risk information necessary to discuss surrounding a medical procedure to a legal requirement where it became necessary to disclose enough information about risk to enable a "reasonable person" to make an informed choice (Hamilton & Bowers, 2003).

The informed consent dialogue expanded after the *Canterbury v. Spence* case with additional requirements that information provided to patients by a physician should not only be comprehensive enough to allow for a patient to withhold consent, but also stated in language the patient can understand (Ormond, Banuvar, Minogue, Annas, & Elias,

2007). Additional medical legal cases throughout the 1970s and early 80s continued to increase patient rights and involvement in their own medical decision- making. Further requirements of the informed consent process include the expectation that physicians assess how well the patient understands the information he is hearing throughout the consenting process, to ensure the patient is making a fully informed decision. Additionally, physicians need to establish that their patients are not under duress at the time of consenting and that in their role as a medical expert, they do not influence or pressure their patient into making decisions they might feel are the best for the patient. In other words, the physician presents the discussion about a recommended course of treatment and all possible risks, in an unbiased manner, such that the ultimate decision for a recommended course of action is a voluntary act (Lidz, 1983).

Discussion about patients' rights and the protection of subjects in medical research was reenergized in the United States again in the 1970s, following the previous decade of disappointing ethical failures in medical research trials. An extension of the Surgeon General's suggestion that a human subjects review committee should be established for proposed research trials in the U.S. in 1966, became a requirement by the government with the National Research Act in 1974 (Stark, 2012). Several noteworthy outcomes from this legislation included; empowerment for the federal government to regulate research studies conducted on people, and the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published a statement of principles on research ethics known as the Belmont Report ("The Belmont Report," 1979). As with the

Nuremberg Code, the first ethical principle of the Belmont Report is respect for persons. The Belmont Report states that respect for persons incorporates two ethical convictions: first that; 'individuals should be treated as autonomous agents' and second, that; 'protection should be provided for persons with diminished autonomy' ("The Belmont Report," 1979). Bioethicists have touted the legal mandate embodied within the National Research Act, as a triumph for the protection of research subjects (Stark, 2012).

The current ethical criteria all informed consent protocols must fulfill are based on the international guidelines from the Nuremburg trials and the American Belmont report. These guidelines are well described and delineated in research literature and required as part of federal guidelines and state laws for both clinical care and as a component of medical research studies. The core principles of informed consent are the same for clinical medicine as well as for medical research studies. The legal mandate of informed consent protocols in clinical care resulted in the creation of a checklist of required information to be disclosed with the patient by the physician recommending the procedure, test, or treatment. Ethical obligations for informed consent in clinical care are based on the principles of promoting patients' self-determination and rational decision-making about their medical care (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Making Health Care Decisions, 1982). The core ethical principle of autonomy is at the heart of the idea of self-determination (Goldstein, 2010).

The ethical rational for informed consent in medical research protocols is the same as informed consent obligations in clinical care, although the focus in medical research is towards ensuring that study participants are fully aware of any possible risks

from participating in a study. The voluntary nature of participation in a medical research study is emphasized more strongly in the research informed consent process compared to clinical informed consent protocols. Laura Stark describes the aims of informed consent, as portrayed by medical researchers, to get potential research participants to recognize themselves as "human subjects" (Stark, 2012). The ethical requirement of a conversation between study participant and researcher, might never occur because this requirement is instead met by the 'network of declarative bodies' (IRBs), which serve to evaluate the ethics of medical research studies on behalf of the patient (Stark, 2012). The failure of medical research studies at fulfilling the ethical obligations will not be explored in this dissertation since the focus of this dissertation is on the effectiveness of informed consent protocols in clinical medicine, in particular for genetic/genomic testing. I felt it was important to mention the struggle of medical research studies at fulfilling the ethical obligations of the informed consent process since, throughout the remainder of this dissertation, I discuss how and why informed consent protocols in clinical medicine, fail to fulfill the ethical obligations of the consent process. After exploring the reasons informed consent practices in clinical medicine have failed to fulfill the ethical obligations in chapter three, I come back to this rationale for why informed consent practices in clinical research have failed to illustrate how the failures between clinical and research consent are similar.

The fact that informed consent practices in clinical care struggle to fulfill the ethical obligations of the consent process was highlighted in the 1980s when a second federal commission was created in response to the perceived failure of the informed consent process, as well as the lack of regard for the informed consent mandate. In

response to criticism by physicians that the informed consent process is burdensome to medical practice as well as ineffective for medical decision-making, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research issued a report in 1982. In the summary of this report, the Commission wrote that informed consent is not just a legal imperative, but an ethical imperative as well. The Commission reminded physicians that an "ethically valid" consent process includes a conversation in which physicians treat the patient with respect and reach a mutual decision regarding health care decisions (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Making Health Care Decisions, 1982).

Throughout this dissertation, I explore why our current informed consent protocols fail to fulfill the ethical obligations summarized in the 1983 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. This historical background describing the legal and ethical obligations of informed consent practices provides the necessary foundation for building a discussion in the next two chapters for how genetic and genomic testing introduce new complexities for informed consent practices in clinical care. These informed consent practices were struggling to fulfill the underlying ethical obligations they were meant to protect before more complex testing became available. I reference Bill and Melinda's genome sequencing experience to answer the question of whether our current informed consent practices succeed in providing adequate information to individuals about genetic and genomic tests. I also discuss whether current informed consent practices provide an opportunity for individuals to fully explore their understanding of genomic testing and

time to discuss individual goals for undergoing genomic testing. Finally, I explain why all of these components are necessary to fulfill both the legal and the ethical obligations of informed consent mandates.

To illustrate how informed consent is achieved in clinical practices today and to delineate the complexities of informed consent practices in genomic medicine, the next chapter introduces the field of genetics into clinical care and describes how informed consent protocols from the 1950s were rewritten to address the challenges of genetic testing. The last section of chapter three provides an analysis of the perceived effectiveness and ineffectiveness of current informed consent practices in medical genetics.

CHAPTER 3

EVOLUTION AND EFFECTIVENESS OF INFORMED CONSENT PRACTICES FOR GENETIC TESTING

The field of genetics was first described in 1905 by an English biologist, William Bateson. In a letter to a colleague, Bateson used the word genetics as a noun to define a new field of science with a focus on the medical and biological study of heredity and variation (Bateson, 2002). The creation of the field of genetics occurred on the heels of the suggestion in the late 1800s by Francis Galton: "eugenics" is the study of "agencies under social control that may improve or impair racial qualities of future generations, either physically or mentally" (Baker, Schuette, & Uhlmann, 1998). William Bateson's definition of a new field in genetics provided a scientific method to fulfill the ideals of eugenics; improving the human condition through the identification of hereditary factors that contribute to social and behavioral conditions such as poverty, crime and mental illness (Baker et al., 1998).

The eugenics movement gained notoriety in this country with the creation of the Eugenics Records Office in 1910 at Cold Springs Harbor, Long Island (Baker et al., 1998). The Eugenics Records Office was partially funded by the Carnegie Institute of Washington's Department of Genetics and was the country's central training facility for eugenics. Eugenic field workers gathered data about human traits by drawing family pedigrees. This data was used by the Eugenics Records Office to influence families' reproductive decisions after they had a child affected with a birth defect or abnormality (Stern, 2012). The Eugenics Records Office disbanded in 1939, primarily from criticism

over their methods of data collection, which was reported to be scientifically unsound because the studies were influenced more by political and social agendas than science (Baker et al., 1998). This criticism was less about the eugenics movement and more about the politics behind the studies conducted at the Eugenics Records Office. Despite the closing of the Eugenics Records Office, the eugenics movement continued to gain momentum in the U.S. and across Europe and Scandinavia in the early 1900s. By the late 1920s, 23 of the 48 states in the U.S. passed laws mandating sterilization of the "mentally defective." In 1939 it was legal to euthanize the "genetically defective" resulting in the death of over 70,000 individuals with a hereditary disorder (Baker et al., 1998).

Shortly before the Nuremberg Trials began, three heredity clinics were founded in the United States in 1941; the three clinics were instituted at the University of Minnesota Dight Institute, the University of Michigan Heredity Clinic and Wake Forest University (Stern, 2012). These clinics were all founded on eugenics principles and supported the sterilization laws from the 1920s and 1930s. Throughout the 1940s, 1950s and 1960s many geneticists did not object to the characterization of applied medical genetics as the practice of eugenics (Stern, 2012).

During the mid-1940s however, diagnostic testing to confirm a suspected hereditary disorder was not yet available and therefore conversations about genetic risk factors were based on empirical observations. Human geneticists worked to assess the relationship between actual or potential medical conditions and genetic inheritance based on family pedigree analysis (Stern, 2012). This practice constitutes the emergence of genetic counseling. In 1947, Sheldon Reed, a geneticist and director of the Dight Institute at the University of Minnesota, was credited for coining the term "genetic counseling"

(Kessler, 1979). Reed however, began to distance himself from eugenics ideas by counseling families on genetic disorders and providing risk information in a non-directive manner to empower individuals to make decisions most consistent with their cultural, religious and personal values (Stern, 2012).

The next decade began with a pivotal scientific breakthrough by James Watson and Francis Crick who published their understanding of the physical structure of the DNA molecule in 1953 (Watson & Crick, 1953). A second pivotal breakthrough for genetics was the identification of the correct number of chromosomes reported in 1958 by Tijo and Levan (Dave & Sanger, 2007). The discovery of the DNA molecule and the corresponding relationship to human chromosomes, signify the beginning of the modern era of genomic medicine in which genetic testing was used as a tool for establishing or confirming a suspected genetic diagnosis. By the late 1950s it was possible to characterize and diagnose common chromosomal alterations such as Trisomy 21 (Down Syndrome), Klinefelter's Syndrome (47, XXY) and Turner Syndrome (45,X) (Baker et al., 1998).

The ability to diagnose chromosomal alterations and some biochemical genetic disorders made it possible to diagnose a fetus in utero (through an amniocentesis procedure) with a possible genetic condition or chromosomal alteration, by the late 1960s (The NICHD National Registry for Amniocentesis Study Group, 1976). An amniocentesis procedure is performed by inserting a long thin needle into the amniotic sac to withdrawal amniotic fluid containing fetal cells (Mueller & Young, 2001). The cells are then cultured in a laboratory and examined for a particular condition. While the first amniocentesis procedure was performed in the 1800s to remove excess fluid from

the amniotic sac (Genetic Counseling Faculty, 1993), it wasn't until 1967 and 1968 that amniocentesis was performed during the mid-trimester of a pregnancy (15-17 weeks gestation) to diagnose a fetus with a metabolic disease or chromosomal alteration (The NICHD National Registry for Amniocentesis Study Group, 1976).

With the availability of prenatal testing, couples were faced with options surrounding what to do with the genetic information they learned about their unborn baby. These options were often not straightforward and further, the amniocentesis procedure itself has the potential to result in serious complications to the pregnancy, such as a miscarriage (The NICHD National Registry for Amniocentesis Study Group, 1976). A medical specialist trained in the area of genetics and counseling was needed to discuss: risks from the amniocentesis procedure, risks for having a child affected with a genetic disorder, and to provide information about a hereditary condition and help couples handle the difficult information they are learning, to facilitate the process of making decisions about the pregnancy or help them adjust to the new diagnosis.

The fact is genetic testing provides information with a more complicated set of medical consequences than most other medical tests. The diagnosis of a genetic disorder is problematic for most individuals because a genetic disease is a permanent condition. Many genetic conditions are untreatable and, most significantly, a hereditary condition is transmittable to future offspring and has possible implications for other blood relatives. Lori Andrews, a prominent lawyer specializing in policy issues surrounding genetic testing, has published extensively about implications of genetics diseases on individuals and on society. In the 2001 *Washington University Law Quarterly* she summarizes the social and psychological implications of genetic testing: "Genetic testing generates

information unparalleled in scope compared to other areas of medicine. People can learn that, decades later, they will suffer from an untreatable disorder, that they have an increased risk of cancer, or that their children have a one-in-four chance of dying of a serious disorder in childhood. The impact of this knowledge can affect people's lives by challenging their self-image, by altering their cultural and social identity, by changing their relationships with family and friends, and by causing them to think about their life, health, and responsibilities in new ways" (Andrews, 2001). Researchers estimate that approximately 30% of patients with a genetic condition will adjust in maladaptive ways after learning about the possible risk of being diagnosed with a hereditary disorder or the knowledge they have a genetic disease (B. Biesecker & Erby, 2008). In response to the need for this type of medical provider, along with the anticipation that additional types of genetic testing would be available in the future, the field of genetic counseling was created (Stern, 2012).

The first graduate program in genetic counseling was established in 1969 at Sarah Lawrence College in Bronxille, New York (Marks & Richter, 1976). The training in this profession was designed as a terminal master's degree with two years of graduate training focusing on the medical, psychological and social aspects of a genetic disease (Baker et al., 1998). Genetic counselors today are trained to present complex technical and scientific information in understandable language and assist individuals in the process of determining the most appropriate next steps (Stern, 2012). Genetic counseling is essentially a comprehensive in-person method for obtaining informed consent before undergoing genetic testing. The original definition of genetic counseling proposed by the American Society of Human Genetics (ASHG) in 1975 is cited in many publications:

"Genetic counseling is a communication process, which deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family. This process involved an attempt by one or more appropriately trained persons to help the individual or family to: (1) comprehend the medical facts including the diagnosis, probable course of the disorder, and the available management, (2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives, (3) understand the alternatives for dealing with the risk of recurrence, (4) choose a course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder" (American Society of Human Genetics Ad Hoc Committee on Genetic Counseling, 1975).

The core tenet of the genetic counseling process is to promote autonomy and place a priority on the need(s) of an individual and/or their family, over society's concerns (Kessler, 1979). The practice of genetic counseling was purposefully designed to reject the traditional paternalistic model where the physician advises a patient on a particular course of care without incorporating the values of the patient. This goal is fundamentally in line with the legal obligations and the ethical underpinnings of informed consent.

For approximately twenty years after Watson and Crick published their description of the double helical structure of the DNA molecule, genetic testing was used infrequently and primarily to diagnose a chromosomal alteration or some biochemical

diseases. Hereditary traits however, had already been classified over a hundred years before Watson and Crick's publication in 1953. In 1865 Gregor Mendel presented the findings of his breeding experiments on garden peas (Mueller & Young, 2001). While Mendel's work did not receive much attention in his time, genetic diseases were initially defined as Mendelian because they occur statistically, in fixed proportions among offspring of the same parents. Initial descriptions of Mendelian inheritance patterns for genetic diseases were simplistic by modern comparisons, because most disease were thought to be caused by a single genetic mutation, otherwise referred to single-gene or monogenic disorders. These inheritance patterns were known as: autosomal dominant, autosomal recessive and X-linked (Nussbaum et al., 2001). In clinical medicine, before the availability of molecular genetic testing (the ability to identify genetic mutations in the laboratory by analyzing a gene with a known association to a hereditary disease), a pattern of inheritance was based on observation of the clinical expression of a particular phenotype in family history (Stern, 2012). Initially Mendelian disorders were catalogued in several large volumes of a textbook known as *Mendelian Inheritance in Man (MIM)*. The first print edition of *MIM* was published in 1966 and featured 1,486 entries; most were clinical descriptions of suspected hereditary conditions (Yakutchik, 2010).

The field of genetics evolved very rapidly after the development of recombinant DNA technology in 1972 (Nussbaum et al., 2001). Recombinant DNA technology made it possible for scientists to isolate fragments of DNA and analyze these fragments for possible variants, or mutations. The isolation of these fragments allowed for an efficient method of replicating DNA to search for genetic mutations (Nussbaum et al., 2001). With improved technologies, scientists became better equipped to appreciate more

sophisticated molecular causes of genetic disorders. This resulted in the description of more complex types of monogenic inheritance; mitochondrial inheritance, imprinting and expanding triplet repeat disorders (Nussbaum et al., 2001). The number of Mendelian disorders grew so rapidly that the written volumes of *Mendelian Inheritance in Man* was replaced with an online version in 1985, now known as Online Mendelian Inheritance in Man (OMIM) (McKusick, 2013).

Due to the rapid increase in the number of genetic tests available by the early 2000s, as well as the variety of adult onset or predisposition genetic tests available, the National Society of Genetic Counselors revised the original definition of the purpose of genetic counseling in 2005, to reflect a broader scope of practice for genetic counselors. "Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates; interpretation of family and medical histories to assess the chance of disease or occurrence or recurrence; education about inheritance, testing, management, prevention, resources and research; counseling to promote informed choices and adaptation to the risk or condition" (National Society of Genetic Counselors, 2013).

Informed Consent Practice Guidelines for Three Types of Genetic Tests

The non-directive practices embraced by the genetic counseling profession are reflected in the informed consent protocols written for individuals considering genetic testing in the 1970s and 1980s. To maintain a safe ethical distance from the eugenics movement, professionals in medical genetics labored extensively over the informed

consent protocols to be followed before ordering any type of genetic test, to ensure both the legal and ethical obligations of informed consent were achieved.

These practice guidelines serve as a mechanism for genetic counselors to fulfill their professional obligations to promote autonomy while educating individuals about the issues associated with genetic testing and have been widely published in the literature. The reasons the informed consent protocols for genetic testing have been more widely published than any other type of informed consent protocols in medicine is because decisions made about undergoing a genetic test are multiple and sequential; decisions are based on probabilities and uncertainties; genetic testing has broader implications for family; genetic testing can disrupt an individual's sense of themselves and their place in the world; and genetic testing can lead to worries over insurability, job stability and relationships. Medical geneticists define an ideal type of informed consent process for genetic testing as a non-directive genetic counseling session that includes pre and post-test counseling (Burgess, 2001). The genetic counseling process is truly an oral dialogue and many in the field of genetics will criticize a written document as the only required method of informed consent.

This section will summarize the practice guidelines for three types of informed consent protocols in genetics to provide a thorough background of current genetic counseling practices before exploring the effectiveness of these practices. The application of these practices for WGS/WES will be explored in the next chapter. The three types of consent protocols I will review are pre-disposition genetic testing, carrier screening in the prenatal setting, and genetic testing for hereditary cancer syndromes. Throughout the discussion of these three informed consent protocols, I will explore the rationales offered

for why informed consent protocols for genetic testing have been so widely studied and scrutinized in the literature, compared to other standard medical consent protocols.

The first type of genetic test most relevant to the consenting issues also pertinent to WGS/WES is pre-disposition genetic testing or genetic testing for adult onset disorders. Pre-disposition testing is controversial within and outside the field of medical genetics. Many argue that it is futile to test for any condition that may or may not affect someone in the future and for which no treatment is readily available. Huntington's disease has been the most widely cited disorder for which pre-disposition testing remains problematic and controversial (Sharpe, 1994). Huntington's disease is an adult onset neurodegenerative disorder that affects individuals at the prime of their lives, between 35 and 44 years old (Warby et al., 2010). The symptoms of Huntington's disease are so significant that an affected individual can expect to have to quit their job, change how they communicate and interact with family and friends and require assistance eating, and taking care of themselves at the end of life. Most tragically, until treatment options become available, an affected individual has to prepare for an eventual demise within fifteen to eighteen years of diagnosis. The suicide rate for individuals with Huntington's disease is four times higher than what is reported in the Caucasian population in the United States (Andrews, 2001).

Even when individuals who are at risk for Huntington's disease learn they do not carry the mutation, they often suffer from "survivor's guilt," and a loss of who they are. Many report only thinking of themselves as being at-risk for this devastating disease. After learning she tested negative for the HD mutation, one at-risk woman stated; 'If I'm not at risk-who am I? (Andrews, 2001).' Others assume they have the genetic mutation

and live as though they are positive (even before undergoing genetic testing). One gentleman, believed he was destined to have this disorder, and made decisions not to commit to a long-term relationship, get married or have children, to ensure he would not pass the genetic disorder to subsequent offspring. He spent frivolously, and ran up credit card debts. Later in life he elected to undergo testing only to learn that he did not have the genetic mutation associated with Huntington's disease (Andrews, 2001).

The reason Huntington's disease became one of the first adult onset genetic tests available was because the testing was highly specific, and because the relatives of an affected individual often had very strong feelings about whether they wanted to know if they would be affected with the condition in the future. To prepare individuals to learn whether they inherited the genetic mutation associated with Huntington's disease, detailed guidelines for obtaining informed consent were published in the *American Journal of Medical Genetics* (AJMG) in 1994. The requirements for informed consent for Huntington's disease are summarized in the AJMG article written by Neil Sharpe who wrote that informed consent should include a discussion of: 1. "Potential limitations in securing test results, 2. Explanation "that linkage or mutation analysis is not synonymous with a diagnosis of HD", 3. "That at this time, neither linkage nor mutation analysis provides an ability to predict the phenotype", 4. "Of the potential psychological responses that may occur both before, during, and after, testing", 5. "Of the potential effects of a positive or negative result on the patient's family, including emotional and psychological effects of a positive or negative result on the patient's family, including emotional and psychological distress that may be experienced by relatives, 6. "of the potential hazards, including stigmatization, insurance and employment discrimination", 7. "of the patient's

attitude toward sharing the diagnostic results". Sharpe's article also emphasizes the importance of allowing enough time before scheduling the genetic test so the patient may consider the information and make a thoughtful and certain decision (Sharpe, 1994). The process of undergoing genetic testing for Huntington's disease is so controversial, that many clinicians and researchers who work with individuals at risk for Huntington's disease recommend that everyone who elects to undergo genetic testing must follow a specific protocol including a neurological evaluation, a psychiatric evaluation and genetic counseling (Wexler, 1990) (Quaid, 1992). This recommendation is a means to ensure the informed consent process has been fulfilled due to the perceived high stakes of learning about such a devastating genetic disorder.

Returning again to our couple, after receiving the reports from their whole genome sequencing studies, Bill and Melinda spend the next six months scheduling appointments and meeting with various medical professionals. Melinda was informed she carries an adult onset disease, familial amyloidosis, which is similar to Huntington's disease in that her symptoms would not begin until she was in her 40s, or 50s or older. Melinda and Bill met with specialists in cardiology, hematology and neurology. She underwent numerous blood and imaging tests to determine whether she was beginning to exhibit symptoms of this condition. This couple spent thousands of dollars on the medical expenses incurred from her multiple physician visits. From a psychological standpoint Melinda could not stop worrying about whether she would suffer the same early demise as her father. She starts to wish she was not pregnant and became convinced she had already passed both of her genetic mutations to her baby.

If Melinda had undergone a more comprehensive informed consent process, she would have understood before she underwent genomic sequencing the fact that she might test positive for an adult onset disorder, with many implications for her health. She would have understood that obtaining health insurance would have been a good idea in the event she did test positive for a medical condition requiring many diagnostic tests and physician appointments. In addition, she also might have been better prepared psychologically for learning about a disorder that would have a significant impact not only on her life, but for her future children as well.

An individual who tests positive for a deleterious gene mutation, whether the mutation increases the probability to have an affected child with a hereditary condition, or whether the mutation causes symptoms in the individual himself, will often struggle with self-esteem and experience a loss of sense of who they are. Psychologist Seymour Kessler spent his career researching the psychological ramifications of being diagnosed with a genetic disorder. He writes that the process of undergoing the diagnosis of a hereditary disorder is; "ego-threatening in that the counselees must expose themselves to the risk of being shown to be flawed, imperfect, defective or abnormal" (Kessler, 1979).

The possible emotional reactions after learning about a hereditary condition can also have implications on intimate relationships between spouses or with a significant other. Because a genetic diagnosis often infers risks for future offspring to also be affected, couples considering having children are forced to reconcile their desire to have a child with the potential risks to pass a hereditary condition to their child. The ability to reproduce and give birth to a healthy child has long been an acknowledged and expected rite of passage into adulthood. Some couples elect to end a relationship after undergoing

genetic screening and discovering both partners are carriers for the same autosomal recessive disorder. A research group in Greece conducted a study in which they surveyed couples' decisions regarding marriage after learning information about their carrier status for sickle cell anemia. This study reported that 20% of sickle cell carriers broke off their engagement after learning their partner also carried the same sickle cell mutation (Andrews, 2001).

Cystic fibrosis is the most common autosomal recessive disorder in the United States and United Kingdom (Nussbaum et al., 2001). Carrier screening for this condition was initially controversial for two reasons; the first is because the disease does not result in developmental or intellectual delays, parents who had a child affected with CF advocated against carrier screening during pregnancy because of their fear many couples would terminate an affected pregnancy; and second because the detection of mutations in the CF gene was initially quite challenging due to the sheer number of mutations present in the gene. Nevertheless, a multidisciplinary group of scientists, medical professionals, and parents of children with CF, convened in 1998 to explore the process for implementing carrier screening into clinical practice. This group addressed such issues as patient and provider education, and laboratory requirements and protocols for follow-up after a positive screening result (Haddow, Bradley, Palomaki, & Doherty, 1999). The recommendations for how to implement carrier screening into prenatal practice were published in the *Journal of Medical Screening* in 1996 and provide justification for why and how to implement genetic screening into prenatal care clinics (Haddow et al., 1999).

One interesting aspect of this publication is that informed consent is only briefly mentioned in the article. There is one small paragraph devoted to this topic entitled, 'How

will consent be obtained?" The authors agreed that while carrier screening for cystic fibrosis is performed under research protocols, then "written informed consent" is, as a rule, required. They went on to write that when carrier screening for cystic fibrosis transitions from the "research stage" into "clinical practice," then informed consent should be performed by a health care provider and involve an oral consent process (Haddow et al., 1999). The authors did not offer the details of what should be discussed during this oral consent process, but one could assume the protocol would follow the recommendations for informed consent for other hereditary disorders.

One rationale I suggest for why the details of the oral consent process was not discussed in this article is because the researchers who were interested in implementing cystic fibrosis carrier screening into clinical practice were biased by their own motivations of promoting carrier screening for this common disease. The inherent bias of this group of experts slanted the recommendations towards the implementation of the process, without considering or more fairly remembering, that individuals have a choice of whether they want to undergo screening, and this choice should always be emphasized or at least available to parents throughout the screening process.

