EXPERIENCES WITH WHOLE EXOME SEQUENCING:  
A COLLECTIVE CASE STUDY

BY

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Experiences with Whole Exome Sequencing: A Collective Case Study

Abstract

By

DANIELLE MOUHLAS

Whole exome sequencing (WES) is a complex genetic test involving sequencing of the protein-coding regions of the genome. Interpreting and reporting WES results involves complex counseling, medical and ethical issues. This study explored parental perspectives on the process of WES; assessed parental knowledge and understanding of their child’s WES results in comparison to the WES laboratory report and genetics evaluation; and analyzed the similarities and differences between the parents’ and clinicians’ perspectives regarding the WES process. This collective case study included interviews with four families, a corresponding chart review of WES documents, and interviews with genetics providers involved in the WES process. Major themes that emerged from the data included motivation to end the diagnostic odyssey, learning through genetic testing, counseling needs, returning results, and empowerment. This study demonstrated the importance and necessity of thorough and transparent genetic counseling and its ability to empower patients regardless of WES testing outcome.
CHAPTER 1: Introduction

Whole exome sequencing (WES) involves the simultaneous sequencing of targeted protein-coding regions in the genome. Researchers have demonstrated the ability of WES to determine a specific diagnosis for approximately 25% of individuals with a condition of unknown genetic etiology (Choi et al., 2009; Solomon et al., 2012; Yang et al., 2014). Because WES does not sufficiently cover 100% of the genome’s coding regions, and mutations that cause genetic disease can be outside of the coding region, it may miss a disease-causing mutations. In addition, WES may uncover incidental findings, variants of unknown clinical significance, and other alterations that could have a substantial clinical impact, but are unrelated to a patient's presenting symptoms. There are also a number of genes without a known function; thus the effect of a mutation in one of these genes is also unknown (Bamshad et al., 2011; Ng et al., 2010b; Ng, Nickerson, Bamshad, & Shendure, 2010c).

Interpreting and reporting results from WES involves complex medical and ethical issues (Downing, Williams, Daack-Hirsch, Driessnack, & Simon, 2012; Jamal et al., 2013; Tabor et al., 2011; Townsend, Adam, Birch, Lohn, & Rousseau, 2012). Studies have demonstrated that the general public often has an incomplete understanding of genetic information and test results (Christensen, Jayaratne, Roberts, Kardia, & Petty, 2010; Condit, 2010; Haga et al., 2013; Klitzman, 2010; Lanie, Jayaratne, Sheldon, Kardia, & Anderson, 2004). While clients seem to have a better understanding of genetics and test results after genetic counseling, and most accurately remember the topics that they considered to be important (Kaphingst et al., 2012; Michie et al., 1997; Meiser et al., 2011; Reiff et al., 2012; Visser & Bleiker, 1997), little is known about how individuals
respond to receiving WES results and the counseling process. Patient experiences with previous genetic testing approaches (i.e., karyotyping and single gene testing) may not be comparable to the experiences involving WES because WES involves additional complexities relating to incidental findings, variants of unknown significance, massive amounts of genetic information being analyzed, unknown gene function, and the numerous possibilities that could arise from WES.

In the clinical setting, WES may be pursued with the goal of determining a diagnosis when other testing resources have been exhausted or when WES is the most cost-effective option. Identifying the underlying etiology of a medical condition can be a significant factor in medical management and counseling about prognosis, recurrence risk, and/or prenatal testing options. Parents of children with undiagnosed medical conditions often report the importance and strong desire to find a specific diagnosis for validation, acquiring educational and medical services, facilitating the coping process, as well as many other reasons (Graungaard & Skov, 2006; Lewis, Skirton, & Jones; Rosenthal, Biesecker, & Biesecker, 2001). Research has shown that when these parents finally receive a diagnosis for their child’s disabilities, they often report experiencing validation for their concerns and peace of mind (Makela, Birch, Friedman, & Marra, 2009).

Most research on WES has centered on the ability to achieve better targeted exon coverage, finding disease-causing mutations for complex and monogenic disorders in undiagnosed patients, handling incidental findings, and other bioethical considerations such as informed consent and appropriate data management. There is minimal research on the experiences of those undergoing the WES process. Given the complexities
surrounding WES, the variety of possible findings, the uncertainties in the results, and the variety of diverse phenotypes of children undergoing WES, understanding the experience of WES is critical to having genetic professionals engage in anticipatory guidance and appropriate pre- and post-test counseling.

This research project aimed to explore parental perspectives on the process of WES, assess parental knowledge and understanding of their child’s WES results in comparison to the reported WES laboratory results report and the genetics evaluation and counseling clinic note; and analyze the similarities and differences between the parents’ and clinicians’ perspectives regarding the WES process.
CHAPTER 2: Purpose and Specific Aims

The purpose of this qualitative study was to investigate, describe and analyze individual clinical cases involving WES and to explore parental knowledge and understanding of WES test results in order to inform genetic counseling practice.