The third type of informed consent protocol most commonly cited in the literature is a protocol for genetic testing for hereditary cancer syndromes. A hereditary cancer syndrome is another type of adult-onset disorder, which significantly increases an individual's risk for cancer above the general population risk. Hereditary breast and ovarian cancer syndrome (HBOC) is the model disorder for this type of informed consent protocol. HBOC syndrome is caused by a mutation in one of two tumor suppressor genes, BRCA 1 and BRCA 2, known collectively as BRCA. These genes were isolated in 1994

(Miki et al., 1994) and 1995 (Wooster et al., 1995) respectively. A mutation in either gene is associated with an increased risk for breast, ovarian and other cancers (Barnes-Kedar & Plon, 2002).

To reduce increased risks for breast and ovarian cancer, many women choose to undergo genetic testing before a diagnosis of either breast or ovarian cancer. When a woman tests positive for a BRCA mutation, she is faced with complex decisions regarding follow-up screening and surveillance or prophylactic surgical options. After learning about her positive BRCA result, one woman was quoted to say; "It felt as if there was a time bomb ticking away inside of me" (Andrews, 2001). Many other women who tested positive for BRCA 1 mutation reported experiencing psychological distress (Andrews, 2001). The diagnosis of HBOC creates a heavy emotional burden for women who are in their 20s and 30s, given the decisions young women are forced to deal with, such as whether to undergo risk-reduction surgery, or more frequent screening. Both options are likely to result in more stress and worry. Many women in their 20s or 30s have not yet married, and a positive BRCA result can cause additional complications with dating and finding a partner who will accept them despite their "genetic imperfections." Additionally, women who carry a BRCA mutation are recommended to undergo a preventative oophorectomy in their 40s (Barnes-Kedar & Plon, 2002) which further complicates decisions about whether to have children.

Shortly after the BRCA 1 gene was cloned, the NIH recommended genetic testing for HBOC is offered only under strict research protocols before allowing the test to become available in the clinical setting. It should be noted that this reaction to requiring that informed consent protocols be developed in the research setting before offering

genetic testing in clinical care, occurred in response to the development of most new types of genetic tests, such as Huntington's Disease, cystic fibrosis and now whole genome/exome sequencing. The NIH funded several studies in 1994 to investigate the ethical and psychological implications of cancer predisposition testing. A group of investigators established a task force to better understand the issues related to informed consent, both in the research and clinical arena for HBOC (Geller, Botkin, et al., 1997). The publications summarizing the findings from these research studies recommended the informed consent process include a discussion about women's personal beliefs and understanding of cancer.

A truly informed patient, according to a summary of several focus groups whose purpose was to assess women's attitudes towards informed consent protocols for BRCA 1 testing, should incorporate an assessment of women's perceptions about breast cancer risks, causes and treatment for cancer, into the pretest education part of the consent process. The individual obtaining consent should clarify any misconceptions women had about any issues related to breast cancer as well as incorporate women's values and experiences into the consenting dialogue. In other words, the consenter should ask the woman undergoing genetic testing what her understanding is of her risk for being diagnosed with breast cancer based on a positive genetic test result and clarify any inaccuracies or misconceptions about the accuracy of the test. In addition, a consenter should ask the woman undergoing genetic testing how she is feeling about undergoing genetic testing and ask the woman to share her experiences with a family member who might have been diagnosed with breast cancer and acknowledge her feelings throughout the consenting process (Geller, Strauss, & Bernhardt, 1997).

In anticipation of future genetic tests for other hereditary cancer syndromes and other adult onset genetic disorders, the informed consent protocols for HBOC were written as a model for informed consent protocols for other types of hereditary cancer syndromes. The central components of informed consent for hereditary cancer syndromes were published in the *Journal of the American Medical Association* in 1997 and include a discussion about; "the purpose of the test (including testing which is part of a research protocol), costs, turnaround time, and documentation of results, the predictive value of a positive, negative or indeterminate result, and corresponding cancer risk information (Geller, Botkin, et al., 1997)." Implications for possible cancer treatment and protocols for cancer screening and management if the test were positive, negative or indeterminate need to also be reviewed. Possible psychological reactions to the test results and implications to family members as well as a discussion about insurance and job discrimination concerns and protective legislation for those concerns are components to be addressed as well. As is true for all types of medical consent protocols, patients should have time to consider their options and be informed of their right to choose not to undergo testing as well as to delay testing until a future time (Ensenauer, Michels, & Reinke, 2005).

The American Society of Clinical Oncology (ASCO) published their recommendations for informed consent before ordering genetic testing for HBOC in 1996 and updated their recommendation in 2003. Both versions are greatly watered down when compared to the checklist published in the *JAMA* article in 1997 as they were written to address only the backbone of the informed consent process recommended by genetic specialists. ASCO recommends pre- and post-test counseling and suggests the

content of these session include a review of the medical options and consequence of test results on family members in the pre-test session; and a discussion about recommended follow-up and test interpretation in the post-test session (American Society of Clinical Oncology, 2003). The ASCO recommendations lack the requirement for detailed discussions about the psychosocial and psychological components associated with undergoing genetic testing stated in the genetic counseling protocols. This notable void creates a tension in the informed consent process for genetic testing between what is "minimally required" and what "should" be addressed. Ultimately, the justification for what to include while consenting a patient is based on the bias of the professional society or organization writing the consenting guidelines.

A review of the literature focusing on the rationale for informed consent in genetic testing as well as the practice guidelines for how to obtain consent, suggest that the methods for obtaining consent vary greatly based on who is performing consent, the expertise, experience, and communication style of individuals obtaining consent. Also time spent consenting the patient is variable. The reason for this variability is because, while multiple published guidelines for what should be discussed during an informed consent protocol are available, there is no standardized requirement for how to obtain informed consent before genetic or genomic testing. As a result, informed consent can be achieved in a conversation between the consenter and the patient in a shared decision-making format where patients and the consenter engage in a dialogue regarding options for testing, implications of testing and a discussion of how the results will affect medical care and what psychosocial and psychological consequences the results will have on the patient and their relatives. The length of the conversation and extent to which questions

are solicited by the consenter varies according to the amount of time allowed for the consent process and is largely determined by the consenter.

Another method for obtaining informed consent would be to ask a patient to read and sign an informed consent form, without engaging the patient in a dialogue and allowing time for the patient to ask questions and consider options. The published practice guidelines from professional genetics organizations state that written consent is not truly informed consent because individuals are not given the opportunity to ask questions, and engage in a dialogue about anticipated reaction to a positive or negative test result. What confounds the discussion at this point is that, by signing an informed consent paper, most institutions have fulfilled their legal obligation to promote patient autonomy because these informed consent documents are written to state that the inherent risks, benefits and limitations of the recommended test have been reviewed by a physician and that the patient has been given a chance to ask questions. Whether or not these issues were reviewed by the physician, evidence that informed consent was attempted and achieved is illustrated by the signed informed consent form. While a signed informed consent form provides a legal documentation that consent was achieved, there is no method for determining the degree to which the information was understood by the patient. Many laboratories require a signed document when a specimen is received, but according to most genetics professionals, this document does not guarantee informed consent was successfully obtained (Miesfeldt, Jones, & Cohn, 2000). Neil Sharpe is an outspoken critic of written consent. He believes the act of signing a paper provides no evidence that the patient has an understanding of the information they

received or were given time to ask questions and consider the potential risks and consequences of genetic testing (Sharpe, 1994).

Despite the criticism from genetic professionals over written consent, medical institutions and laboratories require only a signed informed consent form as evidence that consent was obtained. A written consent form often serves as documentation that the consent process took place and provides the patient with written information about the information discussed during the consent process. The tension between fulfilling the minimal legal obligations and fulfilling the ethical obligations for informed consent is a problem that has existed since the inception of informed consent practices for genetic testing in the 1960s.

Despite this tension, institutions continue to perpetuate the practice of informed consent for genetic testing by using the written consent form to satisfy the legal requirements for informing patients. The laboratory that performs genetic testing for hereditary breast and ovarian cancer syndrome requires all Medicare patients sign a consent form before undergoing genetic testing for BRCA 1 and BRCA 2 mutation analysis, but, if the patient is not a Medicare patient, then the informed consent signature is optional. The point is, Medicare patients may or may not have undergone genetic counseling, or engaged in an in-depth conversation with their physician, but as long as they sign the paperwork, their test is processed and paid for by Medicare. The same policy is in place for the commercial labs offering genetic testing for Huntington's disease. As long as the laboratory receives a signed informed consent document which states that the patient was offered genetic counseling and had an opportunity to have their questions answered before undergoing testing and acknowledge that the test is optional,

the test will be completed and results will be reported back to the ordering physician. Therefore, institutions offering genetic testing through a clinical practice defer to the laboratory conducting genetic testing to fulfill the legal obligation that consent was obtained.

The laboratories, in turn, trust that physicians have fulfilled their obligations for consenting a patient and can be entrusted to provide the appropriate follow-up counseling and recommendations once the results are returned from the lab. Medical institutions assume their physicians are competent and adequately trained in the area of genetics to provide consent. While informed consent documents must be scanned and recorded into the medical records before a surgery or minor medical procedure, there are no legal requirements for such documentation for the medical institutions that offer genetic testing. This legal requirement is mitigated by the fact that the laboratories where their patient samples are sent are obligated to fulfill the legal obligation of ensuring patients fully understand the ramifications of undergoing genetic testing vis-a-vis the signed informed consent document that accompanies the patient's sample.

Returning again to the case of our couple, Bill and Melinda, for whether legally informed consent was obtained. The laboratory met their legal obligations by providing a written consent document. The form states that WGS results might benefit healthcare decisions and that it might not benefit health care decisions, but no specific examples relevant to this couple are provided. The consent form also states results from WGS are similar to all other types of genetic tests, in that genomic results might have consequences to family members. Again, no global, hypothetical examples are provided on the form, or examples relevant to Bill and Melinda specifically. The possibility that

genomic information could lead to insurance, job or other types of discrimination is mentioned on the form, but, for details, the form states individuals should contact their physician or a genetic counselor.

Ethically, can it be argued that informed consent was obtained? The answer to this question ultimately depends on how medical professionals define their ethical obligations for obtaining informed consent. Some would argue that the ethical requirements of informed consent were appropriately met assuming the written consent explicitly reviewed the options for learning results and by stating that this type of testing is voluntary. Others would argue that to fulfill the ethical obligations of informed consent, the consenting process should be completed within a conversation between the consenter and the individual. A major component of the genetic counseling practice is an informed consent dialogue. If individuals are not referred for genetic counseling before undergoing genetic testing, it does not represent a violation of the legal requirement for informed consent.

The ethical obligation for a medical institution or laboratory to ensure that informed consent is obtained is, in reality, a conceptual ideal. The ideal consenting process is what is described in the literature through practice guidelines and professional recommendations. The oral consent process for genetic counseling is both well described and delineated in the literature. Professional training in the practice of genetic counseling is available as well as board certification requirements. There are however, no legal or ethical obligations for institutions to employee genetic counselors as the designated medical professional capable of performing informed consent and no legal obligation to guarantee those providing consent are competent. Despite published findings that the

most effective form of informed consent for genetic testing is that of an oral consent process (Burgess, 2001), there are no legal implications if genetic counseling is not made available to individuals undergoing genetic testing. As a result, the informed consent process prior to undergoing genetic testing including the extent of a consent conversation before undergoing genetic testing is highly variable between institutions and between laboratories.

Analysis of Informed Consent Practices in Medical Genetics

Since the inception of the legal requirement for informed consent in medical care, the informed consent process has been criticized as largely ineffective and more of burden to patient care than a benefit. Empirical research and clinical observations have reported that the informed consent process is an empty ritual where patients are given complex information they cannot understand and which ultimately does not impact their decision making process (Lidz, Applebaum, & Meisel, 1998). Physicians have expressed their frustration over the informed consent model and report that it is a waste of their valuable time. Further, many physicians believe that the consenting process produces the opposite outcome it is intended to in that patients ultimately make the wrong decisions surrounding their medical care (Lidz et al., 1998).

As Laura Stark points out, the *Salgo* case had only a symbolic effect on doctors' practices. She also alludes to the fact that in medical research, the institutionalization of the IRB process has perpetuated practices that change little over time because these practices came to be intuitive to their participants and required less justification and explanation over time (Stark, 2012). As I describe in the next several pages, this

explanation is similar to the explanation for why informed consent practices fail in clinical care as well, linking the two practices of informed consent together.

Informed consent practices for genetic testing have also been criticized for a variety of reasons. The ineffectiveness of an informed consent process for genetic testing has been blamed on the following issues: physician lack of knowledge and understanding about genetic diseases and risk probability, and likewise, inability for many patients to be able to understand risk information and apply statistical data to their own situation, especially while experiencing emotions associated with learning about the possibility of being diagnosed with a hereditary condition. Melinda's emotional reaction to her genomic test results is a good example. She was so overwhelmed with the fear that she might die from the same disease as her father, and with feelings of guilt over possibly passing on her mutations to her baby, that she had a difficult time coping and understanding the data presented in her genomic sequencing report. Melinda would have benefited from the opportunity to talk with someone during the informed consent session before deciding to undergo genome sequencing, about her fears that she might someday be affected with the same illness as her father, or pass along this genetic condition to her own children. The idea is that if she had an opportunity to express her concerns and fears before she learned her test results, she would have either been more prepared to hear the information, or she might have elected not to undergo genome sequencing at all. Finally, individuals vary in the ways in which they learn and communicate.

The reason that physicians and medical providers are blamed for the failure of the informed consent process for genetic testing is because several studies published on providers' knowledge about genetic disease, report that many physicians struggle with

understanding risk assessment and probability (Kegley, 2003)(Miesfeldt et al., 2000). The uncertainty in understanding and interpreting genetic test data often results in clinicians purposefully avoiding the discussion about important probabilities on the accuracy of the test or risk for a genetic disease (Metcalfe, Hurworth, Newstead, & Robins, 2002). In addition, incorrect information may be communicated to their patients about the genetic test results. One study reporting on the use and interpretation of genetic testing for familial adenomatous polyposis (FAP), an autosomal dominant hereditary colon cancer syndrome, concluded that 20% of physicians erroneously ordered genetic testing for this condition. Their findings also indicated that physicians misinterpreted the results in 31.6% of the cases (Giardiello, Brensinger, Peterson, Luce, & Hylind, 1997). In addition, physicians are criticized for not recognizing the standards of communication and counseling that are components of the informed consent process for genetic testing (Sharpe, 1997).

The National Coalition for Health Professional Education in Genetics developed a document on Core Competencies in Genetics for Health Professionals in 2007 (National Coalition for Health Professionals Education in Genetics, 2007). This document provides a comprehensive coverage of the necessary knowledge base a medical professional should have in genetics, however no mechanism is in place in our health care system to evaluate clinicians on their understanding and use of such competencies in everyday practice. As with published informed consent models, the written requirements for establishing competency do nothing for determining the level of competency of a provider consenting patient. There are also competencies written for medical geneticists and genetic counselors. The American Board of Medical Genetics (ABMG) requires that

physicians, PhD geneticists, as well as genetic counselors, master the communication skills necessary to; “elicit necessary information from the patient or family to reach an appropriate conclusion; “and “transmit pertinent information effectively, i.e., in a way that is meaningful to the individual or family (American Board of Medical Genetics, Inc, 1992). In addition, the ABMG, the Royal College of Physicians and Surgeons of Canada issue similar standards of care in medical genetics (Royal College of Physicians and Surgeons of Canada, 1992). These competencies and certification requirements do not guarantee the medical provider is capable of fulfilling these obligations, or even more concerning, that a medical provider is willing to fulfill his professional obligation to provide informed consent.

A consequence of the fact that physicians are critical of the informed consent process is that they do not respect the very process they are obligated to perform. This results in a consenting process that is often overlooked, abbreviated or performed incorrectly. In most cases, the act of consenting a patient occurs just before a blood or tissue or saliva sample from the patient is collected (Lidz, 1983). At this point, the decision to undergo genetic testing has already been made and the consenting process becomes just a formality. The responsibility for who should be consenting a patient is often not even considered since the signed consent form is all that is required to meet the legal and ethical obligations to verify consent was obtained. The exception to this situation is when a patient undergoes genetic counseling during which a formal informed consent process occurs. Outside of a designated genetic counseling consult, there is no consistently established time or “space” for consenting to occur before most patients undergo genetic testing.

A similar concern surrounding the effectiveness of the informed consent process for genetic testing is whether the patient understands the information provided to them. Research studies have reported that patients struggle with understanding genetic terms and risk information (Robert Klitzman, 2010). This fact places additional requirements on the consenters, who need to have the necessary expertise in genetics and an understanding themselves of the medical and psychological implications of a genetic condition, to be capable of explaining the information in a meaningful way to the patient. Variability of patient comprehension of science and mathematical probabilities requires a stratification of the scientific and mathematical information presented during informed consent sessions.

Another significant challenge to the informed consent process from the patient perspective is the fact that individuals vary considerably regarding their interest in learning about their own genetic makeup, along with how they respond to a positive or negative test result. Patients also differ widely for learning preferences and likewise, how they incorporate complex information into their lives and derive meaning from such information. Some researchers therefore advocate for the inclusion of individual decision-making styles into the design of informed consent protocols (Ormond et al., 2007).

The criticism of the informed consent process in medical care and genetic testing, stems from the inability to apply a legal doctrine onto a constantly evolving, interactive and complex medical decision making process that occurs when deciding whether or not to undergo genetic testing. Our current informed consent protocols provide no ability to factor in the inherent trait of uncertainty present in daily medical care into the model.

Katz has written, “The prevailing climate of professional conduct is first to pay lip service to uncertainty and then to proceed, while interacting with self and patients, as if uncertainty did not exist “ (Plaut, 1989). Genetic testing and the subsequent test results have an inherent component of uncertainty and whole genome sequencing is sure to offer more uncertainty than actionable and interpretable knowledge.

Other reasons the informed consent process for genetic testing has been found to be ineffective is the overwhelming burden for some when learning new statistical risks, while experiencing a range of emotions in response to the scientific information. Multiple studies report how patients are unable to correctly interpret and apply risk information to their own situation (Miesfeldt et al., 2000). The psychological implications of learning about a genetic diagnosis, confounds the ability to correctly understand and act upon risk information provided during pre-test genetic counseling. 21% to 75% of individuals do not remember or understand the information they received following a content-only orientated counseling session (Kessler, 1979). Therefore, for informed consent to be successful, many argue that medical providers or those providing the consent need to address the emotional issues when providing statistics and information about genetic conditions (Robert Klitzman, 2010).

I, along with others, blame the ineffectiveness of the informed consent process in both medical decision making and informed consent practices for genetic testing, on the fact that the informed consent mandate is being perpetuated as a legal doctrine based on underlying legal requirements, with no relevance to the realities of medical decision making (Lidz, 1983). The medical care of a patient, especially when considering a complex test such as whole genome sequencing is constantly changing and evolving.

Multiple decisions are required over time in patient care, but the process of informed consent was established as an event that occurs in one visit. Even some lawyers have agreed with this criticism arguing that despite the fact promoting patient autonomy was the driver for writing informed consent, the legal framework of the protocols fails to encourage individual values of patients (Goldstein, 2010). A member of Duke University's institutional review board summarized the current status of the informed consent in medical research in a recent *Nature* article; "Institutions use informed consent to mitigate their own liability and to tell research participants about all the things they cannot have, and all the ways they can't be involved (Hayden, 2012b)."

Is there really any way to measure the effectiveness of informed consent? What would be the outcome that would signify a successful consent process? Consider the fact that one woman who tested positive for a BRCA 1 mutation elected to undergo bilateral mastectomies to reduce her risk for developing breast cancer. Following her surgery she said, "I had wonderful counseling beforehand but nothing prepared me for the feeling of loss [and] of mutilation. A woman's breasts are very much tied up with the image she has of herself and however perfect the reconstruction you are aware they are not your own. It was far more emotionally traumatic than I had expected" (Andrews, 2001). This scenario really begs the question, is any form of consenting really capable of fully preparing patients for possible emotional responses to a positive genetic test result and the consequences on their lives?

Many believe there is no real medical benefit that can be measured from the informed consent process of genetic testing given the very fact that the testing is designed to determine whether someone will be affected with a hereditary disorder that cannot be

cured. Therefore, the effectiveness of the informed consent process in research studies has focused more on the psychological outcomes following genetic testing. A Canadian study on the effectiveness of the pre- and post-test genetic counseling sessions before Huntington's disease genetic testing, reported positive outcomes from the patients who underwent testing through this protocol. The positive findings included increased patient autonomy and improved emotional welfare (Burgess, 2001). Overall benefit reported from a thorough informed consent process for genetic testing are: increased sense of empowerment, improved understanding of a medical condition, and a sense of having more choices (Burgess, 2001).

Genetics professionals advocate for informed consent protocols that focus on the psychological consequences of a genetic diagnosis. They believe that if these issues are addressed appropriately, the medical provider has the possibility to intervene if necessary when someone is not adjusting appropriately to the information, and in turn positively encourage the individual as they adjust to the risk for or diagnosis of a genetic condition (B. Biesecker & Erby, 2008) (Robert Klitzman, 2010).

The precise nature of an effective informed consent process is difficult to define, as the goals of consenting are really determined by the individual who is undergoing consent. In other words, the consent process was designed on the principle of autonomy; every person has his own personal manner of dealing with a medical diagnosis and recommended treatment, etc. While a particular treatment plan might be based on standardized protocols, the reaction to the treatment plan will vary from patient to patient, thus the rationale for why informed consent was implemented into medical care. In

chapter five, I describe an informed consent process that is capable of responding to an individual's goals for undergoing WGS/WES.

In the meantime, the effectiveness of informed consent practices in medical genetics, as with other medical specialties, is legally achieved by a signed informed consent document. This signed form represents the minimal requirement of informed consent practices in clinical care and neither guarantees that consent was adequately obtained, nor that a conversation occurred between the consenter and the individual undergoing testing. The institutional requirement that a signed informed consent document is all that is necessary to demonstrate consent is achieved, when in fact a large part of the consent process is neglected, follows the pattern established with the creation of informed consent practices in medical care and medical research just reviewed in chapter two. This is the reason the practice continues to perpetuate without consideration of whether the practice of informed consent meets the ethical obligations it was written for.

As illustrated throughout this chapter, a signed informed consent form is not evidence the ethical obligations of promoting patient autonomy and informed decision making are accomplished. The next chapter describes how a more complex type of genetic test (WGS/WES) further challenges the already ineffective practice of informed consent. After reviewing the complexities of WGS/WES, I describe the proposed and current informed consent practices for WGS/WES and assess whether they achieve the ethical obligations of informed consent.

CHAPTER 4

HOW WGS/WES TECHNOLOGIES CHALLENGE EXISTING INFORMED CONSENT PROTOCOLS FOR GENETIC TESTING

As a more sophisticated understanding of single gene disorders was elucidated, scientists began to suspect complex genetic contributions to common diseases, such as cardiovascular disease, diabetes and cancer (Mueller & Young, 2001). The traditional assumption that genetics was a rare specialty in medicine began to fade as researchers started to identify underlying genetic etiologies for most common diseases. In 1987, the term "genomics" was coined and defined as: "the study of the functions and interactions of all the genes in the genome (Guttmacher & Collins, 2002)". The new appreciation of a genomic contribution to disease became the driver and rational for mapping a human genome. In 1988 the U.S. National Research Council of the U.S. National Academy of Sciences announced their support of a 15-year project to map the human genome to better understand and treat all diseases. The official funding for the Human Genome Project began in 1990 with an astounding budget of $200 million a year (Collins, Morgan, & Patrinos, 2003).

The Human Genome Project was completed ahead of schedule, and under budget with a total cost of three billion dollars (Collins et al., 2003). The reason for a more timely completion of the project was because of advances made in DNA sequencing techniques. DNA sequencing is the name of the technology used to sequence a DNA molecule and can be described in three simple steps: 1. Sample preparation: 2. Physical sequencing: and 3. Re-assembly of the sequenced DNA (Schadt, Turner, & Kassarskis, 2010). To better manage the 3.2 billion base pairs found on a single strand of DNA, the

first step in the sequencing process is to break up sections of the genome into multiple fragments that are more manageable for the process of sequencing. In many cases, these fragments are copied multiple times to have enough DNA sample to complete the sequencing steps. During the second step of the process, physical sequencing, each base pair of the fragment is read, one at a time. A read length is defined as the number of bases in a specific fragment. The third step in the process of sequencing is reassembly of the fragments creating a contiguous sequence of base pairs representing an individual genome. Bioinformatics software is a critical component of the reassembly process because it helps identify where to align overlapping reads.

The first generation of sequencing technology was developed by Frederick Sanger in 1975 and is known as the Sanger method or the chain-termination method (Schadt et al., 2010). The Sanger method was performed manually when the Human Genome Project began, but became automated during the project, which allowed for a more efficient and less expensive endeavor. Despite these advances, first generation sequencing is still more costly than current technology and is only able to produce read lengths between 800 and 1,000 bases (Meyerson, Gabriel, & Getz, 2010). In 2003, marking the fiftieth anniversary of Watson and Crick's publication on the structure of the DNA helix, Francis Collins and Craig Venter announced the completion of the first draft of a complete human genome (E. Green & Guyer, 2011). Seven years after the completion of the human genome project, the online version of Mendelian Inheritance of Man (OMIM), reported over 20,000 entries of genetic conditions (McKusick, 2013).

The ultimate benefit to humankind from mapping the human genome through the Human Genome Project was to fulfill the promise of individualized medicine.

Individualized medicine is defined as the ability to; tailor treatments for individual patients based on their own genomic profile; more accurately predict genetic risk factors for common diseases such as heart disease, cancer, diabetes and others; better understand individual susceptibility or response to infectious diseases and; determine the etiology for hereditary disorders with a known mendelian inheritance pattern, but a yet elusive genetic cause (Drmanac, 2011).

Once a complete human genome was mapped, these initial promises (many of which were published before the completion of the Human Genome Project) were still only promises. In reality, the hard work had just begun. That is, understanding the meaning of the sequence of our 3.2 billion base pairs and the function of the approximate 50,000 genes (now believed to be roughly 22,000 genes) and the biologic pathways of gene-gene and gene-environment interactions (Collins et al., 2003).