The specific aims of the study were to:

1. Explore parental perspectives on pretest counseling, factors influencing the decision to have their children undergo WES testing, post-test results counseling, satisfaction with the process, impact on medical management, parental family planning issues, and the meaning of WES results.
2. Assess parental knowledge and understanding of their child’s WES results in comparison to the information that was reported in the WES laboratory results report, the genetics evaluation, and counseling clinic note.
3. Analyze similarities and differences between parents’ and clinicians’ perspectives regarding the WES process.

Significance to genetic counseling

There is minimal research on parental and patient experiences with WES, and little is known regarding how parents might feel about their experiences with WES counseling. Because genetic counselors are often involved in pre-test and post-test WES counseling (Jamal, Yu, Chong, Dent, & Conta, 2013), understanding parental experiences with WES and their interpretation of results can be crucial to providing appropriate counseling, facilitating decision making, and offering anticipatory guidance.

Understanding needs of parents and areas of concern or confusion can help counselors to
meet those needs, address concerns, and clarify information. Beginning to explore parental experience can guide future research, help inform the practice of genetic counseling, and assist in the development of guidelines on counseling for WES.
CHAPTER 3: Background

Whole exome sequencing

Whole exome sequencing (WES) utilizes next-generation techniques that simultaneously sequence vast amounts of DNA in an attempt to quickly and precisely detect variants in genomic coding regions (Choi et al., 2009). These coding regions, called exons, include the portions of DNA that are directly made into proteins, the protective, untranslated regions at each end and some pieces of DNA for splicing. The protein-coding region encompasses approximately 1% of the human genome, and mutations within these coding regions are estimated to be responsible for approximately 85% of monogenic disorders (Choi et al., 2009; Solomon et al., 2012). Approximately 25% of clinical WES yields a genetic diagnosis (Yang et al., 2014).

The ability to analyze this 1% of the human genome, and having the potential to uncover the majority of disease-causing mutations, is an attractive prospect in the clinical setting. However, WES is not perfect in its diagnostic potential, as mutations can be missed within the coding regions. WES depends on targeted capture of the coding regions and in-depth coverage, and studies of WES have demonstrated that approximately 5-10% of the targeted coding regions are missed or have insufficient coverage (Choi et al., 2009; Bamshad, Ng, Bigham, Tabor & Emond, 2011; Ng, Buckingham, Lee, Bigham, & Tabor, 2010b; Ng, Nickerson, Bamshad, & Shendure, 2010c). Also, based on the nature of WES, mutations outside of the coding regions typically will not be identified, which includes deep intronic (or uncoding DNA) that can still affect gene function (Choi et al., 2009). There are also a number of genes without a known function; the effect of a mutation in
one of these genes is difficult to interpret. While there is substantial research on the laboratory procedure of WES, there is minimal research examining the human experience of going through the process of WES and receiving results.

*Research on the utility of WES*

Research has been conducted using WES in order to identify genes and mutations that cause or contribute to known disorders. For example, O’Roak et al. (2011) utilized WES in an attempt to identify candidate genes and causative mutations for sporadic autism spectrum disorders (ASD). Researchers sequenced the exomes of 20 individuals with sporadic ASD and their unaffected parents and found likely disease-causing *de novo* mutations in four individuals in four different genes (O’Roak et al., 2011). A study by Vissers et al. (2010) used WES to find possible genes and mutations responsible for *de novo* intellectual disability (ID). WES was performed on ten children with *de novo* ID and their unaffected parents. They found six likely causative mutations in six different individuals.

Need et al. (2012) performed WES on 12 phenotypically different unrelated individuals with undiagnosed genetic conditions and their unaffected parents with the hope of identifying a gene mutation causing the presenting symptoms. WES was performed on each of their parents for comparison of variants. This testing resulted in a likely genetic diagnosis explaining the symptoms for six of the twelve affected individuals. A mutation was also found in a seventh individual, which was the likely cause of that individual’s visual symptoms but did not explain the child’s full phenotype. In addition to finding likely disease-causing mutations in over half of the affected
individuals, the study found that two unrelated individuals had mutations in the *EFTUD2* gene. The *EFTUD2* gene is a spliceosomal GTPase that plays a regulatory role in splicing (Lines et al., 2012). A study by Lines and colleagues found *de novo* mutations in *EFTUD2* in twelve individuals with mandibulofacial dysostosis, microcephaly, and global developmental delay (Lines et al., 2012). These two studies offered the first evidence for *EFTUD2* involvement in genetic disease (Lines et al., 2012; Need et al., 2012). Numerous other studies have also provided evidence that WES can be a useful diagnostic tool in identifying a genetic etiology for an undiagnosed condition. (Ashley et al., 2010; Lupski et al., 2010; Ng et al., 2010a, 2010b; Ng et al., 2009; Roach et al., 2010; Worthy et al., 2011).

Along with the potential to discover disease-causing mutations, technological advances have decreased the cost and increased the speed of next generation sequencing platforms, making WES an even more realistic and practical option for the diagnosis of genetic disorders. WES may even be a more cost-effective option than traditional single-gene testing or gene panel testing for those with symptoms that do not point to a clear diagnosis or that could involve numerous genes (Worthy et al., 2011). With scientific advancement, WES is expected to continue to decrease in cost, while the coverage and speed of sequencing will improve in the future (Ashley et al., 2010; Bonnefond et al., 2010; Ng et al., 2009, 2010a, 2010b; Worthy et al., 2011). WES can be an exceptional tool in the clinical setting for diagnosing genetic disease, and with more patients undergoing WES, it will be important for genetic professionals to understand patient experiences with WES in order to appropriately counsel for the test and address individual concerns.
One aspect that complicates WES is that it identifies incidental findings, such as numerous variants of unknown clinical significance or mutations in genes that could have a clinical impact, both now and in the future. Due to the complexities of the information uncovered by WES, there is controversy regarding which results to return, who should make that decision, and how to appropriately handle incidental findings during pre- and post-test genetic counseling (Hogan, Turner, Tucker, & Warwick, 2012; Jackson, Goldsmith, O’Connor, & Skirton, 2012). While many recent studies have focused on the perspectives of genetic professionals in regard to returning incidental findings in exome and genome sequencing (Downing, Williams, Daack-Hirsch, Driessnack, & Simon, 2012; Lemke, Bick, Dimmock, Simpson, & Veith, 2013; Lohn, Adam, Birch, Townsend, & Friedman, 2012; Townsend, Adam, Birch, Lohn, & Rousseau, 2012), minimal research has been performed on parents’ perspectives of having incidental findings reported from WES in the clinical setting. These parents’ perspectives, as examined in a research setting, may not be representative of those generated in a clinical setting because the people who are participating in a research setting are often healthy individuals, unlike those undergoing WES in a clinical setting. Moreover, little is known about which types of results are desired by parents or patients who are undergoing clinical testing; thus, it is important to understand parental concerns and take them into account in order to maximize patient autonomy.

The opinions of medical geneticists, genetic counselors, nurses, and laboratory professionals have been assessed to evaluate whether there is a consensus on disclosure of incidental findings from WES in the clinical setting. Overall, most agree that
mutations causing clinically actionable, childhood-onset conditions should be reported for pediatric patients, even when unrelated to the child’s presenting phenotype. However, there is significant debate on how to handle other incidental findings, such as results for adult-onset conditions, variants of unknown significance, consanguinity, and misattributed paternity (Downing et al., 2012; Lemke et al., 2012; Lohn et al. 2012). Outside of the WES setting, the American College of Medical Genetics (ACMG) does not support carrier testing for children when being a carrier does not pose any substantial health risks (Ross et al., 2013). The ACMG also generally recommends against testing children for adult-onset conditions because testing a child for these conditions removes their right to decide whether testing will be best for them in the future; although, with careful genetic counseling, it may be deemed appropriate in certain situations to test a child for an adult-onset condition, particularly when not knowing genetic status may do more harm than good to the family (Ross et al., 2013). The purpose of WES is to find a diagnosis for current symptoms, not to find information about adult-onset conditions or carrier status; however, this information may still be inadvertently obtained in the testing process. Because this information can be revealed, there are substantial ethical issues surrounding WES and returning results and incidental findings. Many individuals of the general public, ethicists, and genetic professionals suggest that patients should be able to choose which results they want to have reported and which results they do not want returned in an effort to respect patient autonomy (Tabor, Berkman, Hull, & Bamshad, 2011). A study on the attitudes of genetics providers toward returning WES incidental findings demonstrated that 81% (n=673/836) agreed that patients or families should have options about what information they would like to have returned (Yu, Harrell, Jamal,
Tabor, & Bamshad, 2014). Providers were often much more evenly split on whether or not to offer to return different types of information such as pharmacogenetic variants (Yu, Harrell, Jamal, Tabor, & Bamshad, 2014).

Some suggest a more paternalistic approach is better, allowing clinicians or laboratories to decide what is appropriate, as patients may not have the knowledge or ability to provide meaningful informed consent when numerous incidental findings may emerge (Merrill, Vaidya, & Pyeritz, 2013). Moreover, some geneticists and ethicists recommend against reporting incidental findings because these findings have the potential to cause unnecessary anxiety and misunderstandings (Jamal et al., 2013).