After sequencing a genome, the 3.2 billion base pairs need to be read, aligned and interpreted. The sequencing platforms produce a series of bases (A, T, C and G), also described as nucleotide reads which are reported, but just reporting a large number of base pairs is not informative. The data needs to be interpreted. The first step of data interpretation incorporates computational software programs which both instructs the laboratory where and how to string together the nucleotide bases. A gene is a series of bases strung together. Mutations are identified when the software detects a nucleotide that is out of order from what is expected, based on the template produced from the Human Genome Project.

Once the template is constructed, laboratories apply various types of bioinformatics software programs to each genome to identify variants or mutations. The

type of variant identified is based on the choice of the software analysis program and what kinds of variants the software is programed to identify. For example, if an individual was aware of a strong family history of colon cancer, the lab could then sort that person's genome data for the known variants associated with a hereditary colon cancer syndrome. Identifying the variants that cause a more common disease, such as heart disease or diabetes is a much more complicated process, because many of these variants have not been identified yet, and those that have been identified, may not confer a very strong association to a disease. In addition, variants suspected of being associated with a common disease have to be validated through numerous studies to convince scientists of its association. Whenever a suspected variant within a gene is identified, validation studies are performed to essentially prove that the variant is disease causing, versus a normal alteration, known as a polymorphism. From a biological standpoint, the progression of common disease is complicated by the fact that there are environmental factors and gene-gene interactions that work together to cause a disease (Cirulli & Goldstein, 2010). This type of data interpretation and the identification of rare variants that are less well defined complicate the process of reporting these findings.

Francis Collins and two other leaders of the Human Genome Project published an article in *Science* just after the announcement of the completion of the human genome mapping. This article urged biologists, leaders in science and academia, leaders in societies all over the worlds, as well as industry representatives, to collaborate in efforts to understand the data produced from the Human Genome Project and translate this information in a clinically applicable and useful manner (Collins et al., 2003).

In the year 2013, just ten years after the completion of the Human Genome Project, the medical community is introducing genome sequencing into patient care with great vigor. Despite this enthusiasm, many still argue that the promises widely published on the benefits of mapping our individual genomes are still just promises, with little practical implications at this time (Offit, 2008). Ignoring the naysayers, with the hope that whole genome sequencing will improve patient care, institutions around the world are becoming entranced with the possibilities of this sexy new sequencing. Whole genome sequencing and whole exome sequencing are currently offered in clinical settings at institutions across the world and incorporated into many research protocols. While the complete map of a human genome opened a window for the future utilization of WGS, second-generation sequencing, also referred to as next-generation sequencing, has essentially opened the door for wide access to WGS and WES.

Second-generation sequencing technologies apply the same steps in the DNA sequencing process as first-generation sequencing technology. The major differences between the two generations of sequencing technologies are accuracy, efficiency and cost (Meyerson et al., 2010). Second-generation sequencing became available in 2005 and consists of several different platforms (or methods), offered by various commercial laboratories. There are minor differences between each platform concerning the technology, but fundamentally, the outcomes are similar. Second-generation sequencing is more accurate than first generation sequencing because the process is digital, compared to the analogue approach of first-generation sequencing (Meyerson et al., 2010). This digital component of the sequencing technology allows for the ability to over-sample the genome, also known as coverage depth. The more times the sequencer reads a particular

section of the genome, the more accurate the results because experimental noise can be eliminated, resulting in easier detection of genetic mutations (Meyerson et al., 2010).

Second-generation sequencing platforms provide a higher throughput than first-generation technology as larger numbers of DNA strands are sequenced in parallel. Some sequencing machines are reported to generate more than 300 gigabases of DNA in a single run (Schadt et al., 2010). This greater efficiency drives down the cost of sequencing as well. With first-generation sequencing used to map the human genome, it cost $100,000 to sequence 1 million bases. Comparatively, it costs less than $1 to sequence 1 million bases using second-generation sequencing (Lifton, 2010). Many journal articles as well as articles in the lay press, have predicted the $1,000 and $100 genomes in the not too-distant future (Robertson, 2003) (Zimmerman, 2013). Today, it is estimated to cost between $24,000-$9,500 to sequence an entire genome in a clinical laboratory (Bick et al., 2013). This amount includes the cost required to run the sequencers as well as the cost for data interpretation. It should be noted that because WES is a more targeted approach sequencing only the protein-encoding exons of approximately 22,000 genes, as compared to sequencing the majority of the 3.2 billion base pairs in a genome, WES is less labor-intensive, and correspondingly less expensive than WGS, with the estimated cost of $4,000 (Lifton, 2010). In addition, there are predictions of third-generation sequencing, which will improve both accuracy and efficiency of sequencing as well as make the process even cheaper than second-generation platforms (Schadt et al., 2010).

Whole genome and whole exome sequencing are used in clinical care today in medical oncology, pediatric and adult genetics clinics and in select internal medicine

clinics, for healthy patients who are interested in learning about future disease risks. The medical benefits from undergoing WGS/WES, is in a large part, determined by the indication for why an individual is undergoing the sequencing. In the case of medical oncology, the benefits for a patient with advanced cancer is to learn about a possible chemotherapy regimen that would target cancer cells and hopefully result in remission of their disease. For the child or adult with an unknown genetic condition, WGS/WES might identify the underlying genetic mutation responsible for a disease, but finding the genetic mutation responsible for the condition, often does not lead to a treatment option. Finally, for the healthy patient, the results from genome sequencing might provide information about possible risk factors for a hereditary or common disease. The hope is that this genomic information might be actionable, that is, lead to a possible preventive treatment, and avoid being affected with the disease.

As was initially predicted, the first area in medicine where WGS/WES is clinically applied to patient care is in the field of oncology (Pasche & Absher, 2011). Even before WGS/WES was available for oncology care, using single gene testing, researchers had identified mutations occurring in common cancers which can then be targeted with specific chemotherapy agents designed to destroy specific types of cancer cells based on the genetic profile of cancer cells. Several treatment regiments in clinical oncology practice are available now which are targeted to a specific genetic mutation expressed in the tumor tissue. One example is the use of trastuzumab to treat women with breast cancers that over-express a protein from the proto-oncogene HER-2/new (Hudson, 2011). Trastuzumab works as an anti-HER-2 antibody, blocking the expression of the HER-2/neu protein, resulting in decreasing the risk of recurrence of breast cancer (Ross

& Fletcher, 1998). While this is a good illustration of personalized medicine, I want to note that this and other examples of targeted therapies for specific forms of cancer are based on a single gene mutation identified in a tumor genome. The differences between the application of this type of treatment and whole genome sequencing is that there is much more data generated on the tumor genome with WGS/WES and the fact that patients germline genome is also sequenced which is considered by most to be "incidental" data.

Since 2010, many large academic cancer centers all over the world have been offering whole genome tumor sequencing for individuals with metastatic cancer (Hudson, 2011). The knowledge that cancer is caused by a series of mutations that diverge from a normal germline cell, establishes cancer as an ideal disease model to determine how useful whole genome sequencing will be for treating a disease for which a cure has long eluded scientists. The side-by side comparison of the cancer genome to the germline genome allows researchers the ability to detect multiple types of genomic alterations: single nucleotide substitutions, chromosomal rearrangements, and copy number repeats, all of which have a role in cancer initiation and progression (Meyerson et al., 2010). Expanding our understanding of additional molecular processes of cancer development and metastasis will enable researchers to improve tumor diagnosis and classification techniques and subsequent treatment protocols (Drmanac, 2011).

There are some successes reported in the literature demonstrating how sequencing patient's tumor and germline informed the treating oncologists of a more effective and novel treatment option. The number of patients however who are benefiting from this sequencing technology, is still fewer than a hundred reported in the literature (Welch &

Link, 2011). Understandably this number is small in large part because the technology has only been available for several years, so with time, it is expected that more success stories will be published. In the meantime, most patients, after learning about the great promise of WGS/WES, are willing to make the emotional and financial investment and face the uncertainty of whether there will be any clinical benefits from undergoing sequencing, for the chance to extend their life, if even by only several years. Many cancer patients who undergo WGS/WES even state that, if they cannot benefit from the test, they are willing to pay the expense and risk the disappointment of a uninformative result, if the data produced on their own tumor genome sequencing might help researchers better understand their particular type of cancer and how to more effectively combat their disease for the benefit of other patients who have their same type of cancer.

Along with important information about the tumor genome, cancer patients who undergo WES/WGS may learn they carry a variant of mutation for a hereditary disease. Because the germline genome is sequenced alongside the cancer genome, laboratories are able to analyze the patient's inherited information to determine if the patient may be carrying a mutation that could predispose them for other diseases. WGS/WES will also identify many variants of uncertain clinical significance. These variants may or may not have any proven disease association and others may have some potential associations to common diseases. It can be argued that cancer patients, while not seeking WGS/WES to learn about hereditary disease, may benefit from this information because these conditions also have implications for their relatives. Most patients, when learning this possibility, are excited about the possibility to benefit their relatives and want to be

informed of possibly hereditary risk factors identified from sequencing their germline data.

Demand for WGS/WES is going to increase. The reason many physicians will be pursuing WGS/WES for their patients is not just because the cost of performing the sequencing is decreasing. The demand will be driven by the possibility that WGS/WES might provide missing data about a patient that will dramatically improve their patient's health condition, either with a more effective treatment or even an allusive cure for a rare disease. In other cases, the possibilities of WGS/WES are not as ambitious as improved treatments, but simple. Some families who have a child affected with a rare genetic disorder want to understand the cause of the disease; they need an explanation. As WGS/WES becomes mainstreamed into medicine, I anticipate this technology will also be very popular amongst a subset of the healthy population who will be keen on learning about possible risk factors facing them in the future, and even risk factors for their unborn children.

Many of these scenarios have yet to be fully realized, so instead I want to focus on the practical benefits of WGS/WES that can be appreciated today. Bill and Melinda's case nicely illustrates some of the benefits from WGS/WES. Both Bill and Melinda might benefit from knowing about several genetic risk factors all at once and furthermore, be able to act on any of those risk factors promptly. For example, when Melinda received her results, she immediately sought out more information about familial amyloidosis, and since she was already early in her pregnancy when she received her results, she was aware of the risk to pass this condition to her future offspring. Also, since both Bill and Melinda were carriers for cystic fibrosis, immediately they knew there would be a 25%

chance to have a child affected with cystic fibrosis. Knowing these risk factors early in the pregnancy give Bill and Melinda options to pursue prenatal diagnosis during the pregnancy if they were interested. Even if they were not interested in pursuing prenatal testing, the knowledge that their child may be born with cystic fibrosis might help them feel more empowered and help them prepare for caring for a child affected with a hereditary condition.

Another immediate benefit garnered from Bill's WGS experiment with his wife, was an ability to improve their current health status. Melinda shared her drug metabolism profile with her psychiatrist who was able to alter her antidepressant dose, which resulted in a more effective response to the medication and improvement to her overall quality of life. Pharmacogenomics profiles obtained with WGS/WES is one of the most concrete examples of personalized medicine. Physicians can tailor the class of medication and the amount to prescribe, based on the patient's ability to metabolize the medication, identified by mapping the various genetic variants we carry in genes that metabolize common medications.

Bill's WGS results indicate that he is at an increased risk for prostate cancer. While he was found to carry a gene alteration with only a modest risk for prostate cancer, Bill could seek out early prostate cancer screening and at least discuss his screening options further with his physician. Bill might have felt more empowered with this information since he had already suspected he was at a higher risk, and this test just verified what he had suspected. In the case of our couple, WGS fulfilled some of the promises the technology offers; personalized medicine, disease prevention and improved overall health status. This scenario of course, represents the most optimal utilization of

WGS for a healthy couple, but most certainly, there are many unknown variables arising from the complexities of WGS/WES.

The complexities of WGS/WES resulting in several unknown variables include; how to analyze, report on, and store the large volume of data produced from sequencing a genome; the unknown analytic validity of the data analysis component of WGS/WES; the uncertainty of how to adequately interpret genomic data (for example, variants of uncertain clinical significance); how to apply genomic results to patients existing medical care; and; how to contact patients with updated genomic information?

The enormity of genomic data produced from WES/WGS is at the heart of the dichotomy of this technology. The ability to produce large volumes of data predicting individuals' potential disease risk factors is what associates WGS/WES to its promises. Yet, the overwhelming volume of data is also what defines the current limitations and complexities of how to use the data in a clinically relevant manner. Determining a context for undergoing WGS/WES, based on the clinical situation of an individual, is one approach to managing the data and has even been proposed as a solution for how to manage the complexities of WGS/WES (Berg, Khoury, & Evans, 2011). This approach will be discussed in the second half of this chapter when I review proposed informed consent protocols for WGS/WES.

The sheer volume of data produced from WGS/WES leads to several inter-related complexities described in the following five paragraphs. The volume of data produced from WGS/WES is perhaps the most complicating factor inherent to the sequencing process. One dilemma from producing large amounts of data, is how or whether to report on the numerous variants that are detected when sequencing a genome? Approximately

20,000-100,000 variants could be reported with every genome sequenced (E. Green, 2013). Thousands of variants will be reported which have clinical validity but limited actionability and only approximately ten to hundreds of variants with clinical actionability are expected to be reported (Berg et al., 2011). Further complicating the situation is there is no consensus for how laboratories will report these variants, or agreement on how to report them and whether some variants should be reported if they are not related to the clinical indication for testing or have unknown clinical utility.

The next issue related to variants is the controversy surrounding how laboratories report novel variants and variants suspected of being related to a common disorder such as cancer. Many rare variants are now believed to be related to some common diseases and based on preliminary sequencing data, researchers expect to identify between hundreds and thousands of novel variants in every person sequenced (Nelson et al., 2012). Traditionally, more common variants believed to be associated to common diseases were based on the data reported from genome wide association studies (GWAS) (Drmanac, 2011) (Cirulli & Goldstein, 2010). While, several direct-to-consumer labs were quick to begin reporting disease associations as part of their genomic sequencing profiles, academic institutions have been critical of the labs for publishing on a disease association prematurely without the necessary science to validate the disease link. There is a consensus at this time that to fully appreciate the clinical implications of many of these variants, more studies (upwards to sequencing 20,000-100,000 people) needs to be completed before being able to fully comprehend the health implications of these rare variants, and more common variants, both believed to have a role in common diseases (Hayden, 2012a).

With respect to the uncertainty of the analytic validity of WGS/WES, the fact is that even though WGS/WES can sequence all 3.2 billion base pairs in the body, it is not capable of reporting all types of genetic mutations for all genetic disease described. For example, because the sequencers read a genome one base pair at a time, there are entire sections of an individual genome that could be deleted or even duplicated, but because the end-to-end matching of bases during the process of realigning base reads finds the same base pairs around the deletion or duplication that are normally aligned, the particular deletion or duplication will not be detected.

An example of how WGS/WES cannot detection a genetic disorder is in the case of triplet repeat conditions. Huntington's Disease is a triplet repeat disorder. A triplet repeat condition is a genetic disease caused by a sequence of three bases which are normally strung together in a series and repeat multiple times, for example, CAG, CAG, CAG, etc. Within a normal gene, the three bases are repeated between 10 and 26 times. When a mutation occurs, the triplet repeat is expanded beyond 36 repeats (Warby et al., 2010). WGS/WES is designed to sequence the triple repeats but cannot accurately determine how many times these bases are repeated. In order for a patient to learn if they carry such a disorder, they will have to undergo more traditional Sanger sequencing (Bick et al., 2013).

A final example of the unknown accuracy of WGS/WES results is because WGS/WES is performed on several different types of sequencing platforms at different companies, there is varying depth of read coverage for each genome sequenced. These variations will lead to some labs under reporting variants with potential clinical implications and other labs over reporting variants with unknown clinical significance.

Therefore, the type of sequencing technology chosen adds another layer of uncertainty on the accuracy of the reported results (Bick et al., 2013).

Moving beyond the uncertainty about the accuracy of the data reported from WGS/WES is the issue of the clinical utility of the data. How will genomic results be applied to patients' existing medical care so that the data can be used in a clinically meaningful way? There are practical considerations of how to integrate this technology into patient care, our current medical model and even into society. All three of these issues are still being sorted, as WGS/WES is already available in clinical care today. The resolution of some of these practical concerns is important to watch and learn from for application to future technologies that will also be producing large volumes of data. Other examples of biomedical tests that will produce large amounts of data include proteomics (understanding the role of proteins expressed by genes) and applying the science of understanding the genomes of our microbiomes, to clinical care.

Concerns over data volume and data management resurface when considering how the data generated from WGS/WES will be stored. To sequence, analyze and store a genome it costs approximately $50,000 a year (Brown, 2011). It is estimated to take about 10GB of disc space costing $5,000 a year; sequencing, analyzing and storing a genome requires eight medium computers costing $40,000 a year; and 512 GB of memory costing about $50,000 a year (Brown, 2011). Technology is moving fast and soon chips will be developed to store large volumes of data. Until this occurs however, practical limitations are such that if an individual requests his or her raw data, they would need to be equipped with enough computers, memory and hard disc space to handle the demands of data generated from WGS/WES.

A logical next step when considering how to manage the volume of data produced from WGS/WES is how and what type of data should be included in a patient's medical record? Most medical records will be electronic by the year 2015 (MedicalRecords.com, 2013), so obviously an electronic transfer of genome sequencing data would be ideal. The question that needs to be sorted through is what type of genome data should be included in a medical record? Should the raw data be available in the medical records to facilitate future analysis of the patient's genome? Due to the overwhelming volume of data generated, would this place too much of a burden on the health record storage systems? Even more relevant however, is what would a physician do with genomic information? Will physicians know or understand how to integrate WGS/WES into the patient's medical care?

When planning WGS/WES data storage, data transfer and data management, it is important to attend to the privacy and confidentiality concerns of protecting genomic information. Downloading a genome sequence into medical records at a hospital or physician's office, cause many to worry about creating opportunities for misuse of the information resulting in harm to the patient in some way. The reality is that there have been only a handful of cases reported in the literature on a patient who was discriminated through loss of health insurance or loss of employment because of a positive genetic test result or a genetic diagnosis. The Genetic Information Nondiscrimination Act (GINA) was signed into law in 2008 and enacted in 2009 (U.S. Equal Employment Opportunity Commission, 2008). This law offers federal protection from discrimination by health insurance companies as well as protection from employers who are not permitted to use genetic information in the hiring process, or in firing and promotion decisions. While this

law alleviates some concerns about discrimination based on genetic test results, many physicians still warn their patients before undergoing genetic testing that they might experience some type of insurance discrimination after undergoing genetic testing. The law does not provide protection from life insurance discrimination, or disability and long term care insurance (U.S. Equal Employment Opportunity Commission, 2008).

The incorporation of genomic information into patients' medical records will eventually extend beyond a physician's office. As more facilities standardize medical records, patient's medical information will be transferred electronically across facilities. Eventually software will be written which enables WGS/WES data to become imbedded into the patient's medical record so it can be interpreted over a period of several years and be incorporated into the patient's ongoing plan of care. Pharmacogenomics is an area in patient care where genomic information is automatically applied to patient's ongoing care. For example, before pharmacies will fill a prescription for a commonly used blood thinner, Warfarin, a physician is encouraged to order the CYP2C9 and VKORC1 gene analysis to determine how effectively or ineffectively as the case may be, their patient will metabolize this medication. This information has proven to be lifesaving in enough cases that has become a recommendation by the Food and Drug Administration (FDA Center for Drug Evaluation and Research, 2010). I anticipate that this type of information about patient responses to treatments will become more widely applied to medical care very rapidly. Therefore, in the not too distant future, the data produced from WGS/WES will need to be applicable to real time patient care.

As data management issues are being sorted, working towards a better understanding of the clinical significance of the novel variants now being identified is

ongoing. This process is not simple and will not be completed in the next several years. To understand the clinical implications of the variants identified, the data analysis of variants sequenced from thousands of different individual will need to be reported and then compared to one another, to determine the clinical and biological outcomes of the variants on individuals in our population. The more individuals who undergo genome sequencing, the more data can be collected about the biological and clinical implications of the variant (Hayden, 2012a).

Collaboration among laboratories, researchers and physicians all over the world is necessary to better characterize and classify variants. After all the data has been sorted and analyzed, it will hopefully be applied in the manner that it is intended: to predict common diseases, to confirm suspected genetic diagnoses in already symptomatic patients, to identify novel genetic conditions, and to inform clinicians on more effective treatment regimens for patients. Until the time in which the evidence for disease association of these variants is confirmed, (and arguably even when this information is better characterized) individuals who are considering WGS/WES need to be able to understand the information being reported to them. Chapters five and six of this dissertation address how I propose to help individuals better understand the current limitations of the technology and the current and future implications of the information available from the technology. Chapter seven provides a solution for how to incorporate WGS/WES into our current medical model.

As variants are becoming classified over time, older results generated from WGS/WES will soon be outdated. This leads into the complexity of how to contact patients with updated genomic information. Some individuals may carry a variant, which

will eventually be identified as a disease causing mutation. How will an individual undergoing sequencing in 2013 learn about any possible updates to their genomic data in a year or two years? Who should be responsible for notifying a patient when a new finding with clinical implications is available? Will laboratories require another blood sample from the patient or charge the patient for an additional analysis? Currently many laboratories are electing not to re-contact the patient with any new information that becomes available after the initial results were reported back. Medical geneticists were surveyed in 2001 on their opinion of whether it was their responsibility to re-contact a patient when new findings were available about a patient's genetic test result, and they ultimately were divided about their duty to re-contact patients. It was concluded that while the recommendation to re-contact patients with new findings was ethically desirable, it was not a realistic expectation (Pyeritz, 2011). In fact, most laboratories are stating this fact in their consent forms so that patients will be informed before initiating the test that they will have to request additional sequencing if new information becomes available in the future (Ambry Genetics, 2013). This is also the current policy in place for all single gene testing performed in a clinical lab. Because of the enormity of genomic information analyzed through WGS/WES, I am not convinced the current guidelines and policies will be adequate for a test like WGS/WES and will propose an alternative solution in chapters six and seven.

A related issue, which arises from identifying variants of uncertain significance, is the fact that most variants, not already known to be associated with a Mendelian disorder, are not enough in of themselves to cause a particular disease. There have already been many publications supporting the hypothesis that variants for common disease are

influenced by environmental factors and even other genetic variants (gene-gene interactions). This type of disease process has long been defined as multifactorial, in which there are multiple genetic and environmental components working together to cause a disease (Nussbaum et al., 2001). Therefore, researchers working to understand the variants will be reporting on the additive effects of multiple causation of a disorder over time, as the data generated from sequencing many genomes accumulates. Individuals undergoing WGS/WES need to be able to appreciate these complexities when receiving their results. In my opinion, a person's ability to understand of all of these complexities regarding the use and interpretation of their own genome data will ultimately determine the clinical usefulness of whole genome and exome sequencing.

After undergoing WGS Bill and Melinda might be more informed of risk factors for future diseases, and the next step would be for both of them to individually communicate this information to their physicians. The responsibility for reporting results to medical providers may be placed with the individual patient. The medical providers, in turn, are responsible for correctly interpreting the results and ordering the necessary medical tests and screening procedures. Finally, the individual undergoing WGS/WES will need to be diligent in following their physician's recommendations. These three steps encompass the actionability component of WGS/WES. The medical actions resulting from WGS/WES results, is what ultimately will translate this sequencing technology into successful health outcomes. Data needs to be interpreted and once it is interpreted and assuming it was interpreted correctly, the real health outcomes will be determined by the combined effort between patients and their physicians.

Bill was reported to have a particular variant in a gene that has been found to be associated with an increased risk for prostate cancer. Because he has a family history of prostate cancer, Bill, as would most individuals in his situation, associate this result as confirmation of what he was already suspecting, and that is he is at an increased risk for prostate cancer. The fact that his genome result indicates a possible risk, is not a guarantee that Bill will be able to convince his physician that he needs to have more frequent prostate cancer screening and needs to start screening at a younger age than his counterparts.

Assuming Bill could convince his physician that he should undergo prostate cancer screening beginning at a younger age and more frequently, previous studies assessing behavioral health modification after learning about disease risks, have not proved to be optimistic. Most patients were reported to have difficulty implementing the necessary lifestyle changes after being counseled about the need to do so to decrease a risk for a particular disease. This fact has been one which many critics of WGS/WES used to discourage incorporation of personal genome information into patient care. Many criticized WGS/WES for not having any clinical relevance to patient care because even when aware of disease risk factors, patients have not demonstrated the ability to make effective lifestyle changes to modify their disease propensities (Scheuner, Sieverding, & Shekelle, 2008). On the other side of the argument are those that criticize WGS/WES because this type of information may not be applicable to much of the population, thus resulting in minimal impact on improving health outcomes for our health care system (Schultz, Caldwell, & Foster, 2003). There has been reported concern about those who choose not change a potentially harmful health related lifestyle if their genomic markers

suggest no increased genetic risk factors (Sanderson, O'Neill, White, Bepler, & Bastian, 2009).

The layered complexities generated by WGS/WES sum up to a real dilemma for how to adequately inform individuals before undergoing WGS/WES. Whole genome sequencing produces a significant amount of genetic data and subsequent disease risk factors at one time, when compared to traditional genetic testing. Before the availability of WGS/WES, healthy individuals curious about their risk factors for a hereditary condition had the option to learn about only one hereditary condition at a time (single-gene testing). Our current informed consent protocols for genetic testing are designed to inform patients about implications of learning one disease at a time. WGS/WES moves the traditional model of genetic testing from a stepwise approach to the opposite extreme, which is to learn about everything possible at one time. There are efficiencies to this approach and in the cases where time is of upmost importance, such as a patient with a metastatic cancer and no additional treatment options, the advantages of WGS/WES most certainly outweigh any potential disadvantages.

However, there are additional burdens to the healthcare system expected with the implementation of WGS/WES into clinical care. It has been estimated the informed consent process for WGS/WES will require 6 hours of face-to-face counseling (Mayer, Dimmonck, & Area, 2011). The results disclosure discussion sessions are estimated to last 5 hours (Ormond et al., 2010). There are multiple models already proposed for how to tackle the multiple complex and heterogenous issues of WGS/WES. Many institutions and researchers are investigating the effectiveness of various protocols. Other institutions offering WGS/WES on a clinical basis are implementing existing informed consent

protocols into the informed consent sessions and prospectively evaluating the outcomes and effectiveness of these traditional models. In the next section of this chapter, I will outline research and clinical informed consent proposals being proposed for WGS/WES and evaluate the potential effectiveness of these protocols at fulfilling the ethical obligation of informed consent while also addressing the complexities of WGS/WES.

Informed Consent Proposals for WGS/WES

Practice guidelines for how to provide informed consent for WGS/WES have not been formally published, however there are numerous published recommendations for how to approach the complexity of consenting individuals interested in undergoing WGS/WES. Following the pattern from all other new genetic tests that become available for use in clinical care, for example, Huntington's disease and cystic fibrosis genetic testing discussed in chapter three, clinicians are looking to the research community for guidance on how to proceed with creating informed consent protocols for WGS/WES. The hesitancy towards implementing a particular set of recommendations too quickly stems from clinicians' angst and concern about the implications of undergoing WGS/WES on patient wellbeing, longstanding historical concerns over confidentiality and privacy of patient genetic test results, and the potential consequences, both good and bad, on patient care. Therefore, as with all other forms of genetic testing, it is expected that these complex issues will be sorted out through research studies aimed at better understanding the effectiveness of various consent approaches. In this section of chapter four, I identify the major themes emerging in the ongoing debate about how to conduct informed consent before undergoing WGS/WES. I first review recommendations from

the literature discussing both how to design a research study which involves WGS/WES and second, will summarize the conclusions from research studies for how to address the complexities of WGS/WES in clinical care. The last section of this chapter reviews the types of informed consent protocols currently used in clinics offering WGS/WES.

Before I review the research recommendations, I want to point out a distinction worth acknowledging between a research approach to understanding the informed consent process for WGS/WES and the clinical approach for understanding the informed consent process. Most obvious, the research approach is designed to understand the issues surrounding informed consent, possibly studying the effectiveness of various approaches and ultimately proposing models of implementation into clinical care. The goal of a research approach to the informed consent process for WGS/WES is to inform the clinical models. Yet, at the same time, the recommendations for conducting research that utilizes WGS/WES technology, address issues more pertinent to designing a study in which patients consent to undergo WGS/WES. Despite these differences, there seems to be much overlap in the recommendations and strategies for addressing informed consent protocols in the research setting as well as the clinical setting. The research studies aimed at developing strategies for how to properly implement informed consent protocols used before undergoing WGS/WES have reported on the major complexities inherent to the technology but have offered limited novel solutions. The solutions offered from these studies are based on components of existing informed consent protocols.

One of the first attempts at defining an informed consent process for managing large amounts of genetic data can be found in a *JAMA* publication from 2001. This article was notably published before the completion of the Human Genome Project

foreshadowing the complexities of large volumes of genomic data. This article summarizes a suggested informed consent protocol for enrolling patients into population-based research studies (Beskow et al., 2001). The significance of this document is that it represents an early proposal offering strategies for how to corral large amounts of genetic data, with a focus on lower penetrant genes available from population studies, while also addressing some of the problematic components of genetic studies. The problematic areas of genetic studies identified by the paper's authors are; whether to disclose research results; whether and how to re-contact study participants; and how to maintain privacy of study participants. To maintain compliance with the legal and ethical obligations of the informed consent process, the suggested informed consent script proposed in this article is based on federal policy recommendations for the protection of human research participants and the authors met their ethical obligations by referencing the report from the National Bioethics Advisory Commission (NBAC) (Beskow et al., 2001). The twelve elements included in a written informed consent document for population-based genetic research studies are information about the; overview of the study; purpose of the study; nature of participant involvement; privacy of the data; risks; benefits; and costs of participation; disclosure of results; future use of participants sample; rights of participants; contact information; and consent and signature for whether the participants want to be re-contacted (Beskow et al., 2001). While these elements of informed consent can be uniformly applied to all types of genetic or genomic studies, a key conceptual component of this informed consent document and those proposed for WGS/WES studies is whether researchers intend to report results to study participants.

The reasons the authors of this *JAMA* publication give for why they do not believe it is necessary to report results echo the same complexities of the informed consent process for WGS/WES. They advocate against informing participants their results because most population-based research projects involving genetics produce results that lack of clinical validity (association to a disease) of the genetic findings to a specific disease. The second reason not to report results is because in order for the results to be used in a clinical setting, results have to be independently confirmed in a CLIA approved laboratory and most research studies are not able to validate the results in their own laboratories. The third reason for not reporting results is a weaker rationale in my opinion, is because it represents a study design dilemma, not reflecting issues relevant to producing large amounts of genetic information. This last reason researchers stated for not reporting results is because they designed the study intentionally not to report results back to participants and by reporting data, the study would be violating its own consent promises. Finally, the authors write that researchers should not be reporting results, as this responsibility is one that falls outside their role as a researcher. They argue that physicians are trained to discussed the relevance of genetic data on current or future care of a patient, but a researcher is not qualified to act in this role and would be stepping outside their area of expertise if they acted as a physician (Beskow et al., 2001).

The first tension emerging from this early recommendation is whether to report results with unknown clinical utility and validity. This theme is central to all the current publications addressing research ethics of WGS/WES. In 2008, *Nature Reviews* published an article on the ethical concerns and challenges of whole-genome sequencing. The first major ethical consideration the authors addressed was circumstances where

research results are disclosed to the study participants (McGuire, Caulfield, & Cho, 2008). Because multiple results are generated with this technology, the issue is not just whether to report results but if some results are reported, which ones and why? When not reporting results, what is the rational for these decisions? When results are reported, how will they be reported?

A qualitative thematic review of 30 written consent forms used in cancer genome sequencing research studies conducted across the world was published in 2011 in the *BMC Medical Ethics.* The authors conducting this review reported that 30% of the studies sampled stated general study results would be available to study participants. Of these ten studies, only one of the research groups provided participants a choice whether they wished to learn their individual results. One study stated individual results would be returned (with no choice given to participants), seven indicated no individual results would be made available to research participants and one study did not mention the return of individual results (Allen & Foulkes, 2011). The remaining twenty studies segregated similarly in that nine studies indicated individual results would not be available, three studies did not state whether individual results would be available and four stated individual results will be returned whether the participant wished to receive them or not. Four studies gave participants the option for whether they wanted to learn their individual result (Allen & Foulkes, 2011).

What is noteworthy about this particular publication is that the author identified seven themes in her qualitative review of the written informed consent documents for cancer genome sequencing studies, but return of results was not considered a separate theme. Instead it was incorporated into the category of re-contacting study participants.

The reason for not including return of results as a separate theme in my opinion is because the studies she reviewed were not emphasizing the return of results for the reasons already discussed. This review article demonstrated a lack of resolution in the research studies on whether it is necessary to report results. Because the issue has not yet been resolved, many have not started to formulate strategies for how to report results on incidental findings generated from WGS/WES research studies.

A commentary piece published in *Genome Medicine* in 2010 highlights ten core scientific, cultural and social components necessary to consider when writing informed consent protocols for genomic research. One of the ten components discussed is whether to report individual study results to participants. The authors do not advocate for or against reporting individual study results, but rather suggest that when study results are to be reported, researchers should effectively state the risks and benefits of learning genomic information in a manner which is consistent to the study participants' cultural and socioeconomic environment (Rotimi & Marshall, 2010). Essentially, the authors advocate for incorporating a discussion of the social, psychological, family, financial and medical implications of learning genomic results from a research study and incorporating these possible implications into the informed consent documents (Rotimi & Marshall, 2010). This article provides more guidance on what the authors consider to be key components of what should be included in a study design with the aim of reporting research results. Yet, these components do not differ from those already endorsed in our current informed consent protocols for single gene testing.

After determining whether to return research results, the next problem to solve is what type of result will be reported? This is the second theme I identified in a review of

informed consent proposals for genomic research studies. The long-standing ethical obligation from genetic research which resonates into WGS/WES studies, is that before reporting a research generated result to a study participant, the result must have demonstrated clinical utility to the study participant and be validated by an outside clinical laboratory. This guideline has proven to be problematic when it is applied to the large volume of variants identified through WGS/WES, many of which currently have uncertain clinical validity or utility, but have the potential to later be associated with a known disease and therefore become clinical useful.

Additional themes were noted in most of the publications I reviewed are whether researchers will re-contact study participants when more data becomes available and when the study is designed to re-contact participants, it becomes important to state how and when the investigators will fulfill this obligation. The importance of making data available to other research studies was a noted theme as was the emphasis on recommending study participants share any data revealed from the study with family members. All the publications I reviewed discussing WGS/WES studies agreed that when designing studies, researchers should take all of these issues into account. There was also consensus reached on the issue that informed consent protocols for WGS/WES should be first evaluated in a research setting, before implementing into clinical practice (Rotimi & Marshall, 2010).

In response to the many ethical dilemmas rising to the surface from the initiation of WGS/WES in the research and clinical arenas, the Presidential Commission for the Study of Bioethical Issues published their report on *Privacy and Progress in Whole Genome Sequencing* in October of 2012 (Presidential Commission for the Study of

Bioethical Issues, 2012). The focus of their document was on the privacy issues associated with WGS, however an important component of the privacy issues is informed consent, which was addressed in four recommendations. These four recommendations are based on the ethical principle of respect for person, as was initially described in the *Belmont Report*. The commission further described "privacy" in the context of WGS to be synonymous with autonomy when associated with self-regarding conduct. The commission intended to use the definition of privacy for the purpose of WGS/WES as the "absence of substantial government or other outside interference with individual's decisions and choices." With this background in mind, the commission recommended the consent process adequately inform research participants and patients who will have access to their data and how the data might be used in the future. The commission recommended that informed consent documents for WGS fulfill Common Rule obligations to: 1) 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 (Presidential Commission for the Study of Bioethical Issues, 2012).

Incidental findings are also to be discussed within the context of the consent process and, specifically, the commission recommends that individuals be made aware of the possibility of incidental findings and recommended studies inform participants how and which findings will be communicated, and to whom. Finally, the commission recommends that those who support WGS invest in studies to better understand methods

for reporting incidental findings, and individual preferences and expectations for learning about incidental findings (Presidential Commission for the Study of Bioethical Issues, 2012).

These last few recommendations by the commission really emphasize the fact that incidental findings are the central, recurring theme for WGS/WES simply because, the number of variants that would be expected to be reported is so great. While many of the early genetic studies followed the underlying assumption that results will not be reported to the patient (Beskow et al., 2001), there is increasing pressure for researchers to report results back to study participants. The rationale now given for why it is important to report back results is because the generation of so much data makes it much more likely results with important clinical implications will be revealed making it imperative that researchers provide this information to patients (Rotimi & Marshall, 2010).

The reporting of incidental findings is not new to medical research studies. A brief review of how these issues have been addressed in the past might provide insights that can be applied to the informed consent process for WGS/WES. A research group from Stanford University, concerned over the ethical dilemma of re-contacting research participants if an incidental finding was clinically significant, specifically one related to a fatal disease responsive to therapy or that might alter a couple's reproductive planning, recommend researchers use thoughtful consideration for this type of ethical situation when planning and designing a study. While this group did recommend incorporating research ethicists, clinical geneticists and genetic counselors into the discussions surrounding study design, they offer no specific strategies for tackling this issue (Tabor & Cho, 2007).

The Institute of Human Genetics in Germany published their own response for managing incidental findings in the clinical findings in the *Journal of Medical Genetics* in 2009. This group revised their informed consent protocol to include three options for patients potentially faced with an incidental finding: learn about genetic findings that have implications for the patients' health and possibly his/her family members; learn about these types of genetic findings only if effective treatment options or surveillance programs are available; and learn about carrier status for an autosomal recessive disorder (Netzer, Klein, Kohlhase, & Kubisch, 2009).

The data produced from studies conducted using individual samples stored in large bio-banks is another example of an area in research that recently began addressing how to manage incidental findings. In a collaborative effort, a large group of researchers from 19 major academic institutions across the US and Canada, published ten specific recommendations on the roles and responsibilities for the return of incidental findings and individual research results. The ten recommendations are quite detailed and do a thorough job of explicitly stating the roles and responsibilities of all the players involved in designing and managing bio-banks. These recommendations are certainly worthy of mentioning but do not offer specific guidelines for how to re-contact study participants or how to disclose those results.

Some bioethicists and others in the research and clinical communities even question whether there is an ethical duty to disclose research results. Miller, et al. argue against the ethical duty to disclose research results given a lack of agreement over what types of results should be disclosed and further, how to accomplish the disclosure in clinical practice (Miller, Christensen, Giacomini, & Robert, 2008). The summaries from

studies on incidental findings have made broad conclusions that provide no useful guidance for the WGS/WES process. The conclusions have essentially all been similar: researchers conducting genetic studies in which genetic test results might reveal information that has clinical relevance outside the intentions of the study being conducted should state this possibility in the consent forms (Cooper, Nelson, & Ross, 2006).

The experiences published to date for how to report unexpected genetic test results further informs the academic, scientific and medical communities on how to think about handling these issues, yet no specific resolution has been offered for managing the issue in real-time. In addition, these previous examples were not adequate for tackling the scope of the data produced from WGS/WES. Finally, while the above examples provide recommendations specific to addressing incidental findings, and most medical professionals involved in genetics today will agree that WGS/WES are fraught with the complexity of dealing with incidental findings, I demonstrate in chapter seven when considering the technology of genome sequencing, if individuals request to learn as much as they can about their genome, there are no "incidental" findings.

The two largest ongoing studies working to address the informed consent dilemmas created by WGS/WES are the Coriell Personalized Medicine Collaborative (CPMC study), and the ClinSeq project conducted at the NIH Clinical Research Center. The Coriell study is the first collaborative effort for exploring the implementation of genomic information into the clinical arena. The study has already enrolled 6,000 individuals and provides personalized reports on genetic and non-genetic risks for multifactorial diseases, such as cardiovascular disease and diabetes (Keller, Gordon, & Stack, 2010).

A secondary aim of the study is to learn how to better educate individuals interested in undergoing WGS/WES as well as medical providers and the public about the components of personalized medicine and facts about genomics. The evidence-based research conducted with this program is anticipated to help inform the discussion of best methods for informing patients on genomics and personalized medicine. In this study, participants are given the option of receiving their results as part of the study design. The initial outcomes from disclosing results for potentially actionable health conditions to study participants discuss the group's development of a method for reporting results, which they argue is more effective than the methods used by DTC genetic testing companies. The Coriell group elected to present genomic risks for actionable diseases only. An independent advisory board known as the Informed Cohort Oversight Board (ICOB), reviews the variants identified during the sequencing to determine which variants associated with common diseases can potentially be prevented with specific actions (such as medical or lifestyle interventions) (Stack et al., 2011). These results are reported in relative risks to study participants and according to the Coriell investigators, this is a more understandable format for individuals to comprehend risk factors than methods used by direct-to-consumer testing laboratories (comparing genetic risk factors to non-genetic risk factors or general population risk factors) (Stack et al., 2011). Study participants in the Coriell project are offered in-person or telephone genetic counseling, but beyond this mention, little has been written about informed consent protocols for individuals enrolled in this study (Keller et al., 2010).

The second project is being conducted through the NIH Clinical Research Center and is known as the ClinSeq project. This is a pilot project designed to investigate

utilization of whole-genome sequencing in clinical research (L. Biesecker et al., 2009). The goal of the project is to learn how to apply large-scale medical sequencing (LSMS) into a clinical setting. In order to narrow the focus for the initial pilot study, the investigators choose atherosclerotic heart disease as a prototype for other phenotypes they expect to study in the future. Study participants were selected therefore to represent a spectrum of atherosclerotic heart disease based on the Framingham score (L. Biesecker et al., 2009). This pilot study was designed to use LSMS focusing on candidate genes for cardiovascular disease, but the expected 1,000 study participants will also be consented to undergo WGS for additional disorders in the future. The primary goal of the ClinSeq project is to create an infrastructure and protocols for conducting clinical research studies focusing on understanding the genetic basis of health, disease and drug response. A secondary aim of this study is to ultimately develop informed consent protocols for participants undergoing similar studies as well as protocols for how to return results and incorporate data into the clinical setting (L. Biesecker et al., 2009).

The ClinSeq project acknowledges the difficult consenting issues inherent to WGS and in response to these challenges in this project implemented a conceptual consent form and process for the participants to have control over the type of results they receive through an "opt-in, opt-out" model (L. Biesecker et al., 2009). The study investigator however, designed the consent form with the expectation that only results for disease-causing variants, and specifically high-penetrance, mendelian variants, would be reported to participants. Less-penetrant variants would not be reported for fear that participants would be overwhelmed with the amount of information presented to them and that the results themselves would not be clinically useful (L. Biesecker et al., 2009).

What is problematic about this study design choice is how would it be possible to determine a participant's choice for what type of genomic information they desire, if not all the information is available for them to learn? As with all other genomic research studies, all results reported to participants in the ClinSeq project are validated in a CLIA approved laboratory before being reported back to the participant and only the CLIA approved results are entered into the medical record.

Participants in the ClinSeq pilot study were asked to complete a baseline survey designed to better understand participant intentions for learning their own results. This survey was completed in conjunction with an in-person informed consent interaction with a genetic counselor. The genetic counselor explained the type of results WGS/WES could produce along with benefits and limitations of the technology; un-interpretable results, limitations on understanding results in our current time, with the possibility this would change over time, etc. The participants then completed another survey asking again about intention to receive results and whether results might affect their health-related behavior. Participants were given four categories of possible results to consider: variants with a known association to a disease that is preventable or treatable, variants with a known association to a disease that is not preventable or treatable; variants that establish a carrier for a disease (such as an autosomal recessive condition); and variants of uncertain clinical significance (L. Biesecker et al., 2009).

Recently, the investigators of the ClinSeq pilot published their findings on the first 311 participants enrolled into their study and to the investigators' surprise, all but 6 of the participants indicated they wanted to learn their results. The other six did not state they did not want to learn their results. They were undecided meaning that none of the

participants declined the opportunity to learn results. Another surprising revelation reported by the investigators, was that study participants were more interested in learning about variants of uncertain significance than they had anticipated. The authors concluded that while the study participants clearly expressed confidence that the data generated from sequencing would have a positive impact on their overall health, this finding was concerning because the hopes perceived from the study participants are likely to overshadow the numerous limitations of WGS/WES. They even suggest that investigators might need to learn how to "temper" such expectations for future study participants (Facio et al., 2013).

Before discussing current informed consent protocols for WGS/WES in the clinical setting, I want to first review several literature reports for how to tackle these issues. I have selected two proposals that attempt to create more innovative approaches to the informed consent process. This review will be followed by a summary of current clinical practices of informed consent for WGS/WES. I will conclude with an analysis about whether the themes emerging in the literature and in current research studies and clinical practice, translate into recommendations that will effectively address the complex issues generated from WGS/WES.

Acknowledging the difficult data management issues head on, several geneticists published their suggestions for implementing WGS/WES into the clinical setting with a commentary piece published in *Genetics in Medicine* in 2011. The approach they recommend is essentially to downsize the data to manage it more effectively. The downsizing of data refers to a method of compartmentalizing the data into "bins" that are characterized based on results with clinical utility (bin 1), clinical validity (bin 2) and

unknown clinical implications (bin 3) (Berg et al., 2011). The clinical validity bin is further divided into three subsets, “low risk incidental information”, “medium risk incidental information” and “high risk incidental information.” The variants reported in each bin are further characterized according to whether it is an allele that is known deleterious, presumed deleterious, a variant of uncertain significance, presumed benign and known benign (Berg et al., 2011). The overall approach to data management is one in which decisions about what type of variants should be used in clinical practice is based on the clinical context of the reason for pursuing WGS/WES. The fundamental component of this model is different clinical contexts require distinct approaches and that the consent process, as well as data analysis, results disclosure and recommendations for how or whether to use incident findings in clinical care, should be based on the specific context in which WGS/WES is applied (Berg et al., 2011).

To manage the consent issues, the authors are recommending a traditional model of informed consent, but one, which focuses on the type of results expected from the sequencing, based on the clinical context of the situation (bin) chosen for the patients. This system, they argue, allows patients the opportunity to be informed about possible implications of learning the results to prevent any adverse and negative consequences on patient wellbeing. In addition, they argue genetic counseling hours can be scaled to a manageable time and the impractical discussion about possible variants can be avoided (Berg et al., 2011).

The problem inherent to this type of model is that many clinical contexts will not be known when WGS/WES is ordered. In addition, as was demonstrated in the ClinSeq pilot, patients are expressing a desire to learn as much information as they can about

possible health issues and may want to be informed about variants. As a result, it would seem to be a bit paternalistic for the clinician to determine what type of information the patient has access to, regardless of the clinical utility of the data. This proposal is not suggesting an innovative approach for informed consent, rather another approach for managing the volume of data by applying the traditional model of informed consent into several different contexts.

A geneticist in Canada proposed an interesting approach to the informed consent conundrum with his article describing a "data-first" model (Trakadis, 2012). The "data-first" model is designed to approach WGS/WES in a simpler manner, and that is run a patient's genome through a search engine known as Individualized Mutation-weighed Phenotype On-line Search Engine (I-MPOS). This search engine will filter all irrelevant variants and match the patients' variants that known a known pathogenic association to a disease that has been described. All other "incidental findings" will be ignored and not reported (Trakadis, 2012). This is an interesting approach and certainly offers a more novel way to look at the data, however the fundamental principles of the model are paternalistic in that a clinician controls how the data is analyzed based on phenotype information. Also, the model does not provide options for the patient to learn about other genomic risk factors, not related to their clinical presentation.

WGS/WES is currently offered in various clinical settings across the country. Recall, there are two primary reasons for pursuing WGS/WES in clinical care at this time; to assist with determining the cause of a genetic condition with a suspected, but yet unidentifiable genetic etiology; and in the area of oncology, to assist with identifying a treatment regimen for a patient with metastatic refractory cancer. The third indication for

pursuing WGS/WES is predisposition testing, similar to the sequencing experience of Bill and Melinda. Many healthy individuals interested in undergoing WGS/WES are able to undergo sequencing through a direct-to-consumer genomics company. I describe the manner in which informed consent is provided in this setting after reviewing informed consent protocols in the medical oncology and pediatric and adult genetics clinics.

The process of undergoing WGS/WES typically begins when a physician identifies a patient who is believed to be a good candidate based on the two indications mentioned above. The ultimate decision of whether a patient is a good candidate or eligible to undergo WGS/WES is often determined by a physician and in some cases, a committee of individuals with an expertise in genetics who discuss individual cases and reach a consensus for which patients might benefit the most from such sequencing. While clinicians want their patients to benefit from the possible findings revealed from WGS/WES, they are also quite cautious when pursuing the testing because of the uncertainty inherent in the process. In the history of medical tests employed in clinical practice, WGS/WES produces more uncertainty than clinicians are comfortable managing. Individuals also learn about WGS/WES through their own research or after reading articles in a publication or newspaper and seek out the sequencing on their own.

The overall integration of WGS/WES into the clinical model has been essentially parallel to the existing medical genetics informed consent construct. The type of consenting which occurs before WGS/WES in the clinical setting follows our current health care structure where the individual undergoing sequencing will meet with a genetic counselor or other health care provider trained in genetics and review together the implications, both good and bad, of learning about genomic information and uncertainties

expected from the sequencing results. This is an expanded version of the traditional model of informed consent, and is the template for what all clinics are following at this time. The content and details of information discussed in a consent session is likely to be inconsistent between institutions.

After informed consent is achieved, the clinician sends the appropriate patient sample to a CLIA based laboratory for analysis. The laboratories performing WGS/WES all require patients sign an informed consent document which state the type of results a patient can expect and the limitations of the laboratories' interpretation of the results. The written informed consent document is intended as supplemental material to the more in depth informed consent process conducted by the clinician ordering the test. Families who elect to undergo WGS/WES to determine the genomic cause of a particular disease for their child, are required to submit a sample for the affected child, or children when more than one child is affected with the condition, as well as both parents.

Results from sequencing are interpreted by the laboratories and sent back to the referring physician, who will report them to the patients. The laboratories conducting WGS/WES publish their data on the success rates of sequencing that is how many patients received results, which provided either clinical resolution for a diagnosis or effective treatment in the case of cancer patients. The laboratories performing WGS/WES also decide which types of variants to report and how to report them.

Since WGS/WES has become available in the clinical setting one leading professional organization in medical genetics felt it was important that clinicians ordering genomic sequencing had some guidance for how to deal with incidental findings. Incidental findings are defined as any genomic result that does not directly relate to the

specific indication for why the individual is pursuing WGS/WES. After convening a working group to explore the issue in great deal, the American College of Medical Genetics recently published their recommendations for how the clinical community should respond to the ongoing controversy surrounding the management of incidental findings reported from WGS/WES. In their position statement released in March of 2013, the American College of Medical Genetics (ACMG) recommends that regardless of the clinical indication for WGS/WES, laboratories should report out mutations found in 57 genes encompassing 24 Mendelian conditions (R. Green et al., 2013). The recommendation further states that this list is only the first attempt for addressing incidental findings, and clinicians should expect ongoing changes and additions. The Working Group from the ACMG also specified that mutations identified in the 57 identified genes should be reported back to the clinician regardless of the age of the individual undergoing testing. A final key component of their recommendations I would like to comment on is the fact that the Working Group places the clinician who orders the initial WGS/WES test as the individual responsible for providing pre- and post-testing counseling to the patient regarding the implications of receiving possible incidental findings (R. Green et al., 2013).

This recommendation represents a significant departure from the traditional philosophical approach in medical genetics to honor autonomy. As a result these recommendations have generated tremendous amount of negative responses from individuals in the medical genetics community who provide clinical genetic testing. Most do not agree with these recommendations because by providing incidental findings to a patient in the manner suggested, patient autonomy is violated as the patient right to

choose what he wants to learn is taken away. Neil Holtzman wrote a letter to the editor in response to the ACMG recommendation and stated that the ACMG recommendations "are flawed scientifically as well as ethically (Holtzman, 2013)". He goes on to make the argument that such recommendations are premature because no one has adequately established what the benefits, limitations or costs are from disclosing incidental findings (Holtzman, 2013).

Another letter to the editor written by a group from the University of British Columbia wrote that these recommendations have not considered the voice of the patient and families who are considering genome sequencing. Similar to my own argument for a patient centered informed consent practice (discussed in chapters five, six and seven), this group argues that to produce a more ethical and effective outcome, recommendations for disclosing incidental findings must include patients' perspectives (Townsend, Adam, Birch, & Friedman, 2013).

Healthy individuals interested in undergoing WGS/WES often seek out genome sequencing on their own and can accomplish sequencing through a direct-to-consumer laboratory. Direct-to consumer genomic testing provides direct access to genome information without the involvement of a physician or other medical provider. The debate over how to inform a patient on the implications of learning about multiple genetic risks factors identified through genome sequencing was initially addressed in 2007 with the introduction of personal genome testing marketed directly to consumers by commercial laboratories. These types of tests are marketed as a personalized risk assessment designed to provide individual information about genetic risk factors for a variety of common diseases, such as cardiovascular risk factors, cancer and other common illnesses.

Information about carrier status for more traditional Mendelian disorders such as cystic fibrosis or hemochromatosis as well as autosomal dominant conditions, are also available with personal genome testing.

Reaction to direct-to-consumer genetic testing from the academic medical and research communities was swift and sharp. Bioethicists, medical geneticists and academic researchers bemoaned the companies who offered genetic testing for not including a medical practitioner into the personal genome testing protocols. Most criticized these direct-to-consumer laboratories for offering genomic testing prematurely without the appropriate scientific validation for many of the common disease variants being reported or the required laboratory regulations in place (McGuire, Diaz, Wang, & Hilsenbeck, 2009). Medical professionals and researchers feared DTC personal genome testing would harm individuals who underwent such testing. The chief medical director of the Cancer Genetics Clinic at Baylor College of Medicine expressed her concerns about direct-to-consumer marketing of genetic testing in a *New England Journal of Medicine* article; "...members of the public are getting tests that they don't understand, and their physicians may not understand, and they may be making big decisions that are ill-informed" (Wolfberg, 2006).

Individuals who participated in personal genome testing also expressed caution to others who are considering ordering a genetic test online. A survey conducted on social networkers attitudes about direct-to-consumer genetic testing felt it was important a medical professional who is an expert in the field of genetics, remain involved in the process of personal genome testing and be available to help individuals understand their results. This cohort of individuals also reported that they planned to consult with their

own primary care physician about their personal genome results which implies, that although the personal genome test was not designed to be used in medical decision making (as stated by the companies themselves), individuals undergoing personal genome testing consider the information reported to them to be medically actionable (McGuire et al., 2009).

The initial outcry after the debut of direct-to-consumer genetic testing has all but disappeared. WGS/WES sequencing has taken center stage. What solutions for how to better inform patients before undergoing personal genome testing were offered from the initial spark of interest generated from personal genome testing offered directly consumers? In my estimation, no solutions were proposed. The companies offering the testing claimed the type of information reported from their service is not intended to be used in standard medical care and therefore, they largely ignored the issue of informed consent. They fully informed individuals undergoing testing that the data should be considered research and not incorporated into clinical medicine. In addition, because this is a commercial product, as with any other product on the market, it is a buyer beware world. Direct-to-consumer marketing of personal genetic tests can be considered a superficial dry run of the issues now facing WGS/WES.

Effectiveness of Informed Consent Proposals for WGS/WES

The problematic areas of the consenting process which have risen to the surface throughout this discussion are; (1) how to manage and report on a large number of variants, including mutations and variants of unknown clinical significance; (2) whether

and how to report variants of unknown clinical significance; (3) whether and how to re-contact individuals when new information is made available about their genome; and (4) how to incorporate results into patient care and our current health care system. The solutions offered from a review of recommendations published in the literature for both research and clinical WGS/WES consent protocols offer no innovative approaches for addressing these consenting complexities. Instead, these solutions represent inconsistent solutions on how to report genomic data, due in large part to the lack of agreement on what type of data to report and how to interpret variants identified. Further, there is no standard method for incorporating data into a patient's medical record. There is no solution proposed for how to follow-up with patients when new data is available about their WSG/WES results, and many times, much of the genomic data produced from sequencing is not made available to patients. Finally, there is no standard policy for how to report variants with unknown significance.

While there has been no consensus reached throughout the community of genetic stakeholders: research, medical, private sectors or patient groups, for how to obtain informed consent for WGS/WES, there is a unified appreciation of the complexity involved in obtaining informed consent for WGS/WES. All stakeholders agree that we are grossly unprepared for what is already upon us, and that is the desire to try and incorporate data generated from WGS/WES into a patient's clinical care. Acknowledging the enormity of the situation and spotlighting some of the major departures from the traditional genetic testing model WGS/WES takes us, is where the common ground stops. At the point of considering a solution tailored towards solving informed consent issues of WGS/WES, clinicians and researchers alike are adhering to the traditional approach of

the existing model of informed consent. As has already been discussed, the nature of WGS/WES does not lend itself to providing an opportunity for patients, or their clinicians, to know exactly what will or will not be identified at the completion of a patient's sequencing. Nevertheless, traditionalists adhere to their principles; reveal only genomic information that the patient consents to receive; incorporate genomic data with clinical implications only into the medical care of the patient; and develop practice guidelines for how to best present genomic information (McGuire et al., 2008).

There are some who I will refer to as innovators, who have started to discuss ways in which to consider new consent models. In response to the criticism of direct-to-consumer marketing of genomic tests, an editorial written in *Nature Biotechnology* challenged the policy makers and members of the medical community to reevaluate their roles as gatekeepers for access to genomic testing ("In need of counseling?," 2008). The author expressed concerns over the possibility that by promoting old models of informed consent in which the physician would determine who is best suited for undergoing genomic testing, the process of undergoing genomic testing and realizing the benefits from the testing will be stalled before the potential of this testing is even realized. A solution offered in this editorial would be to develop a system of stratification for the various tests based on which ones required medical oversight and which required no oversight ("In need of counseling?," 2008). While the innovators are beginning to offer solutions that help researchers design informed consent models that push us to think outside the box, the suggestions offered are inadequate for addressing all the issues relevant to WGS/WES and further do not push the current standard of informed consent

models far enough to be considered novel and capable of managing the complexity of WGS/WES.

The status of the informed consent process for WGS/WES today is essentially at the point where most agree the current protocols are not going to be effective and many agree that pretest counseling for genomic testing is going to require significant changes to the existing models (Sharp, 2011). Yet, at this time, most proposals for informed consent are enhanced versions of the existing model, modified enough to incorporate discussions surrounding the different type of data produced from WGS/WES, but not enough to fully reflect on the dynamic nature of the technology. While many of the articles I reviewed focusing on informed consent challenges for WGS/WES, acknowledge the types of complexities inherent to genome sequencing, none of the articles or clinical protocols for WGS/WES consider the issue of whether the informed consent protocols used in clinical practice since 1957, are even effective at fulfilling the ethical requirements of the informed consent experience. In my opinion, the most concerning issue with the proposed informed consent protocols just reviewed is that while there is unequivocal acknowledgement that WGS/WES is a game-changer for the informed consent process, I did not review any articles or identify any studies that acknowledge the limitations and ineffectiveness of existing informed consent processes and the subsequent relevance of this fact to the discussion on how to write informed consent protocols for WGS/WES. This is problematic when considering how complex whole genome sequencing is as a technology, but what is more important, is that individuals who are seeking important and critical information for their health care, may not benefit from WGS/WES if the informed consent process is ineffective.

As I discussed throughout my analysis of the existing informed consent process by physicians and health care providers in chapter three, most agree that the informed consent process is not focused on the goal of the informed consent process, but on whether consent is achieved and how institutions document the fact that the consent process occurred. The primary driver of the traditional informed consent process is to fulfill the legal obligation of informed consent as a requirement in medical care. While there are ethical underpinnings identified in the legal components of informed consent protocols, the consenting process is largely written as a check list of what information should be covered to ensure a patient is fully informed of the risks, benefits and limitations of a recommended test. The protocols are not written to allow flexibility for physicians to tailor the consent process towards the patient's values, beliefs or goals. As a result, the consenting process never adequately addresses the purpose of informed consent, which is to ensure individuals fully understand the implications on their lives and their families for undergoing WGS/WES. Herein exists the most fundamental criticism of current informed consent protocols; the process was developed in response to the legal requirement to fully inform a patient of possible risks, benefits and limitations of a recommended procedure or treatment option, and continues to perpetuate in medicine, as a legal requirement, while largely ignoring or avoiding the question of whether the process itself is truly effective in achieving the goals of the informed consent process to promote autonomy, encourage rational decision making and self-determination in making medical decisions.

The fact that our current informed consent protocols for genetic testing are not effectively addressing the ethical obligations they are required to embody, but are

becoming implemented into the creation of informed consent protocols for WGS/WES, should be a real concern to everyone engaged in the conversations about how to design informed consent protocols for WGS/WES. My review of the literature and my experiences with the implementation of the informed consent process for WGS/WES in clinical care, and even within research protocols, identified no groups who are asking whether our existing informed consent protocols are adequately obtaining consent. Instead all the groups who are focusing on this issue at this point are struggling with the issue of reformatting traditional informed consent practices to fit around the complexities of WGS/WES. Much of the discussions surrounding informed consent are also focused on how to appropriately manage the information obtained from genomic sequencing. Yet, in the context of informed consent discussions, the term "manage" does not refer to how to analyze or interpret that data, but rather, how to control what type of genomic information an individual receives from their own genome sequencing and how to explain a large amount of information during a single informed consent session. While establishing what type of genomic information is relevant to the clinical care of individuals is no doubt a critical component of genome sequencing, this issue might be irresolvable because that data is continuously changing, and further, this issue in of itself does not deal with the underlying problem of how to properly consent individuals before WGS/WES. Most researchers and clinicians therefore, are not solving the right problem, which is; regardless of the complexities inherent to WGS/WES, how can medical providers effectively obtain informed consent in the manner that fulfills the underlying *ethical* obligations of the consenting process.

The remainder of this dissertation is going to focus on solutions for the two major issues discussed throughout this document; how to effectively consent individuals undergoing WGS/WES in a manner that upholds the underlying ethical obligations of the consenting process? And, how to perform informed consent for a complex technology such as WGS/WES?

CHAPTER 5

SOLUTIONS FOR IMPROVING INFORMED CONSENT PROTOCOLS FOR WGS/WES

The fact that we are considering alternative consenting protocols for WGS/WES provides an important opportunity to evaluate our current methods for obtaining informed consent. These alternative protocols should draw on the components of current protocols that are effective and work well. Yet, there is also a unique opportunity to evaluate the components of informed consent, which have not worked effectively in the past, and to modify these components when designing informed consent protocols for WGS/WES. Incorporating components of current informed consent protocols that are effective and modifying those that are not effective will ultimately result in the creation of a novel and more meaningful informed consent process for WGS/WES. As I demonstrated in chapters three and four, current informed consent protocols are largely ineffective at promoting patient autonomy or rational decision making because the process itself is more about an obligatory recitation of possible legal issues arising from undergoing a specific procedure or following a recommended therapy. The content of the consenting process is mostly designed to protect medical providers and medical institutions from litigation following an adverse outcome. In this chapter, I will offer a solution to this problem that will enhance the informed consent process for both patients and medical professionals.

The solution I offer to enhance the informed consent process for both patients and medical professionals is to restructure the informed consent process according to the original intent and goal of the process. The original *ethical* purpose of informed consent,

stripped of its legal underpinnings, is to tailor a consent discussion around the goals, values and belief system of an individual patient (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Making Health Care Decisions, 1982). Much like an individual genome is unique to the person who is sequenced, so too should the informed consent process be unique to the person considering sequencing. The idea that a patient's goal for undergoing WGS/WES should remain at the center of the informed consent protocol sounds intuitive, yet my analysis of the informed consent protocols for genetic testing and other medical procedures revealed that current protocols have not honored this objective. This chapter describes a consent protocol for WGS/WES that is structured around the patient's goal(s) and/or intent for undergoing WGS/WES. I propose a design of an informed consent process for WGS/WES that is guided by four key principles that serve to preserve and enhance the existing informed consent process: 1. Identify patient goals for undergoing WGS/WES at the beginning of the informed consent process, 2. Structure the informed consent session around stated goals for undergoing WGS/WES and patient's understanding of why they are pursuing WGS/WES, 3. Incorporate a psychological/psychosocial assessment into the informed consent process, 4. Offer online and in-person methods for obtaining informed consent.

These four principles are drawn from: original ideas grounded in the ethical principles of what informed consent was written to achieve, new ideas developed in response to the complexities of WGS/WES and, existing genetic counseling informed consent protocols. In this chapter I discuss how these four principles result in an informed consent process that empowers patients to make an informed decision about undergoing

WGS/WES. In the next chapter (chapter six), I describe each step of the informed consent process for WGS/WES and illustrate how the four principles outlined in this chapter guide the informed consent process to accomplish a more effective consenting interaction capable of responding to the complexities of WGS/WES. The subsequent chapter (chapter seven) demonstrates how the informed consent process described in chapter six occurs within the larger context of whole genome sequencing and how WGS/WES can operate within our existing medical model. Chapter seven concludes with a description of how the informed consent process and model described in chapters six and seven, enhance existing informed consent protocols, fulfilling the ethical obligations of informed consent and effectively addresses the complexities of WGS/WES.

Principles of a Patient Centered Informed Consent Protocol for WGS/WES

1. Identify patient goals for undergoing WGS/WES at the beginning of the informed consent process

Shaping the informed consent protocol for WGS/WES around the stated purpose(s) and goal(s) of individuals undergoing WGS/WES is accomplished by initiating the informed consent procedure with a discussion about the intention and/or understanding of WGS/WES from the patient undergoing the sequencing. The initial response from the patient will guide the consenter on what information is necessary to discuss with the patient to help the patient further understand and define their goals as well as manage expectations for what they hope to achieve by undergoing WGS/WES. Throughout the remainder of this document, I will use the term consenter to describe the role of the individual responsible for consenting patients. This individual could be a genetic counselor, a physician, a physician's assistant, a nurse or even a psychologist or

psychiatrist. Consenters would undergo advanced training in genomics with an emphasis on many of the same counseling techniques taught to genetic counselors due to the similarities between the consenting process I propose for WGS/WES and components of a genetic counseling session.

If an individual states their goal for undergoing WGS/WES is to learn about their risk for developing any type of disease in the future, the first step in the consent process would be to further delineate which diseases they might be most concerned with and why? After establishing a more focused list of conditions (or even if the list remains broad), the consenter would inquire why the individual wishes to learn about possible disease risk factors? Perhaps there is a family history of a particular disease and this is why the patient is motivated to learn about their genomic risk factors.

Remembering our couple, Bill and Melinda, Bill is worried about his risk for prostate cancer because of his family history of prostate cancer. Melinda is concerned about possible diseases she and Bill might pass down to their future children. In this situation, one of Bill's goals for undergoing WGS/WES would be to learn about his risk factors for prostate cancer. One of Melinda's goals is to identify any genetic conditions they might pass to their children. The consenter at this point has a tangible goal to note and refer to throughout the remainder of the informed consent session. This goal may also be revised throughout the informed consent process as the patient learns more about the process of undergoing WGS/WES. This process will likely be repetitive as additional information is provided to the patient over the course of the consent discussion. The reiterative component of informed consent conversations, in the case of WGS/WES, is likely to result in a more comprehensive understanding of the type of information

individuals will garner from sequencing, in addition to a deeper understanding of the complexities of the sequencing process.

At the same time the patient is explaining their goals for what they hope to achieve after undergoing WGS/WES, the consenter can also ask the patient to tell them what they hope to learn, better understand or discuss during the informed consent process. If a patient had no expectations from the informed consent process, then the consenter could elaborate first on what types of information can and will likely be discussed during the consenting interaction. This review might prompt the patient to consider some component of the sequencing process they might want to know more about. Once the patient and consenter have agreed upon several outcomes that the patient would like to reach at the conclusion of the consent process, the consenter will document this information in the patient's electronic record and ask the patient to complete a standardized form listing several common goals for informed consent, so that these goals can be scored at the completion of the process. Also, patients will have an opportunity to evaluate the process after they receive their first set of genomic results, if they choose to continue with genomic sequencing.

Individuals, whose physicians recommend they undergo WGS/WES, would likewise benefit from this type of informed consent protocol. When a physician recommends WGS/WES, a patient in this situation would begin their consent process by stating what they understand about the testing recommended to them and the possible results that would be available once testing was completed. The consenter is therefore going to help the patient define and understand the reasons WGS/WES was

recommended and how the sequencing might help them accomplish the goal of better defining, understanding and/or treating an ongoing disease.

Additional examples of how individual goals are obtained at the beginning of the informed consent process are provided in the next chapter as well. The goal of this chapter is to introduce the concept and principles of a patient centered informed consent protocol.

2. Structure the informed consent session around stated goals for undergoing WGS/WES and patients' understandings of why they are undergoing WGS/WES

Once a patient articulates the rationale and/or understanding of why they are requesting WGS/WES, or why their physician is recommending WGS/WES, the consent process should be shaped around this stated goal. In other words, all subsequent conversations surrounding scientific information about genomics, the limitations and benefits and unknowns of the technology, should always be discussed with the patient's stated goals as a focal point. For example, Bill wanted to undergo WGS/WES to learn about his genetic risk factors for someday being diagnosed with prostate cancer. His session would therefore be focused around helping him understand how WGS/WES could better quantify, or subsequently not quantify, his risk for being diagnosed with prostate cancer in the future. To better understand his risk factors, the consenter would review his family history of prostate cancer and his personal history if relevant. The session would then move to a discussion about genomic concepts which would help Bill better understand types of results he can expect from his genome sequencing and how these results are used to predict disease risk.

Already established informed consent protocols for genetic testing have identified the education component as a critical factor in fulfilling the obligations of informed consent. Most agree that the genomic education component of all informed consent protocols for WGS/WES needs to be enhanced from the traditional genetic testing protocols, to include additional genomic facts and definitions that are characteristics of the type of data produced by WGS/WES. In order for patients to make informed decisions, they must understand the information presented to them, and given the complexities of WGS/WES, education about genomic terms is absolutely necessary to enable patients' ability to understand the results from WGS/WES. When patients understand the type of genomic information that WGS/WES can and cannot provide them, they will be better able to determine whether WGS/WES will accomplish their stated goals at the beginning of the informed consent session thereby feeling empowered to make a decision regarding what type of information available from WGS/WES about their genome they may wish to learn and why.

3. Incorporate a psychological/psychosocial assessment into the informed consent process

Incorporating a psychological assessment into the informed consent process is not a requirement of the traditional informed consent requirements written in the 1950s, and was only added to the informed consent process once genetic testing became available in clinical care. A key tenet of genetic counseling theory is that complex genetic information provided without addressing underlying psychological concerns or responses to the information presented, will commonly result in the inability for a patient to

correctly understand the information provided to them. The ability to comprehend the inarguably complex medical information presented during an informed consent session is determined to some extent, by a patient's overall psychological state. Studies I reviewed in chapter three suggest that patients are better able to incorporate the implications of being diagnosed with a genetic disorder or the implications of learning about carrying a risk for a genetic condition, and the subsequent implications for their own health and potential risks to relatives, if their psychological concerns are also being addressed (R Klitzman, 2009). Therefore, the psychological implications of undergoing genetic testing require an important space in the informed consent process. The studies which suggest that patients will understand statistical data better when their psychological issues have been addressed should guide us in providing more effective informed consent for whole exome and genome testing.

A recent commentary written by psychologist Steven Pinker, published in a 2009 article in *The New York Times,* discussed the seemingly universal belief that individuals associate ***who*** they are as a person to be primarily determined by their genetic make-up (Pinker, 2009). Regardless of whether scientists support the genetic determinism argument, when a large majority of the population believes in it, then all discussions about individuals' genetic makeups, and implications of such, should incorporate an individual's belief system of how they think their genes define them as a person or the degree to which they believe their genetic make-up causes risk for specific medical outcomes. To adequately address an individual's belief system surrounding their genomic make-up, a conversation needs to occur throughout the informed consent process to help individuals define, anticipate or even better understand, how they might be

psychologically affected when they learn information they might not be expecting and certainly information which predicts the possibility of having a disease they might have always been worried about.

While the incorporation of a psychological assessment of the patient into the informed consent process is new to most who have consented patients in the past, I argue that by addressing patients' psychological status and important psychosocial issues, the informed consent process will become much more patient directed and focused on content that facilitates autonomous and rational decisions. For example, Bill is worried about his risk for being diagnosed with prostate cancer, therefore the consenter would spend time during the consent process providing anticipatory guidance for how he might respond to the information about prostate cancer risks derived from WGS/WES. The consenter would also incorporate a discussion about the type of screening for prostate cancer that would be available, if Bill's WGS/WES results reported an increased risk for this cancer. Essentially, knowing what the patient wants to learn about from WGS/WES can guide the consent process to be as tailored as necessary to each individual case.

Melinda on the other hand is worried about passing on a hereditary disease to her future offspring, as well as possibly succumbing to the same illness as her father. The psychological issues to address with her would to help her anticipate any possible feelings of guilt she might feel if she were to test positive for any of the hereditary conditions she is worried about. She is more than likely also afraid of what she might learn from her sequencing and just asking her to acknowledge this fear, and reassuring her that this is a normal response to learning about her future medical risks, is a supportive strategy for her during her consent process.

4. Offer online and in-person methods for obtaining informed consent

Existing methods for obtaining informed consent before genetic testing vary widely, from structured in-person genetic counseling sessions to signing a form with no discussions about the implications for undergoing the testing performed, as summarized in chapter three. To clarify, I use the word method in this context to explain how the consent process is conducted, which is different from components of the process described in the next chapter. The informed consent process defines the steps of the consenting process and is consistent regardless of the method for obtaining consent.

A patient centered informed consent protocol requires evaluating new methods for obtaining consent. Also, a patient centered informed consent process designed around individual goals for undergoing WGS/WES needs to be accessible and understandable to individuals with varied backgrounds; including everything from gender and age, to a person's cultural values, to education level and socioeconomic status. As I reviewed in chapter three, individuals have different learning styles, and preferences for how they best learn and communicate. This implies that some individuals will require in-person consenting procedures and others may prefer online methods for consenting. Therefore, several methods for obtaining informed consent should be made available to individuals undergoing WGS/WES.

To address the spectrum of differences between individuals who elect to undergo genomic testing, I propose an online version of informed consent, an in-person version of informed consent and a combination of both modalities. The online version of informed consent begins when the individual logs into an online patient portal. One online version

of informed consent could include a virtual face-to-face component over the internet, through a videoconference or Skype. The other type of online version is a self-guided process through the consent process. A self-guided consenting program would be designed to walk patients through the same steps they would take if they were meeting with a consenter in-person or if they were interacting through a videoconference or Skype. Patients who elect to undergo the online version without speaking to a person would be able to request an in-person conference at any point during the consenting process. Therefore, while the patient chooses the method they prefer when they enroll in the informed consent process, it would be possible to change methods at any point in the process. The in-person module begins the same manner, with the patient logging onto his or her own portal to begin the process. An appointment would then be established for the patient to continue with the consenting session in-person.

In my opinion, offering a variety of methods for obtaining consent will greatly improve existing consent procedures for several reasons. The first is that the structure of an online process will eliminate the vagueness of our current consenting process in which there are no specific protocols or methods for assigning responsibility for who obtains consent. Designing an informed consent model build for several types of consenting will result in the creation of set protocols for consenters to follow, which will serve to maintain consistency throughout all consent processes. In every informed consent process, an element necessary for the process to work effectively is to have a medical professional appropriately trained to perform the consent process. The on-line consent process will still include a consenter who interacts with the person undergoing WGS/WES, but it will be a virtual interaction rather than an in-person consult. Each

method however, will have a defined role for the consenter, which allows for not just an assignment of responsibilities, but also puts into place the accountability component of informed consent necessary to fulfill its legal obligations.

A second improvement to existing informed consent protocols achieved by offering several models to obtain consent is that by providing several methods for consenting, patients have specific options, based on their own preferences, for how to be consented. Offering options that fit patient preferences for learning and communication could enhance the practice of consenting by creating a positive, user-friendly experience for the patient. Because the younger generations are being raised with computers and grow up surrounded by technology, the online method for informed consent will most likely be their preferred method for managing health care issues, making this protocol ideal for future generations. I believe by taking ownership of the process, patients will be more invested in the outcome of undergoing WGS/WES and be attentive and interactive in the consenting process. The positive experience would likely result in increased understanding of the consequences from undergoing WGS/WES ultimately resulting in a more successful informed consent experience.

A third improvement is that the enthusiasm of the patient could also enhance the experience of the consenter. When a patient is participatory and interactive, the consenting process will be more effective and the individual providing consent will better appreciate their role in the process and feel that their interactions with the patient might make a difference with the patient, when results are disclosed after sequencing is completed. Another benefit for an online process of informed consent is how well it will work with electronic medical records as well as with the transfer of genomic data

between the laboratory and the patient as well as the physician's office. This process will be further described in chapter seven.

These four principles, which shape a patient centered informed consent process, have the potential to be more effective at fulfilling the legal and ethical goals of informed consent as they were written in the 1950s. Constructing an informed consent process according to the patient's goals allows the patient to guide the consent process thereby creating an environment where the patient is able to make an autonomous decision. In addition, patients will be active participants in their own health care decisions when informed by medical specialists on the meaning of possible genomic test results, implications of such results, and therefore, be empowered to make decisions that fit with their stated goals and understanding of the type of information available if they elect to undergo WGS/WES.

The education component of the informed consent protocol addresses the legal obligations for medical professionals and researchers to fully inform a patient regarding the possible limitations, benefits and consequences from undergoing WGS/WES. Also, the education component of the protocol provides the necessary information for a patient to feel empowered when making important decisions. The psychological component of the informed consent protocol allows space for the patient to consider some of the potential negative effects from WGS/WES and the consequences of knowing the results for themselves, and family members.

In addition, and perhaps most importantly, the informed consent process I am proposing is constructed around an ongoing conversation or dialogue with the patient. An ongoing conversation in this context refers to multiple consenting conversations, which

occur over several years in many cases. The example for how could be achieved is provided in chapter seven. A give and take exchange of information is more consistent with both the legal and ethical requirements of informed consent practices. Providing a "space" for this dialogue allows for patients to ask questions, and for the consenter to provide clarification to the patient. The goal would be for a patient to have enough time as well as opportunities to fully comprehend the implications of undergoing WGS/WES. I believe that this is the type exchange, which was initially intended by the authors of the initial informed consent protocols.

In the next chapter, I apply these four principles for how to design and informed consent protocol for WGS/WES, to the actual consenting steps. Further elaboration for why and how this novel informed consent approach more adequately accomplishes both the ethical obligations of informed consent while addressing the complexities inherent to WGS/WES is reviewed at the end of chapter seven.

CHAPTER 6

PATIENT CENTERED INFORMED CONSENT FOR WHOLE GENOME AND EXOME SEQUENCING

In this chapter, I outline the design of my proposal for a patient centered informed consent process for WGS/WES structured around the four principles reviewed in the previous chapter. To fully appreciate the components of my proposed informed consent process, I will describe the consent process for WGS/WES, from beginning to end, incorporating Bill and Melinda's story to illustrate the real-time flow of the informed consent process.

A consenter guides the consent process. As described in the last chapter, a consenter is an individual trained in the area of genomics. The consenter in my model could also be an online module for patients who elect to undergo sequencing through a self-guided consenting process. The consenting steps I will outline in this chapter will be the same whether the consenting occurred through an online self-guided protocol, or online through a videoconference or Skype interview or with a traditional, in-person interview. The role of the consenter is to help the patient through the process of understanding the results and implications from undergoing WGS/WES, thus fulfilling the legal requirements of informed consent. The goal of a consenter is also to facilitate the patient's process of undergoing WGS/WES by following the patient's goals as discussed in the next nine steps, thereby fulfilling the ethical requirements of informed consent.

Informed Consent Process for WGS/WES

1. Patient portal and data entry

In keeping with the theme that the patient, not the technology, the information, or the physician, should be the central focus of a more effective informed consent proposal for WGS/WES, I propose the informed consent process start when a patient initiates the process on their own. Initiation of informed consent specifically means that a patient will create their own portal by entering demographic information, family history, and medical history as well as stated goals and their understanding of why they are electing to pursue WGS/WES (or their physician is recommending the patient consider pursuing sequencing).

For example, if Bill were to log onto the patient portal, his goal for undergoing WGS might be to learn about his lifetime risk for prostate cancer and to learn whether he carries the genetic mutation for Huntington's disease. Melinda's stated goal might be to learn which genetic conditions her future children could be born with and to learn whether she has a genetic pre-disposition for heart disease.

Whether the patient or their physician is recommending WGS/WES, the patient will always initiate the process. Since the consenting methods include options for on-line consenting or in-person consultation, if the patient elects to meet with someone for in-person consenting, the process will still be initiated with an online account created to maintain consistency of the basic demographic information, family and medical history as well as a summary of the stated goals for undergoing WGS/WES, from the patient.

The consenter will contact the patient to make an appointment to meet with the individual who will provide consent.

Upon completing the initial intake process, a software program designed specifically for the informed consent process for WGS/WES will format and analyze the patients' demographic and medical information and the consenter, before the first interaction with the patient, will review the family history information. The individual who consents the patient will schedule either an interview with the patient through a videoconference, Skype, in-person or a final option for consenting, a self-guided online consent process.

2. Stated goal(s)

The first interaction between a patient and consenter will include a discussion about the rationale for why the patient is interested in pursuing WGS/WES or the patient's physician is recommending the patient consider WGS/WES. In the case where the physician is recommending the sequencing, the consenter will determine what the patient's understanding is of the physician's rational for recommending WGS/WES. Once the patient can articulate the rational for undergoing WGS/WES, the consenter will focus on defining the patient's goals for pursuing WGS/WES. For example, a patient might tell the consenter; I am interested in having my genome sequenced to learn what my chances are for being affected with heart disease, colon cancer and multiple sclerosis in the future. When asked why they want to know about the risk to be affected with these diseases, the patient might respond: To inform my doctor of potential risks for heart disease for example, so that my doctor can 'screen me more carefully.' The consenter

would then pursue what 'screening me more carefully' means to the patient. At this point, the consenter would inquire why they are concerned about these diseases specifically. The patient's family and medical history would be added to the discussion and reviewed with the patient at this point as well. Often patients have concerns because of a family history of a particular disease, and therefore, a review of the family history fits nicely while clarifying and understanding patients' reasons for pursuing WGS/WES. In other cases, the patient may have symptoms that might suggest the patient has a possible disease so they elect to undergo WGS/WES for further clarification of a possible diagnosis or increased susceptibility for a disease.

If Bill were asked to state his goals for undergoing WGS/WES, he might prioritize the list of conditions he is concerned with: prostate cancer, Huntington's disease, and possibly other conditions which he might pass along to his children. Bill would share his family history information and explain why he was interested in pursuing genetic testing for Huntington's disease when he had no family history of this condition. The consenter would be able to explore Bill's fears surrounding this condition, and provide the necessary education (next step) to help Bill understand why he is not at an increased risk for Huntington's disease.

Melinda would state that she is primarily concerned with cardiac disease and any conditions that might affect her future children. The consenter would be able to spend time learning more about what types of conditions she was afraid to pass to her children and discuss why she was concerned about these particular diseases. Also, discussing the types of conditions, which she might pass to her future children at this point in the consent process, gives the consenter information for how to address Melinda's education

section of the consent process. Specifically, that she needs to discuss autosomal recessive inheritance patterns and review prenatal testing and screening options with Melinda.

In many cases, a physician requests their patient undergo WGS/WES to provide additional support for a suspected diagnosis. When the physician is recommending WGS/WES, then the initial discussion regarding the goal for undergoing WGS/WES should be focused on what the patient understands about why their physician is recommending they pursue WGS/WES. If the patient does not fully understand the reasons, the consenter might inquire how much more the patient wants to learn about the reasoning for pursuing WGS/WES. I believe in many of these scenarios a patient will be appreciative of more discussion about the sequencing and what type of information is available and how the information learned from sequencing will help them from a medical standpoint.

Of course, there are other implications of undergoing WGS/WES, beyond just obtaining a better understanding of a specific diagnosis, and an ideal time to determine how much information beyond understanding the reason sequencing was recommended the patient would like to know is at the beginning of the consent process. The reason for this is so that the patient and consenter can decide together what type of information to focus on as they continue the consenting process. If the patient is unaware of what other diseases they might learn about through sequencing, the consenter might ask if they are worried about risks for other diseases or whether they might have concerns about diseases they could pass to their children?

As important as discussing what type of information patients want to learn from WGS/WES is, it is also important to review the type of genomic information regarding

possible risk for diseases the patient would not want to learn of. Focusing the first part of the consent process on what it is a patient may not want to learn is unique to WGS/WES due to the vast amount of information available at the conclusion of the sequencing. At this early stage of the consent process, it would be unrealistic to expect the patient to fully understand all the various types of results, which are possible from WGS/WES, and the purpose is not to insist that the patient fully understand the various results that might be available. The purpose of discussing what the patient would and would not want to know about the type of potential disease risks or carrier risk information obtained from WGS/WES is for the consenter to gain insight into what the patient understands about WGS/WES and what type of disease risk the patient does or does not want to learn before further information about WGS/WES is provided to them.

Bill might not have any concerns for learning about his genomic risk factors, whereas Melinda might not be interested in knowing about adult onset conditions for which there is no treatment due to her fear of passing this information to her children. On the flip side of course, she may want to know everything about all possible diseases. The consenting conversation is designed to elucidate what information matters to Bill and Melinda, and why, so the consenter can explain how well WGS/WES will accomplish their goals and what the limitations of the technology are for accomplishing their various goals.

The process described above can be compared to the first part of a genetic counseling session and is known as ‘contracting.’ Contracting is where genetic counselors learn what it is a patient understands about their genetic counseling appointment and why they were referred for genetic counseling. Contracting is a way in

which to establish 'rapport' with a patient, and build trust with the patient (Baker et al., 1998) as well as establish agreed upon set of topics to review together during the genetic counseling appointment. After eliciting the patient's understanding of the appointment, the genetic counselor will often clarify any misconceptions about the appointment if necessary, and then continue with a summary of what will be discussed with the patient during the genetic counseling session. The patient is also asked at this time whether they have additional questions or concerns they would like to discuss. Most genetic counselors have their own 'checklist' of issues they feel are relevant to helping the patient understand the type of genetic testing the patient was referred to discuss, as well as implications from the testing. Due to the often-large amount of information the genetic counselor feels is necessary to cover during the session, the priorities of the patient are often not readdressed because there is not enough time remaining in the session.

While my proposal for identifying a goal at the beginning of the informed consent process for WGS/WES is similar to the contracting component of genetic counseling, the major difference with my proposal is that after learning what the patient's goals are for undergoing WGS/WES, the consenter remains focused on these goals. I am not proposing eliminating all the current informed consent components now recommended, but rather propose these comments be incorporated when possible, into the patient's goal as discussed below. In my experience, the most effective informed consent sessions are those that remained focused on what the patients want to learn rather than on what the experts believe is most important to discuss. As I hope to illustrate as I continue to build my informed consent process, ultimately all the information about WGS/WES necessary for a patient to be able to fully understand the rationale and expectations and

consequences of undergoing WGS/WES can be addressed when the consent process remains focused on what matters to the patient.

3. Education module

After the consenter and patient have agreed upon a preliminary list of the type of diseases the patient is interested in learning about through sequencing their genome, the education component of the consenting process begins. The education elements of the informed consent process consist of providing the necessary scientific background about genes, genomic testing, and methods of testing related to the various types of genomic information the patient is interested in learning. Critical to the education component of the informed consent process is a review of key definitions, such as understanding the differences between a mutation, a variant, a variant of unknown clinical significance and polymorphisms.

Other information reviewed with the patient at this point would be an overview of how risk for diseases is determined by the laboratories performing the sequencing, the accuracy of the information generated from WGS/WES and how and why the results might change over time. If the patient wants to learn about their risk for colon cancer, the education would build from basic genomic terms, to an overview of current understanding about the role of genetic mutation in causing colon cancer, to a discussion of inheritance patterns of known hereditary colon cancer syndromes, and concepts surrounding genome wide association studies.

Bill is interested in learning about risks for prostate cancer. Because most genetic risk factors for prostate cancer are based on genome wide association studies, the

education component for Bill would be shaped around the necessary genomic terminology relevant to GWAS, such as the definition of a polymorphism, a variant and mutation. Other necessary background information helpful for understanding GWAS is to provide an overview about the design of GWAS and how the data is analyzed and disease associations are identified.

Unlike all of our current, more traditional informed consent process, this consent process can occur online. Education material provided online provide a unique opportunity for the consenter to use visual aids to describe the genomic terms as well as to review concepts of risk. Even if a patient does not elect to be consented online, they would have access to online visual aids after their first in-person consenting session, which can be advantageous for many, since multiple exposures to this information will likely lead to better comprehension of the information. In addition, patients can review the education module after their results are available and share the visual aids with family interested in learning the information.

Melinda did not have the same background in science as Bill and therefore might have benefitted from spending more time understanding what type of information would be available from genome sequencing. It can be surmised that a better understanding of genomic information would assist her with understanding the implications of her results. Melinda's schedule was sporadic because she did mostly freelance work. An online education module, that she could log onto at her convenience, would fit her lifestyle nicely and allowed her the freedom to go through the consenting steps at her own pace.

The purpose of incorporating an education module into the consent process at this point is to: 1. Prepare the patient for the risk assessment component of the informed

consent process where the consenter will explain how effectively WGS/WES might be able to meet the patient's stated goals and 2. To assist the patient with understanding the consequences of learning information about their genome, for their own health, their future health (because results will be expected to updated over time) and for their family members. In addition, at this point in the consenting process, the consenter will be able to pause briefly to "check in" with the patient to inquire how they are handling the information. If the consent process occurs online, patients can stop the process at any point, or continue onwards depending on how well they understand the information and how they feel about continuing. Many may feel overwhelmed at this point or some need time to absorb the information and the online module provides an opportunity to pause the process and continue at another time.

4. Risk assessment

The next component of the informed consent protocol would be consistent with existing informed consent protocols in genetic counseling practices (Baker et al., 1998) and that is to incorporate the patient's medical history and family history into the discussion of the likelihood WGS/WES would be able to meet the patient's expectations for WGS/WES. For example, an individual wants to learn about his risks for developing heart disease, colon cancer and multiple sclerosis. The consenter for this individual would take into account his family history, medical history, and integrate this into the discussion of what is known about cardiovascular disease genomic markers, colon cancer genomic markers, and multiple sclerosis genomic markers, to help the patient understand how effectively WGS/WES will better delineate their risk for developing these diseases. In

addition, the consenter would discuss whether other diseases the patient was interested in learning about could be identified during WGS/WES and how their baseline risk for the disease may or may not be changed at the completion of WGS/WES.

Also during this part of the consent session, the consenter would explain what other types of genomic data could potentially be revealed during WGS/WES, based on the individual's family history or personal medical history or population statistics. For example, 1 in 40 individuals of Ashkenazi Jewish ancestry test positive for a BRCA 1 or BRCA 2 mutation (Struewing et al., 1997). The types of genetic conditions which might be revealed during genome sequencing are Mendelian disorders, rare hereditary conditions, common diseases caused by common disease causing variant and of course, while not definitively diagnosed with sequencing, individuals need to be informed about the possible of having a disease linked to a variant of unknown clinical significance, but until the variant is fully understood, the initial results will report an unknown significance to a possible hereditary disease.

Equally important to the discussion at this juncture is to review with the patient the type of information WGS/WES cannot provide. For example, at this time, there is limited data available to determine which variants are associated with common conditions, such as cardiovascular disease or multiple sclerosis and therefore the patient would be informed it is not as likely this information will be identified through WGS/WES.

Both Bill and Melinda would have benefited from a risk assessment discussion since they were both interested in diseases with complex genetic causes (prostate cancer and heart disease). Because Bill was interested in learning about his risk for Huntington's

disease, which cannot be detected with WGS/WES, he would be informed at this point that this sequencing could not provide him with that information. Melinda would be able to inform the consenter about her family history of heart disease and the consenter would incorporate that information into her overall risk for developing heart disease based on her family history alone and based on the potential results from WGS/WES.

After reviewing the type of genomic information that could potentially be revealed at the completion of WGS/WES, the patient and consenter would reevaluate the patient's initial goals for pursuing WGS/WES. The patient would be given an opportunity to articulate how well they believe WGS/WES will fulfill their goals based on their understanding of the technology. In addition, the patient could decide what other types of genomic information they may wish to receive regarding disease risk factors they might not have been aware they could learn about until this point in the conversation. Alternatively, they would be able to decide what type of information they do not want to know at this time.

5. Psychological support

The psychological components of the consent sessions do not consist of a thorough psychological evaluation by a trained psychologist or psychiatrist, but are brief interludes conducted throughout the consent process to help a patient articulate how the information they are learning is affecting them. Most people are not aware that they might have an emotional reaction to the information they learn about their genome. Processing their emotions with another individual (consenter) provides an opportunity for

patients to be able to more effectively integrate the complex information they are learning about their genome into their psyche (sense of who they are) (Kessler, 1979).

The degree to which patients will require psychological support will of course vary with each individual, but, at a minimum, this part of the consent process might consist of a conversation with the patient about how they anticipate they will respond to the results, how they will communicate their results with family and friends and how this potential information will affect their medical care and lifestyle choices. Recall, addressing the psychological/psychosocial issues associated with a genetic diagnosis is already a standard part of the genetic counseling informed consent protocols discussed for Huntington's disease and Hereditary Breast and Ovarian Cancer Syndrome in chapter three.

The psychological component of the informed consent process might be as straightforward and simple as acknowledging and validating the patients' feelings at the time he is undergoing WGS/WES. For example, for a patient who learns through the consent process that their family history suggests a hereditary colon cancer syndrome and that WGS/WES would potentially be able to confirm this suspicion, the consenter might ask the patient if this new information was overwhelming to learn. The consenter would be validating the patient by stating that it is normal to feel overwhelmed with this possible threat of learning about a risk for colon cancer.

Providing normalization to feelings that arise during a discussion about genetic information is another genetic counseling strategy (Baker et al., 1998). Kessler has written that the knowledge one might be diagnosed with a genetic condition is all ego-threatening (Kessler, 1979). Therefore, medical providers who are involved in presenting

genetic information, or making the diagnosis of a genetic disease, have an important opportunity to help their patients effectively incorporate the news of this diagnosis into their lives which can result in a positive psychological adjustment to this otherwise disappointing diagnosis (B. Biesecker & Erby, 2008) (Burgess, 2001). While not a guarantee, the more effectively a patient responds to the knowledge of a genetic disease or risk for a genetic disease, the greater the chance for the patient to be willing to follow a recommended treatments or lifestyle modifications.

Melinda potentially could have benefited a great deal from a consenting experience that allowed her time to realize emotions (guilt, fear, anxiety) she might experience about the possibility she could have a child born with a genetic disease. She would have also been given an opportunity to discuss how she planned to work through these emotions if the results indicated she might test positive for an adult-onset disorder. Alternatively, because of the strong emotional reaction she had when she did learn about the genomic risk factors, both for herself and future offspring, if she had the opportunity to think about this potential outcome before she underwent WGS, she might have elected not undergo WGS at this point in her life.

Melinda also did not have health insurance and Bill had not yet bought a life insurance policy. The best time for individuals to obtain life insurance is before they learn about future disease pre-dispositions and the consent process for WGS/WES would allow time for individuals to postpone the initiation of a genomic analysis until they felt they had the adequate insurance policies in place.

Ideally, the same person who starts the consenting process with the patient will continue to work with the patient throughout the consenting process allowing ample time

for the patient to establish a comfortable level of trust with the consenter. Since there will be multiple opportunities to assess the patient's psychological status throughout the consenting process, there will be more opportunities for the consenter to intervene when necessary to assist the patient as they learn new, potentially threatening information. Psychological inventories, such as Beck's Depression Inventory (Beck, Ward, Mendelson, & Mock, 1961), could be incorporated into the online only version of the consent process. When a patient's survey noted a possible adverse psychological response, the on-line consent module would prompt an individual to reach out to the patient for an in-person discussion.

6. Evaluation of goals

Following the education module, risk assessment component of the process and after several brief psychological assessments, the consenter and patient will review the patient's initial goals for undergoing WGS/WES to determine whether these goals will remain the same or be altered because of new information learned through the consent process. For example, the patient who wanted to learn about his risk for heart disease, colon cancer and multiple sclerosis might learn that it will be unlikely WGS/WES will be able to delineate his risk for developing multiple sclerosis. The patient may choose not to learn about markers for this condition. Often times, patients may be informed that there are no identifiable genomic markers for a particular disease, but, in the future, this type of information might be available. Another possible scenario is that this patient may have learned that WGS/WES could inform him about whether he is at risk for carrying a mutation for a hereditary colon cancer syndrome. After learning of the possibility the

patient could review with the consenter the possible inheritance of the specific colon cancer syndrome he is at risk for and potential risks for developing colon cancer, the consent will check-in with the patient at this juncture to ask if this is information they may still wish to learn.

At this point in the consent process Melinda may decide not to learn about any possible adult-onset hereditary disorders because she knows she want to become pregnant soon. She might elect to only learn about any possible autosomal recessive hereditary conditions, which she might carry and potentially pass to her future children. The implications of knowing about these types of conditions might be all she could handle at one time.

7. Identify preferences

At this point in the process, the consenter will also provide the patient a list of the types of diseases that were discussed during the consenting process. The limitations of what is known and not know about various potential results will also be reviewed with the patient at this time. In addition, the consenter will discuss the limitations of WGS/WES and the uncertainty inherent in the type of results which could possible be revealed upon the completion of WGS/WES. After all the patients' questions have been satisfactorily answered, the patient will make their choices on what type of genomic information they wish to learn from their analysis.

The patient may select options based on their own goals for why they are pursuing WGS/WES or select options based on what their physician is recommending. The patient

may elect to learn no other information outside of their specific goals or they may elect to learn about as many diseases they can.

The patient will then be asked to select their preferences for how they want to be notified when their results are available. Because the process is online, patients may elect to receive an email message that their results are available. Patients can also elect to receive their results in person and request a phone call from the consenter to set up an appointment to discuss results together. A designated amount of time will be estimated for when results are available so that the follow-up can be scheduled at the appropriate time.

Due to the evolving nature of results generated from WGS/WES, patients will also be asked at this point in the process to select their preferences for receiving updated information. For example, when a variant of unknown significance is updated, patients select whether they want to be notified and if so, in what manner, either through email, letter, or a phone call, etc. For patients who are interested in having their genome reanalyzed over time, when the sequencing technology has been upgraded, there will be an option to select where they can be contacted when the technology has improved. In the next chapter, I discuss the manner in which a patient's genome can be reanalyzed without requiring an additional blood sample be sent to the laboratory.

Patients can also select which medical providers they want their genomic analysis to be sent to by indicating preferences for data transfer. Patients may request that their genomic information also be de-identified and distributed to a research database. The research database would 'store' de-identified genomic data and share the patient's data with the appropriate research studies. The communication of patient's genomic

information between the sequencing laboratories, medical professionals working with the patient, research studies interested in obtaining genomic data and the patient's family, will be further described in next chapter.

8. Sample obtained

Once the patient has indicated their preferences for what type of genomic analysis they would like performed as well as how they want to be notified of their results and updated when new information is available, the patient will be scheduled to have their blood drawn and possibly also have a tissue sample obtained. In some cases, patients could collect their own saliva sample and send this directly to the sequencing laboratory. The decision for how the sample will be obtained and what type of sample is necessary will be dictated by the reason the patient is electing to undergo WGS/WES.

For example, if the patient wants to learn about genomic risks factors out of curiosity and personal interest, it would likely be most convenient for them to send a saliva sample to the laboratory themselves. On the other hand, if a patient does not feel confident in their ability to collect their own sample, they may want to schedule a blood draw with their physician's office or go to a reference laboratory. Finally for some patients who are undergoing WGS/WES to study the genomic sequence of a cancer, a tissue sample must be obtained and processed through a pathology department in a hospital and sent along with their blood sample. This process will require coordination with the medical center treating the patient.

9. Results disclosure

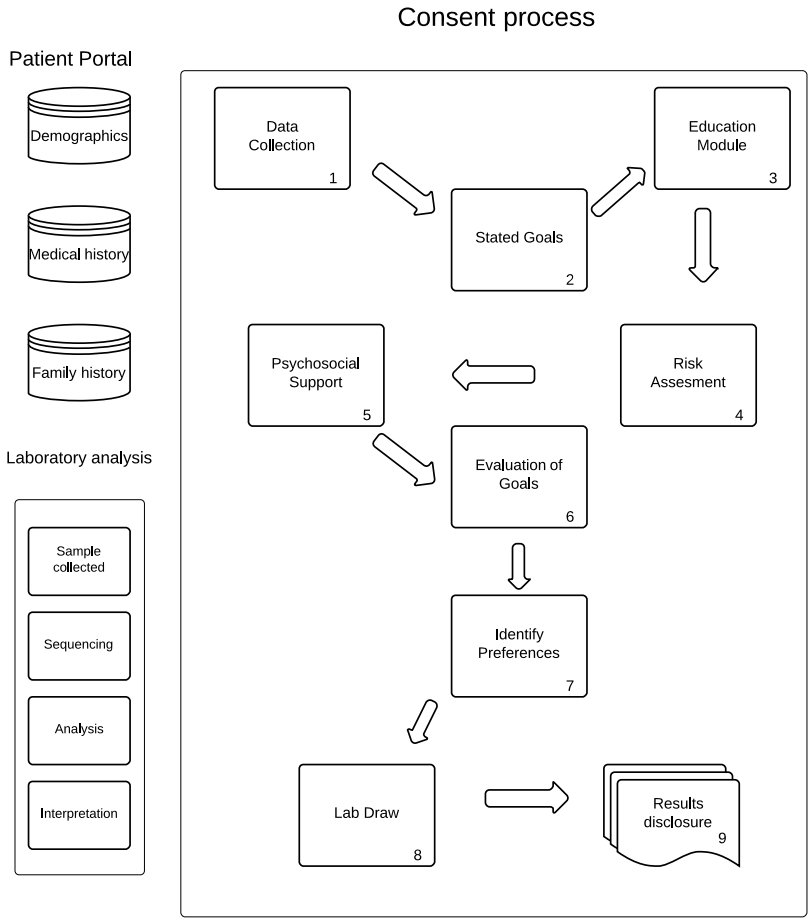
As was described above, the patient will elect how they wish to receive their results before their sample is obtained and a genome is analyzed. When results are available, there will be several methods to select from for how they will receive their results. The first step after the patient has been notified their results are available is for the patient to log into their account to learn what type of result (such as a pharmacogenomics analysis) regarding a specific sequencing of their genome they consented to, is available. They will then be given an option to either review their results with a consenter in-person, or on-line through a Skype conversation with a consenter or by reading the report online. If a patient elects to review their results on their own, they have the option to schedule a time to discuss the result with the consenter in person or through a videoconference any time in the future.

If a patient selects an in-person or virtual conversation, there will be ample time available to discuss the results and implications of the results with the consenter. If the patient is informed of a result, which is uncertain (variant of uncertain clinical significance), they are given the option to be notified (or not) when additional information is available about this variant.

Also, if multiple results are available, the patient will be given the option to learn about as many or as few results at one time. A second result disclosure appointment would be scheduled at the completion of the first appointment. Regardless of the method of result disclosure chosen by a patient, each time a new result is available, the patient will be notified and re-consented to review the new result. Bill might be notified a year after his initial WGS results were available, that there are additional updates to the

GWAS determining his potential risk for prostate cancer. He would be notified of this availability and undergo a follow-up consent session to learn his options for receiving this updated genomic information. Before his results are disclosed, the consenter would review the same basic genomic terminology as occurred during his first consenting session.

Figure 1 Patient Centered Informed Consent Process for WGS/WES



Flow chart for informed consent process for WGS/WES

CHAPTER 7

CREATING SPACE FOR THE INFORMED CONSENT PROCESS WITHIN THE SYSTEMS OF WGS/WES

A parallel concern associated with how to effectively consent individuals before undergoing WGS/WES is the seemingly insurmountable issue of how to adequately address the complexities of communicating patient preferences identified in the consent process, between the "systems" of WGS/WES. The complexities of the system were introduced in chapter four and include: the volume of genomic data produced by WGS/WES, the unknown analytic validity of data analysis, the uncertainty of how to adequately interpret genomic data (for example, variants of uncertain clinical significance), how to apply genomic results to patients' existing medical care (clinical utility), and, how to contact patients with updated genomic information.

The multiple systems operating within the process of undergoing WGS/WES include: the patient, the patient's physician(s), the laboratory where the patient's sample is analyzed (including the sequencing, the bioinformatics analysis of the data, interpretation of the data generated from the bioinformatics laboratory and generation of a report), the medical environment surrounding the patient (including the electronic medical record, the health insurance company, the pharmacy), individuals the patient elects to share their data with (relatives, friends, and social networks), and, the research community where patients' genomic information could be shared between multiple research protocols. To address the complexities between the systems inherent to WGS/WES, I propose the informed consent process become embedded with the systems.

In this chapter I describe how to integrate informed consent throughout the sequencing process and explain why this is a more effective approach to the informed consent process than obtaining informed consent only at the beginning of the WGS/WES. Obtaining consent only once is what is being proposed at this time in research and clinical protocols reviewed in chapter four. Integrating the informed consent process around the systems of WGS/WES involves revisiting and re-discussing components of the informed consent process discussed in chapter six, multiple times during the WGS/WES experience. This chapter demonstrates how a reiterative informed consent process creates a fluid informed consent process shaped to respond to the data reported from WGS/WES and how a reiterative informed consent process is better suited to address the analysis and interpretation challenges characteristic of WGS/WES. The ultimate outcome from utilization of this type of consent process is to be able to more effectively prepare patients for the various types of results produced by the sequencing over a span of many years. Additionally, a reiterative informed consent process allows for a more practical integration of WGS/WES into our existing medical model. In this chapter I elaborate further on this point using diagrams to illustrate the implementation of WGS/WES into our current medical model.

The first step in the framing of an informed consent process around WGS/WES is to provide an environment where the six systems inherent to WGS/WES are capable of communicating with one another. The most effective method of communication between these systems could occur through the electronic transfer of patient's interpreted genome data generated from WGS/WES. To allow for the electronic transfer of information, I propose patients who elect to undergo WGS/WES have their entire genome sequence

stored onto the patient's portal, regardless of why they are undergoing sequencing. The data which has been interpreted will be formatted into a report and be available for transferring to other health care providers, etc., based on the preferences stated by the patient in step seven of the consenting process. A patient's genomic information could be transferred between the laboratory, the patient's home computer, and the physician's office, as well as between the other systems encompassing WGS/WES.

To protect the privacy of the patient's genomic data during the data transfer between the systems, informed consent is obtained before each point of data exchange. For example, once the patient's results have been disclosed, the patient will be given the option to share their reports with their physicians, their pharmacist, family or friends, etc. The data will be sent electronically from the patient's portal. The exchange of patient information will only occur when the patient has released their information, similar to current release of information policies, however in this instance, because the patient's genomic results and data is stored electronically, the patient will provide an email address and point of contact to send their information from their own portal. During the informed consent process, patients will have already entered their preferences for who they would like to receive a copy of their results but, while being consented, they still might not know with whom they would like to share their information.

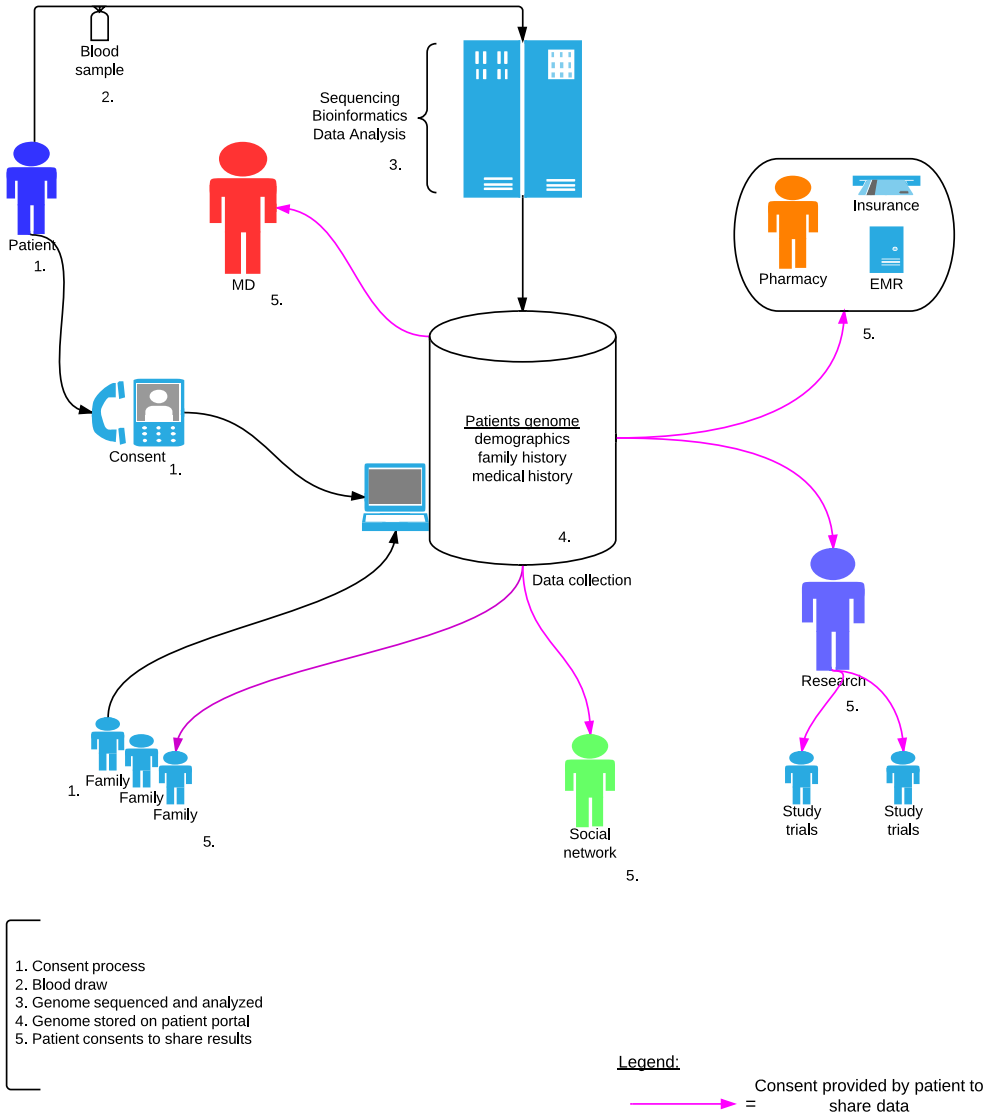
An advantage of the online system is that instead of sharing the entire genomic report, only portions of the data, such as a pharmacogenetics report, could be sent to the pharmacist. The patient could send a separate report to their relatives regarding possible hereditary conditions. Only the patient is able to select what type of results are sent out and to whom.

Also, if the patient elects to have their genomic data updated over time, the patient will continue to be offered options to share results with individuals they specify to send the information to, when the updated version of the results are available. Another option would be for a patient to store his genomic report on his own computer and share this information themselves with their relatives, rather than having it sent from their portal.

The electronic format of data exchange would also make sharing data between multiple research studies more efficient. If, for example, a patient would like their genomic data to be shared with researchers who might have an interest in a specific type of variant they were found to carry, they could elect to have their genome stripped of demographic identifying information, and shared with a research portal. The purpose of the research portal is to store a patient's genomic data and survey results for any findings that might be useful to various studies and then share the relevant genomes with the relevant studies.

An iterative informed consent process provides an opportunity for the technology to perform in the manner in which it was designed: interpret an individual genome in the most comprehensive manner possible and effectively apply this information to a patient's medical care. At the same time, this iterative process may be a conduit for an effective informed consent process because the patient controls the type of genomic information they want to learn as well as how and when they receive and use the information. In other words, this model is built to prepare individuals for every type of genomic result now produced from WGS/WES, regardless of family history, medical history or clinical indication.

Figure 2 Data Exchange Between the Systems of WGS/WES Process



In these next few paragraphs, I illustrate how this model is capable of systematically addressing the complexities of WGS/WES reviewed in chapter four and stated in the first paragraph of this chapter. First, the electronic storage of a genome onto a patient's portal is a mechanism for the data to be transferred, updated and reanalyzed. Additionally, all the data can be maintained in one location for the lifetime of an individual. Current practices for reporting genomic results includes printing a paper report, with no electronic version available for the individual's medical record. Rather than print a large amount of paper data, which is difficult to keep track of for the patient, and difficult to scan into an electronic medical record, the electronic information is easier to access for both the patient and physicians and other medical providers involved in a patient's medical care. Also, the data is likely to be modified over time. An electronic update would be easier to link to an original report, versus generating a new report with every update or addition to the original genomic analysis.

A major limiting factor of WGSW/WES which results in lower utilization of the technology by medical providers is the inability to adequately understand the meaning of the thousands of variants identified through sequencing and apply the data in a clinically relevant manner. These limiting factors, however, are temporal and, while there is still much uncertainty on how much more understanding scientists will gain from studying our genomes over time, it is likely that much more information than we appreciate today will be clinically relevant in the next several to dozens of years from now. It would therefore seem to be shortsighted to design a temporary informed consent model that does not meet the demands of the technology from an ethical or practical perspective.

Assuming all individuals undergoing WGS/WES can expect to be informed of new advances both to the technology and the implications of uncertain results, the electronic model I describe is prepared when the laboratory updates their sequencing technology or provides updates to variants of unknown significance. As variants change from unknown significance to deleterious, or become linked to a known disease, this information will updated electronically to the patient's portal and a message would be sent to the patient informing them there is updated information available. By storing an entire genome on the patient's portal, the data will be available when the patient wants to learn it. The patient can elect to learn about new disease risks factors several years after they started the process. Finally, the laboratory would be able to reanalyze genomic data without requiring the patient to submit another blood sample.

If an individual elects to learn the results, he will be re-consented at this time, as described in chapter six. The patient can elect to undergo a refresher consent process each time new genomic information is available. The consent session would review the type of genomic information that is now available, and most importantly, signify a point in the entire process where they patient can elect to decline learning new information.

From the clinical perspective, accurate and effective transfer of genomic information to all the individuals involved in a patient's medical care is essential for proper utilization of the data. Clinical care of a patient has always been most effective when the communication of information about the patient is timely, accurate and reaches the necessary specialists involved in the patient's care. The transfer of data therefore, will be much more efficient when the process of undergoing WGS/WES is structured in an electronic format. An online and interactive informed consent and data exchange process

will most likely be a necessity in the future, not only to meet the demands of the WGS/WES systems, but also to be able to address the face-to-face consenting burden of current informed consent practices.

Patients would manage their own data throughout the sequencing by selecting options for how to be re-contacted when new results are available and what type of information they wish to learn. Also, an electronic portal will allow patients to enter new medical information about their health over time and this could be considered when the genome data is reanalyzed. Another benefit of the electronic model for WGS/WES is when a patient moves and needs to establish care with a new physician, the electronic model provides an easy mechanism to transfer results without needing to request a large amount paper reports be sent from one physician's office to another.

Rationale for why a patient centered informed consent process for WGS/WES is better suited to fulfill the ethical obligations of informed consent than current and proposed informed consent protocols for WGS/WES

The institutional requirement that a signed informed consent document is all that is necessary to demonstrate consent was achieved has resulted in the current emphasis of informed consent to be about protecting institutions from litigation, and not about protecting individual rights. The resulting problems with addressing the consent process in this manner include: 1. Written consent forms scripted in a template format, 2. Consent processes and forms written by experts in the field of genetics, 3. A consent process that does not engage individuals in conversations about the issues inherent to WGS/WES, and, 4. A consent process that is incapable of responding to the complexities of WGS/WES. In the next few paragraphs, I discuss how these resulting problems prevent

the consent process from fulfilling the underlying ethical obligations of the informed consent process and describe how the informed consent process I outline in chapters five, six and seven is more capable of fulfilling the ethical obligations of the informed consent process for WGS/WES.

1. Written consent forms scripted in a template format

The written informed consent forms for genetic testing and those used for WGS/WES consist of a checklist of multiple components of genomic testing to review with an individual. These checklists are written in a standard format and include the same template with similar scripted information about WGS/WES for everyone whether they are referred for WGS/WES or seeking it on their own. This traditional method is performed the same way, regardless of the differences between individual situations for undergoing WGS/WES, individuals varying education backgrounds, psychosocial concerns, values and thoughts about genome sequencing.

The consent process, which I am proposing, begins by asking the individual what their understanding is of WGS/WES and why they are pursuing sequencing. A consent process, which begins with the individual stating their understanding and/or goals for undergoing WGS/WES, is more consistent with the original intent of informed consent because the content of the subsequent consenting conversation can then be focused on what the individual wants, expects and needs to learn about undergoing WGS/WES. The process is thereby shaped around individuals' values, beliefs, and goals, rather than determined by a checklist created by experts. Structuring the process in this way allows consent to be reflective of the concerns and interests of the specific patient, thereby better

respecting her autonomy and individuality. This stands in contrast to traditional protocols wherein the checklist of topics to discuss reflects the values and priorities of the experts, not those of the patient.

2. Consent process and forms written by experts in genetics

Another way in which the consent process proposed in this dissertation is more consistent with the original intent of the informed consent obligations is that by asking the individual what they understand about the reasons for undergoing WGS/WES, the consenter will know what type of information (education) they might need to provide the individual about the process of WGS/WES to help them either better understand the rational for undergoing sequencing and/or the possible implications of their potential results. If the consent process is developed entirely by experts and presented by a medically trained person, there is built in bias around the entire consenting process. However, if the consenting process is allowed to unfold, as I am proposing, with the natural flow of a conversation about WGS/WES focused on the individual's values about WGS, then the individual can make a decision without being influenced by what the experts might believe is critical to understand or even critical to considering why they might benefit from WGS/WES.

The key difference between my proposed protocol and existing protocols is that in my protocol, the consent session is focused on the type of information, scientific, practical, etc., the individual <u>needs</u> and wants to hear. Existing informed consent protocols (including those now being considered for WGS/WES) focus on what types of information experts believe individuals need to learn about to better understand the

implications for undergoing WGS/WES. It may be the case that much of the time there proves to be minimal differences between the type of information individuals feel is important to learn, and the information the experts perceive is important, but the ethically relevant difference lies in that the individual undergoing sequencing guides the process in the former scenario. They express what they do or do not understand about sequencing and what type of information they want to discuss. In the latter, content is entirely dictated by top down expertise.

In my own experiences consenting individuals in this manner, I find that the WGS/WES related topics that the individual wants to discuss tend to converge with what I feel is important to review, but, importantly, the structure of the discussion and pace of presenting new information is determined by the individual. It is through such experiences that, as a genetic counselor, I have learned to step back and not force my own agenda. The consent process then becomes a conversation, where an individual is engaged and this engagement deepens, as they understand the various layers of the complexities inherent to WGS/WES.

This process, as I describe it here, is what informed consent was created to achieve. It will assist the individual to comprehend implications of medical interventions of WGS/WES, such that they are intellectually, psychologically and practically as prepared as they can be to make informed choices consistent with their own beliefs and values. The role of the consenter is still maintained as the expert, but an expert whose job it is to guide the individual through the consenting process, while employing "gentle paternalism". "Gentle paternalism" is a term used by a practicing medical oncologist at Mayo Clinic, Tom Fitch, M.D., who describes his role in counseling his patients about

the implications of a possible therapy to treat cancer (Fitch, 2013). The implication of his phrase is that patients are not left on their own to inform physicians what they want, but are instead guided by physician's expertise and experience, to make a decision most consistent with their own values.

As the informed consent process I describe progresses, individuals will be asked to share with the consenter what types of genomic results they do and do not want to know. Providing individuals a choice regarding what type of genomic results are important to them is a fundamental component of existing informed consent protocols, but only in theory and not in practice. Current informed practices do ask individuals to select yes or no for whether they would like to learn about genomic results which for the most part, are not considered to be related to the specific indication for why there are seeking out WGS/WES. For example, if an individual is recommended to undergo WES to determine whether his symptoms (a seizure disorder, deafness and congenital cardiac anomaly) are all related to an unspecified genetic disorder, he would be given an option to learn about genetic diseases not likely to be associated to his symptoms. One example is learning whether he is a carrier of an autosomal recessive condition, such as cystic fibrosis. Learning about his carrier status for a variety of genetic disorders is not the reason in this example for why this individual is pursuing WES, yet the information is easily identifiable when he undergoes sequencing. Therefore, current informed consent documents ask individuals to check yes or no: "I do or do not want to know about these types of conditions." How a consenter prepares an individual to learn about possibly thousands of Mendelian disorders, any of which could potentially be identified with sequencing is proving to be an insurmountable hurdle to overcome when considering

informed consent protocols for WGS/WES. To address this insurmountable hurdle, laboratories performing WGS/WES write consent forms that group diseases together based on inheritance pattern (autosomal recessive conditions) or type of diseases (adult onset neurological condition for which no treatment is available) and ask individual to select yes or no, whether they want to learn about possible genetic risk factors for these types of diseases. In some cases, laboratories state which types of diseases they will or will not report (Bick et al., 2013). There is no way to realistically describe all the diseases that can be detected within each group during an informed consent session, since much of this is unknown, plus the amount of information is too much to cover in one session. Therefore, this is the solution by the laboratories performing testing for how to address this issue in the consent process.

The consent process I propose would also discuss the variety of results available from WES, but, rather than pick out specific options for individuals to choose from based on inheritance patterns or various types of diseases, individuals will be asked what type of genetic diseases they might want to know about and which types of diseases they might not want to know about based on their own experiences. A positive family history for a particular disease, concerns stemming from previous interactions with individuals affected with a particular disease, or any other reason might lead to not wanting results. This discussion would occur early on in the consent process after a basic science foundation is in place and the individual learns about what types of diseases WGS/WES is capable of detecting and which disease WGS/WES is not capable of detecting. When the time comes to decide what type of information individuals want to learn about, the consenter can frame this discussion around the goals that the individual initially stated at

the beginning of the consent process. The difference in this approach when compared to existing protocols is that the types of results available for individuals will not be preselected by the experts, but again guided by what the individual suggests is important to them, within the framework of the diseases WGS/WES are capable of detecting.

3. A consent process that does not engage individuals in conversations about the issues inherent to WGS/WES

Incorporating a psychological component to the informed consent process as I am proposing for WGS/WES, fulfills the ethical obligations of informed consent more concretely than current informed consent protocols by creating an opportunity for the consenter to naturally delve deeper into a discussion about the implications of results. These implications can be medical implications, as well as psychological, psychosocial, or financial, and the consequences of learning genomic information for the individual's family members as well as ways in which this type of information might affect his relationships. Helping individuals appreciate the consequences of receiving potential results from WGS/WES has been a major theme of the traditional informed consent protocols created for genetic testing. Yet, it is often not fully explored with individuals undergoing genetic testing. Most informed consent protocols list the possible psychological, psychosocial and financial, etc., implications in written consent forms without engaging individuals in a conversation about these issues, which arguably cannot be as effective for assisting individuals in the process of adequately understanding how to be psychologically prepared for genomic results revealing a possible risk factor or risk factors as the case may be, for any number of unknown diseases.

In addition, because WGS/WES are two technologies that create more uncertainty than certainty, it becomes even more important than in the past to take the time to address these uncertainties, as they may be the reason WGS/WES leads to potential adverse psychological and psychosocial responses. Another fundamental component of WGS/WES technologies is that both the experts (scientists and physicians, etc.), are struggling with the uncertainties of WGS/WES along side the individuals who are undergoing WGS/WES. The uncertainty surrounding what types of results will be available after sequencing is completed is in part mitigated by creating structured informed consent protocols. In my opinion it is not possible to mitigate implications of results that even the experts cannot predict. Instead of worrying about mitigating the uncertainty by creating a structure that helps us feel as though we are dealing with them in a responsible way, I would suggest, as experts, we acknowledge these uncertainties during the consent process and face them along with the individuals undergoing sequencing.

4. A consent process incapable of responding to the complexities of WGS/WES

The ability to engage individuals in a consent process with multiple methods online, in-person and combination of both, lends itself to a more tailored consenting experience. By providing genomic education and information about sequencing, in a variety of media formats, individuals can choose the modality most consistent with their personal learning style. Some would agree with the statement that the better an individual understands how undergoing WGS/WES will affect his or her life, the better prepared an individual will be for making an informed choice. This statement is not consistent with

what frequently occurs in reality. As I unravel the multiple components of the informed consent process, the better I understand the fact there are multiple factors, which work together to constitute a successful or effective informed consent experience. The effectiveness of the process is in reality, truly only determined by the individual who is undergoing the process themselves.

An inarguable fact, however, is that there is an overwhelming volume of information to learn about WGS/WES. By offering several types of consenting methods (online and self-guided consenting process, in-person and a combination of both) there is opportunity for individuals to set their own pace for learning new information. Also, education modules, which are available online, along with electronic versions of an interactive format for individuals to learn more about various genetic diseases they might be at risk for based on the results from WGS/WES, provides multiple opportunities for individuals to review the information on their own, share it with relatives and take the time to consider their options. This is another example for how the consent process I describe is better suited to fulfill the goal of informed consent because the variety of consenting methods provides an environment whereby individuals can optimize their chances to be fully informed and engaged in learning about implications from WGS/WES.

An important nuance I wish to clarify at this point is the consent proposal I outline above emphasizes two key elements of informed consent practices necessary to fulfill the ethical obligations of informed consent: 1. Elicit what an individual wants or does not want to know about genome sequencing and understands about the technology, and, 2. Engage the individual in a conversation. I am not proposing that the content of the

existing informed consent processes for genetic testing be disregarded. The proposal I suggest incorporates the same components of existing informed consent protocols; a discussion of the ways in which genome sequencing may or may not affect medical care, the limitations of the technology, the possibility of uncertain results, the likelihood that the meaning of results will be changed in the future, as scientists develop a better understanding of the result, etc. Therefore, the expert's role, to guide individuals through the consent process based on the knowledge established in the profession of genetics, will remain in tact. The subtle, but important nuance I wish to highlight is that my proposal more effectively incorporates this information into a personalized conversation with the individual undergoing genome sequencing, thereby structuring an informed consent process around the needs of the individual.

CHAPTER 8

CONCLUSION

Whole genome and exome sequencing technologies are ripe with promise to personalize medical care and improve health outcomes. The potential for what genome sequencing promises may never match the real outcomes from genome sequencing. At this point, the extent of how genome sequencing will individualize medical care and improve health care outcomes is not known. Despite this uncertainty, genome sequencing has already made an important imprint onto medical care. The first example of how WGS/WES has impacted medical care is in the area of cancer genetics. The field of medical oncology is poised to appreciate the benefits of individualizing therapy to prolong a life, or halt cancer progression completely. As a result, utilization of genome sequencing is occurring in clinical practices, and now laboratories performing the sequencing, physicians working with patients and researchers examining issues related to genome sequencing, are grappling with real complexities of how to incorporate genome sequencing into medical care. The unifying component for WGS/WES that connects all of the complexities of genome sequencing is the issue of how to provide informed consent for an individual who is interested in undergoing WGS/WES. The consenting process for WGS/WES is complicated by the large amount of data generated from sequencing, the uncertainty of how to interpret the data, uncertainty for how to apply the data to patient care and how to contact individuals over time with updated information about the genomic data.

Informed consent practices were implemented into medical research and clinical care at a time when our society was recovering from the horrifying revelations of the medical experiments conducted during WWII. The ethical backlash from these human

medical experiments resulted in the creation of the Nuremberg Code in 1947, the first in a series of ethical mandates for medical research studies. The ten moral imperatives for conducting research studies summarized in the Nuremberg Code were updated in the 1960s, 70s, 80s and 2002, 2004 and 2008 by the World Medical Association to reflect more contemporary research study designs (Mascalzoni et al., 2008). Additional guidelines for proper ethical conduct in medical research were released by the U.S. government in the late 1970s, with the publication of the Belmont Report. Most recently the medical research and clinical communities were reminded of the ethical embodiment of informed consent with a reported issued in 1983 by the President's Commission for the Study of Ethical Problems in Medical and Biomedical and Behavioral Research (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Making Health Care Decisions, 1982). This report emphasized the goal of an "ethically valid" informed consent process. The report reminds medical researchers and clinicians that the ethical component to the informed consent process consists of a conversation between a patient and physician to encourage an autonomous and informed decision-making process (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Making Health Care Decisions, 1982). The two major themes identified in all the reports are: 1. To protect the autonomy of all individuals participating in a medical research study, and 2. To emphasize the voluntary nature of participating in a medical research experiment.

Despite these highly visible moral imperatives for conducting ethical medical research, numerous medical trials have failed to treat study participants in an ethical manner. The most infamous American medical research failures were revealed

throughout the 1960s and 1970s. The first published scandal was the case at New York's Jewish Chronic Disease Hospital where two physicians injected cancer cells into patients without their knowledge (Stark, 2012). The second widely cited case is the Tuskegee Syphilis Study where, between 1932 and 1972, researchers failed to inform men affected with syphilis that they were being studied, and further, no treatment was offered to the affected men, when treatment became available (Hamilton & Bowers, 2003). These and other studies violated the first moral imperative of medical research studies: to protect the autonomy of all individuals.

Ethical failures occur every day in medical research despite the moral obligations of the informed consent process described repetitively since the late 1940s. The reason for these ethical failures is in large part to be blamed on the ways ethical review has come to be institutionalized in medical research practices (Stark, 2012). Medical research review boards (IRBs) created to evaluate whether a proposed research project is ethical, have not themselves been subject to any review of their process of reviewing studies, or about the mechanism through which they make their decisions. The reason the review process is not questioned is due to the integration of a practice into our medical research community that was assumed to be effective. In reality, IRB practices have never been evaluated and in fact may not be effective (Stark, 2012). In addition, once studies are approved by the IRBs, the study investigators pledge on good faith they will uphold an ethical code of conduct, when again, there is little follow-up to determine if this occurs. The way in which the review process for medical research studies occurs has not changed over time, in part due to the bureaucratic institutionalization of the ethical component of the informed consent process.

Informed consent practices in clinical care followed a similar path as the informed consent practices in medical research. While the implementation for informed consent into clinical care was driven by legal rulings, the ethical obligations of informed consent were always considered to be at the core of why informed consent became a mandate in clinical care. The *Salgo* case (*Salgo v. Leland Stanford etc. Board of Trustees*, 1957) introduced the concept of patient autonomy into medical care and encouraged patient involvement in health care decisions. The legal incorporation of informed consent into clinical care also resulted in the creation of five components of an informed consent conversation including a summary of the patient's diagnosis, recommended treatment options, expected outcome of treatment, risks and benefits of various treatment options, and any alternative procedures and risks or benefits of these alternative procedures (Plaut, 1989). The practice of informed consent in clinical care was therefore shaped by a list of required elements, with the suggestion that the fulfillment of informed consent also includes an ethical responsibility to ensure patients fully understand all possible benefits, risks and options available to them. The consent process was designed to occur in a single conversation, often times, right before the test is ordered or a procedure or surgery is performed. The ethical purpose of informed consent is to protect, empower and respect the individual who is faced with a decision surrounding his/her medical care. But again, despite the reminders of the ethical nature of a consent process through the report issued from the President's Commission for the Study of Ethical Problems in Medical and Biomedical and Behavioral Research, informed consent practices in clinical care have failed to fulfill these ethical obligations for the same reason informed consent practices in medical research have also failed.

As described throughout this dissertation, the ethical obligation of informed consent is secondary to the legal obligations of the consent process. This is demonstrated by the fact that the evidence that consent is achieved is based on the ability for an institution to produce a signed informed consent document. The legal requirement of informed consent is based on the need for medical institutions to avoid litigation. The emphasis on protecting an institution and physicians over protecting patient rights is also demonstrated by the fact that while informed consent continues to be a routine feature in clinical medicine, the practice itself is criticized by physicians who do not respect the intent of the informed consent process and therefore provide only lip service to the process (Lidz, 1983). The practice itself, while arguably ineffective for patients and physicians, continues only because it serves to demonstrate informed consent was obtained, thereby protecting institutions and physicians.

The irony of the situation is that informed consent was developed to protect and empower patients to make informed decisions, as well as prepare patients for all possible outcomes from a medical test or procedure. I have argued that the practice of informed consent is no longer primarily driven by an ethical desire to help patients better understand options available to them, but rather by a bureaucratic obligation to compete a routine step in the process of medical care, a step that is often seen as a nuisance by health care workers who are too busy to take the time and review the necessary information. The informed consent process today lacks the kind of substantive conversation with a patient about implications of a particular medical treatment that the process, properly understood, requires.

This dissertation has demonstrated that these shortcomings are particularly evident-and particularly consequential-in light of new genome sequencing technologies. The field of genetics was introduced into clinical medicine in the early 1900s, with the advent of heredity clinics. These early heredity clinics openly supported eugenics practices, but did not have the ability to confirm a suspected diagnosis of a genetic disease. The 1950s, however, brought two pivotal breakthroughs in the understanding of hereditary components of disease, with the publication of the physical structure of the DNA molecule by Francis Crick and James Watson (Watson & Crick, 1953) and the identification of the correct number of chromosomes reported in 1958 by Tijo and Levan (Dave & Sanger, 2007). These two scientific discoveries paved the way for prenatal testing, which became available in the late 1960s (The NICHD National Registry for Amniocentesis Study Group, 1976). Prenatal testing is performed during a pregnancy, to diagnose a fetus with a chromosomal alteration or genetic disease. The availability of prenatal testing created a new medical test with multiple risk factors requiring couples to make difficult decisions about undergoing a test with risks for miscarriage.

Genetic testing provides medical information that is burdened by the fact that learning about a hereditary disorder has consequences to not just the individual suspected of being diagnosed with the condition, but this information has consequences to the affected individuals' relatives as well. Couples who have a baby diagnosed with a genetic condition may often be informed about the risk to have another affected child while still trying to cope with the devastating news about their current baby. Genetic conditions are permanent and most genetic diseases have no treatment options. The psychological consequences of being diagnosed with a genetic condition are often negative as many

individuals who learn about genetic risk factors suffer issues with self-esteem as their sense of self is challenged. Others fail to adjust appropriately to the diagnosis of a genetic condition (R Klitzman, 2009) (B. Biesecker & Erby, 2008).

In response to the unique consequences of learning about a genetic disease, as well as the difficult decisions surrounding prenatal testing, the profession of genetic counseling was created in 1969 (Marks & Richter, 1976). Genetic counselors are trained to help individuals understand the implications of a genetic diagnosis, including the medical, psychological and familial implications of a disease. Genetic counselors also educate individuals on inheritance patterns, testing options, medical management and prevention of genetic disease, with the goal of promoting informed choices and adaptation to a diagnosis or risk of a diagnosis (Baker et al., 1998). Despite the eugenics backdrop from which the field of genetic counseling evolved, the profession has settled into a non-directive practice of informed consent, where individuals and couples are encouraged to make decisions surrounding genetic testing options consistent with their own cultural, religious and personal beliefs (Kessler, 1979).

Advances in genetic technology changed the practice of genetics as it became possible to diagnose all types of genetic conditions with a variety of inheritance patterns. The new genetic tests were always challenging as each test had a different detection rate, increasing the complexities associated with explaining genetic tests during an informed consent process. Additionally, genetic testing options expanded beyond prenatal testing and pediatric practices into predisposition testing (genetic testing for adult onset disorders). In response to the complexities of genetic testing, the psychological and psychosocial impact of a positive genetic test result, as well as the implications on the

family members of an individual undergoing genetic testing, the informed consent process for genetic testing was designed to occur in large part, during a genetic counseling session. Practice guidelines summarizing the necessary topics to review during informed consent sessions before genetic testing were published throughout the 1990s and thoughtfully addressed all the nuances of both the technical complexities of genetic testing as well as the psychological and psychosocial implications of undergoing genetic testing.

Despite detailed published informed consent practice guidelines for genetic testing, and the recommendation that genetic counseling be offered before a genetic test is ordered, the informed consent process is still criticized as ineffective. The complex nature of genetic testing options, the unfamiliarity of genetic terminology throughout the general population, as well as challenges inherent to understanding genetic risk factors, are reasons cited for why the informed consent process for genetic testing is not effective. Physicians and patients struggle with understanding risk information, and patients especially, who are concerned about a possible risk of a genetic disease, have a difficult time applying statistical probabilities, to their own situation, while experiencing an emotional reaction to learning information about a genetic diagnosis.

I blame the ineffectiveness of the informed consent practice for genetic testing on the fact that, as with other medical tests, a signed informed consent form is all that is necessary to provide evidence that informed consent was achieved prior to undergoing genetic testing. The fact that a signed informed consent form is evidence for medical institutions that informed consent was achieved results in an informed consent process

that values the legal obligation over the ethical obligation to fully engage individuals in a discussion surrounding the consequences of undergoing genetic testing.

An even more complex genomic test is now available, genome sequencing capable of identifying hundreds to thousands of different genetic diseases and genetic variants at one time. The introduction of WGS/WES into clinical care provides an opportunity to re-evaluate the informed consent process and consider the direction of future informed consent practices. The fact that whole genome sequencing could reveal over thousands of different results at one time is one motivation for fine-tuning the informed consent process, to create a more flexible process capable of addressing multiple results. Reasons to modify the informed consent process to be more flexible at managing multiple results reported at once is important, not just for whole genome sequencing, but because the informed consent practices developed for genome sequencing will likely become the model for how to handle other medical tests that produce a lot of data at one time (such as proteomics focusing on the study of the interactions of the proteins expressed by our genes).

Medical professionals and medical researchers interested in developing new protocols for the informed consent process for genome sequencing are considering the complexities of sequencing and how these complexities challenge existing informed consent protocols for genetic testing. The complexities of the genome sequencing described in chapters four and seven and include: uncertainty for how to analyze, interpret, and manage the large volume of genomic data produced from genome sequencing, how or whether to report the numerous variants of unknown clinical significance, how to incorporate results from genome sequencing into individual medical

records, and how to re-contact individuals with updated genomic information. These complexities are well described in the literature, and the researchers, clinicians and ethicists who write about them agree that when designing new informed consent protocols, these issues need to be considered. What is not described in the literature is a real solution for how to address these complexities through the consent process. This dissertation addresses both the issue of how to provide informed consent that addresses the ethical intent of the consenting experience, as well as describes a model for how to implement informed consent into the process of genome sequencing in a way that addresses the challenges of the technology.

A more fundamental motivation for restructuring informed consent practices is to re-design the process around the ethical intent of informed consent, rather than the legal intent. An ideal informed consent process is one designed around the needs of the patient. The fundamental ethical purpose of informed consent is to empower a patient to make a fully informed decision. To empower an individual to participate in the decision-making process, that person needs to be considered and incorporated into the consent process. Current informed consent practices are written by experts, with the same standardized form given to every patient or rehearsed list of benefits, limitations and risks from a specific test, discussed with every person in a rote exchange. These practices are not individualized to address what a patient needs to learn about or discuss. Nor adequate to render the patient capable of participating in the decision making process. Unless the patient is considered in the process, it's difficult to address their needs. The fact that the existing informed consent protocols do not effectively address the underlying ethical purpose of informed consent is an issue that has not yet been adequately confronted in the

research studies considering new informed consent practices for WGS/WES. As a result, I foresee in the development of informed consent protocols for whole genome and exome sequencing the perpetuation of an informed consent process that fails to fulfill the underlying ethical obligations of the process. This dissertation has drawn attention to this problem, and offered the outlines of a solution.

The solution I offer to improve informed consent practices and address the complexities of genome sequencing is to shape an informed consent process around individual goals and understanding of the purpose and implications of undergoing sequencing. I introduced four elements of a patient centered informed consent process for whole genome and exome sequencing in chapter four. The first element I describe is to begin an informed consent process by asking the individual to state their goal for undergoing genome sequencing. The stated goal of the individual may not be achievable (i.e. learn about all the possible genetic conditions listed in Online Mendelian Inheritance in Man (OMIM)), but until the goals of the patient are solicited, the informed consent process simply cannot prepare the patient to make an informed decision. The second element structures the informed consent session around the individuals stated goal and overall understanding of the implications of genome sequencing. For instance, if an individual who wants to learn about all possible genetic conditions reported OMIM, it is only after learning of this goal that the consenter knows he/she needs to elicit the rational for why this individual wants to know about so many conditions. Understanding the goals from the individual undergoing WGS/WES provides useful information to the consenter for how she might approach the education component of the session. Given the large number of conditions that would need to be reviewed in this scenario, asking the

individual for further clarification on what types of diseases they are interested in learning about and why will give the consenter some clues as to what the individual is concerned about and the education can be tailored on helping the individual understand the background for whether or not WGS would detect particular conditions.

The third element is to address the psychological concerns that arise during a consent process. The individual in this example who wants to know about every possible disease might be worried about a specific condition that affected one or more of his relatives. Perhaps he is worried unnecessarily about getting sick and by requesting a sophisticated genomic test, he is gathering information about his genome that provides him with a sense of control. Whatever the reason, addressing the psychological well being of an individual during the informed consent process provides an opportunity for health care professionals to tailor the informed consent process around the individuals' experience for what it means to him and his family, to undergo genome sequencing. The implications of genome results (many of which are unknown) can therefore, be discussed in relation to the individual's own situation.

The fourth element of the informed consent process I propose for WGS/WES is to provide multiple methods (online, in-person and a combination of both) for undergoing informed consent for genome sequencing. The availability of several types of consenting interactions is more consistent with an informed consent process that responds to the needs of the patient, than current methods that provide the same informed consent form for the patient to sign, oftentimes with no additional explanations or opportunities for individuals to ask questions or engage in a conversation about the test. An online and in-person informed consent process also can address multiple learning and communication

styles inherent to our population. For a test as complex as genome sequencing, the impetus to develop a communication model that is flexible enough to meet both the technological challenges of the WGS process, as well as the variety of learning and communication styles in our population, is even more important. By offering informed consent online, or at least portions of the consent process online, methods are established for integrating genome sequencing into an electronic medical world in a way that is responsive to patient needs and interests.

The purpose of proposing an informed consent practice structured around these four principles, is to refocus the consent process on what the patient needs to learn about in order to better understand the rational for genomic testing and more importantly, be able to engage in an informed conversation about the real implications of undergoing genomic testing. The reason for designing an informed consent process around these principles is to incorporate the ethical component of informed consent into clinical practices in a tangible way that might result in improved patient understanding of WGS/WES.

The steps of the patient-centered informed consent process I describe in chapter six, are similar to existing informed consent protocols, but the overall focus of the consent process shifts the focus from the need to protect institutions from litigation or satisfying a bureaucratic requirement, to protecting patient's needs first and foremost. Existing informed consent protocols incorporate information that *experts* feel individuals need to know to be fully informed of the implications of undergoing WGS/WES. My proposal does not reject or even ignore the experts opinions, but renders them subsidiary to, and informed by, patients' goals. For example, the American College of Medical

Genetics recommends physician inform their patient about the various complexities of WGS/WES; the possible risk, benefits and limitations of undergoing WGS/WES, the possibility of finding unexpected genetic alterations during the sequencing process, whether and how individuals will be contacted when results are updated, etc. (ACMG Board of Directors, 2013). All of these components are included into my proposal, but they are shaped around the patient's goals and understanding of how WGS/WES will help them. Therefore, I do not propose eliminating the components of existing informed consent protocols. Rather I propose that these components be framed and woven into the process differently. The consenter is the expert who maintains control over the consent process, but rather than review a list of the issues surrounding the risks, benefits and limitations of informed consent, the informed consent process outlined here integrates this information into the natural flow of conversation with an individual by grounding it in the patient's own narrative about how genome sequencing can and should affect her life.

To address the complexities of how to manage large volumes of data produced from sequencing as well as how to update individuals when results change from unknown to clinically relevant, I described an electronic model for reporting genomic results, which also incorporates informed consent into the systems of genome sequencing in chapter seven. Recall the systems of WGS are, the patient, the physician, the health care environment surrounding the patient (electronic medical records, insurance companies, and pharmacy) patient's family, friends and support groups and research studies. The model I propose is designed to facilitate the transfer the patient's genomic data between the systems of WGS. This model is unique from anything I identified in the literature

because it is the first example of an informed consent process capable of addressing both the complex consenting protocols and the challenges of integrating a patients' genomic results into the medical system.

Furthermore, by storing the genomic data on a patient portal, this model addresses the problem of the uncertainty of the data produced from genome sequencing. Many protocols manage uncertainty by determining, with expert opinion, which types of genomic results should or should not be released to patients. The American College of Medicine Genetics (ACMG) recommends physician should disclose specific types of mutations identified in 57 genes related to medically actionable hereditary conditions, regardless of whether the individual wants to learn about these results or not (R. Green et al., 2013). Other experts advocate the opposite, calling for releasing only those genomic results that bear on the clinical purpose of conducting WGS/WES for a given patient, but nothing more (Sharp, 2011). This dichotomy reflects an unsettled and underdeveloped area in the medical literature for how much emphasis experts place on considering patient preferences when making decisions about what information is important to disclose or not disclose to a patient.

Rather than ask the experts to determine which test results ought to be reported, my model is to store the data onto the portal, and allow the patient an opportunity to determine which results he/she wants to learn about, and when. The consent process I describe in chapter six facilitates patient understanding of what type of genomic information is, and is not available from sequencing, how the information will change over time, and how the results may or may not impact their medical care, and gives the patient time to reflect on how he or his family members might respond to learning about

genomic risk factors. This process results in creating an environment for an individual to make decisions that empower her to use the genomic information in a way that results in a positive outcome. By allowing the patient the right to make decisions on her own behalf (rather than deferring to expert judgments of what is best) and creating the environment through the informed consent process, where she is able to make these decisions, the ethical obligations and fundamental purpose of informed consent is thereby achieved.

To conclude, let us return to Bill and Melinda to see how their experiences would have been different if the consent process has followed my proposed model. Bill and Melinda decide to undergo WGS and embark on this journey as a couple. Recall that they have very different backgrounds in science, different learning styles and different goals for undergoing WGS. Bill is a science writer, who has done a fair amount of research on the topic of WGS. He works from home and spends a lot of time on a computer. Bill is very interested in learning as much as he can about his genome as he is fascinated with the implications of learning about one's genomic information. Bill intellectualizes his desire to learn about his genome, and does not associate any negative emotions to the possibility he might learn something negative (a deleterious mutation for a hereditary disorder) as a result of undergoing genome sequencing.

He initiates his sequencing by creating a patient portal. He enters the necessary demographic information, personal medical history and family history information. When prompted to answer why he wishes to undergo whole genome sequencing, he writes; to learn about genomic risk factors he might carry for developing prostate cancer; to learn about any possible hereditary conditions he might pass to his future children and; to learn whether he might be at risk for Huntington's disease.

After his data is uploaded, Bill is offered three types of consenting methods, online (self-guided) module, online with the option to undergo a live videoconference or Skype interview scheduled at his convenience, or in-person where he can meet with a consenter in a medical office close to his home. Bill elects to proceed with the online (self-guided) module. He begins the consenting protocol a couple of days after he creates his patient portal and finishes the consenting process in just over two hours. During the online process, he learns about the technical limitations of genome sequencing. Specifically, he learns that genome sequencing cannot detect the triplet repeat for Huntington's disease. More importantly, he learns why he does not need to worry about being affected with this genetic condition (because he has no family history of the disease and without a family history, he is unlikely to be affected with the condition).

Bill spends the most time on the education module where he gains a better understanding of the manner in which genomic variants determine his risk for common diseases like prostate cancer, or heart disease. During the risk assessment portion of his consenting process, he is pleased to learn that his risk for prostate cancer, based on his family history, is not as high as he was expecting. He is also informed about the limitations of prostate cancer screening, which he was not aware of. After spending a couple of hours on the module, he pauses the module at the point he is asked to select what type of genomic information he is interested in learning. He wants to wait and select the types of autosomal recessive conditions offered in the screening section of his analysis, until after Melinda undergoes her consenting process, so they can decide together what type of genetic conditions they would want to undergo carrier screening for. Also, after undergoing the consent process, Bill realizes he needs to secure a life

insurance policy before he is tested as well as remember to add Melinda to his benefit plan so she has health insurance.

Melinda's background in science consists of an introductory biology class she completed during her freshman year in college. She is less comfortable with science and math and, therefore, was dreading her consenting process for WGS. Melinda is busy with many appointments during the day, and decided to schedule her consent session over a few days if necessary. She creates her portal on a Saturday afternoon and enters the necessary demographic, and personal medical and family history information. When prompted to ask why she is interested in undergoing genome sequencing, she states her primary motivation is to learn about genetic diseases that she might carry and pass on to her children. She also states she wants to know whether her family history of heart disease increases her risk for developing heart disease in the future. Not understanding what else genome sequencing might tell her, these are the only two goals she lists at the beginning of the process. Melinda is asked to select her consenting option and elects to undergo online consenting through a Skype interview with a consenter. She schedules a day and time to undergo consenting when she is alone in the house and has several uninterrupted hours.

During her first consenting interaction, Melinda is pleased with how much information she learns about genome sequencing. She is most appreciative of the fact that the consenter asks her to explain why she wants to learn about numerous genetic conditions that she and Bill might pass to their future offspring. Melinda has always been a worrier, and having an opportunity to ask someone about different genetic diseases and how they could affect babies or children, relieves some of her anxiety. In addition, she

explains to the consenter that she has always been worried about getting sick and dying young because her father died after battling an unexplained illness for many years. She was only 18 when he died. The experience of losing her father really affected her to the point she is concerned about whether she should have children at all.

Melinda's first consenting interaction lasts longer than she anticipated, and after discussing her goals for undergoing sequencing with the consenter and working through half of the education component of the session, the first session ended. Melinda scheduled two more online sessions. The longest session for Melinda was the second session when she and the consenter reviewed the possible psychological reactions she might have if she learned that she was carrying a hereditary mutation for an untreatable adult onset condition. She also learns about the various types of prenatal testing she might consider if she and Bill carry a mutation for the same genetic condition. The discussion with the consenter about her expected response to learning about hereditary disease and the knowledge she gained throughout the consenting process helped her feel better prepared to cope with the possibility she and Bill might have a risk to have a child affected with a hereditary condition.

In addition to working with a consenter online, Melinda spends some time on her own reviewing the online education module available to her outside of the consenting process. Over time she begins to develop a better understanding of the genomic terminology surrounding genome sequencing. After her third session, she and Bill talk about the types of autosomal recessive genetic diseases they want to be screened for and agree they would like to learn about all possible disorders (those that are treatable and those that are untreatable).

Following this conversation, Bill logs onto his portal and selects his options for which types of genetic diseases he wants to learn more about. He elects to learn about every type of disease that is detectable. He submits his choices approximately eight weeks after he started the consenting process. Bill's life insurance policy was activated at this point and Melinda is now covered under his health insurance plan.

Melinda also schedules another online consent session where together with the consenter, she selects the types of genetic diseases she wants to learn about. She elects only to learn about genomic information that might affect her offspring, as well as her pharmacogenomics results given her troubled history with anti-depressants. She defers learning any information about adult onset conditions or conditions that she might have, for which there is no treatment for another time or perhaps never. After the options are selected, Bill and Melinda go together into their primary care physician's office to have their blood collected and a sample from each of them is sent to the genomic testing laboratory.

Bill receives an email notifying him his results are ready. He logs into his portal once they are available, and reviews his results on his own. His results are not combined with Melinda's carrier test results, because he knew that Melinda would learn her results on a different day. Bill learns about his slightly increased risk for prostate cancer, but based on his more sophisticated understanding of GWAS he doesn't feel concerned about this risk. Because he is young, he decides to wait until he is older, and the risks are better defined, before he shares this information with his physician. He also learns about his carrier status for cystic fibrosis, but since Melinda has not yet received her results, he is not too concerned about this risk factor. He does however, start educating himself about

cystic fibrosis in the event Melinda is also a carrier. Bill's overall reaction to his results is positive and he feels good about his experience. He also elects to be re-contacted whenever new information about the variants of unknown clinical significance identified in his genome is available.

Melinda elects to learn about her genomic results during a pre-scheduled Skype interview with the same consenter who she worked with before she had her blood sent to the laboratory for analysis. The consenter walks her through the carrier screening results first, and while she is disappointed by the number of genetic conditions she tests positive for, she felt prepared to learn this information and ready to consider prenatal testing if Bill is a carrier for one of the same conditions. The comment that the diseases she carries are more likely to be identified in individuals who are of Ashkenazi Jewish heritage does not surprise her, because she was informed about this possibility during the consent process. She decides not to share this information with her family just yet. The pharmacogenomics results were very helpful to Melinda as she finally has an answer for why she metabolizes medications so poorly and is encouraged that this information might help her psychiatrist adjust the medication dose to provide her with more benefit from the medication she is taking. Melinda elects to be emailed with any updates pertaining only to the genomic information reported to her during this first sequencing run. But she understands that if she elects to learn about other disease risk factors in the future, she can always re-initiate the consent process at any time.

This consent process describes a very different experience than the consenting process described in chapter one (reading and signing a written consent form). While the informed consent process I propose is not perfect and will have its own technical and

practical limitations, the exercise of designing a consent process and model for whole genome and exome sequencing, is to illustrate the fact that current informed consent practices (requirement of a signed informed consent document) do not fulfill the ethical obligations of informed consent; in addition, the informed consent process I describe in this dissertation, helps to illustrate the fact that it is possible to design an informed consent protocol centered around the needs of a patient while responding to a complex medical technology.

To counter possible criticism that a patient cannot be expected to know what information they need to learn about to be fully informed before undergoing WGS, as I demonstrate through Bill and Melinda's story, individuals do not guide the consent process in this manner. The consenter guides individuals through the steps, but the order which information is discussed, the pace of the process and degree to which psychological issues are addressed, is tailored towards the individual undergoing sequencing. Bill and Melinda communicate differently, have different backgrounds in science and respond differently to learning about genomic risk factors. The consenting process described in chapter six is designed to take these individual differences into consideration while learning about genome sequencing. A consent process individualized to each person is more fitting for the technology that produces an individualized genomic sequence.

The proposal outlined in this dissertation is not able to address all of the complexities of WGS/WES, nor will it likely result in a successful informed consent experience for everyone interested in pursuing genome sequencing. This proposal is in part an exercise to facilitate conversations about why informed consent is necessary in

medical care. This proposal is written to remind all of us working in health care, that informed consent, while serving to protect physicians and institutions from litigation was really designed to protect individuals from potential resulting harms from undergoing a recommended test or treatment. As medicine takes up diagnostic testing that generate complex and uncertain pictures of our lives and futures, it is imperative that we recognize the failings of the consent process as it stands, and reform our practices accordingly. If informed consent practices can be re-structured around the individual undergoing genome sequencing, they will be more effective, and will lay an important foundation for patients to achieve more successful medial outcomes. This dissertation has sought to interrogate these problems, and articulate a pathway for reform.

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