Previous researchers have highlighted the need for further investigation to address ethical issues from the perspectives of patients, geneticists, ethicists, and other involved parties (Jamal et al., 2013; Tabor et al., 2011; Townsend et al., 2012).

The ACMG has released recommendations for responsible management of incidental findings for exome and genome sequencing in the clinical setting. While these recommendations have been revised since they were first released in March 2013 (Green et al., 2013), the original recommendations included advising clinical laboratories performing WES to report known or expected pathogenic mutations in specific genes determined by the ACMG to be important regardless of clinical testing indication. In addition, clinicians and genetic counselors involved in the pretest counseling and consent process for WES are to inform patients of the possibility that testing may uncover variants and incidental findings, and then discuss the findings that the laboratories will report, regardless of patient preferences, as they can have significant clinical utility. The ACMG deemed it necessary to report known or expected pathogenic mutations in genes
that cause high cancer susceptibility and/or involve high risk for cardiovascular disease. When mutations are found in these genes, different actions such as screenings, prophylactic surgeries, and other medical interventions can be taken to reduce the burden of disease (Green et al., 2013).

The ACMG guidelines have been a subject of ethical debate within the field. Some suggest that there is an ethical imperative to find, report, and disclose these results as they can have a significant impact on patient care. Others say that patients should have a choice about what kind of results they want to receive, as patient autonomy is a basic principle of our health care system. Debate has also persisted around which genes belong on this “minimum list,” whether there is sufficient clinical evidence for the recommendations, what information should be given to children, and whether patients should have the right to opt out of the incidental findings (Ross, 2013; Klitzman, 2013). Following the release of these ACMG recommendations, many laboratories indicated that they would be following the guidelines released by ACMG in the analysis and reporting of incidental findings, but—against recommendations from the ACMG—would still offer the option to decline the report (Ambry; GeneDX). On April 1, 2014 the ACMG released an update to their recommendations on returning incidental findings in WES, stating that “there appears to be a consensus among the ACMG members that patients should have an opportunity to opt out of the analysis of medically actionable genes when undergoing exome or genome sequencing” (ACMG, 2014).

WES is expected to be part of a changing landscape as advancements in technology take place and new information is learned about the genome. Much is left to be uncovered and new challenges will undoubtedly emerge. The ACMG
recommendations are expected to change over time to keep up with the needs of clinicians and counselors offering testing, as well as the needs of patients and their families.

Public knowledge of genetics and experiences with genetic testing

Studies have shown that the understanding of basic genetic concepts (for example, that genes are located on the chromosomes) and genetic test results by the general public and those undergoing genetic testing for disease risk assessment is often poor or rudimentary (Christensen, Jayaratne, Roberts, Kardia, & Petty, 2010; Condit, 2010; Klitzman, 2010; Lanie, Jayaratne, Sheldon, Kardia, & Anderson, 2004). A study by Haga et al. (2013) looked at general public knowledge of genetics and response to genetic risk information. The participants (n=300) in this study were relatively well educated and had above-average knowledge of genetic concepts; however, despite having increased knowledge of medical or disease-related genetic concepts, the study participants were unable to apply these concepts to medical care. In addition, study participants had generally poor knowledge of the benefits, risks and limitations of genetic testing (Haga et al., 2013). Public misconceptions of genetic information are common, and public familiarity with genetics does not necessarily correlate with understanding (Haga et al., 2013; Laine et al., 2004). Because the general public’s knowledge of genetic information tends to be poor, and WES is a complex test that can result in complicated findings, patients who are consenting for testing may not have a good understanding of WES, the information that could be uncovered, and/or the implications of results.
Genetic counseling and patient education

Genetic counseling plays an important role in educating patients. Michie, French, Allanson, Bobrow, and Marteau (1997) showed that comparing what patients remember from a genetic counseling appointment to the genetic counselor’s report can be a valid measure of patient understanding and recall. Results of their study of 35 counselees indicated that patients often remembered what they considered to be important, which often coincided with the genetic counselors’ perceptions (Michie et al., 1997; Visser & Bleiker, 1997). Results of studies by Kaphingst et al. (2012) Meiser et al. (2011); and Reiff et al. (2012) added to previous research and indicated that genetic counseling can help clients make decisions about genetic testing, increase knowledge of genetics, increase comprehension and understanding of test results, increase knowledge of their personal genetic risk information, and help decrease anxiety. Bernhardt, Biesecker, and Mastromarino (2000) conducted interviews and focus groups with genetic counselors (n=10) and clients (n=19) studying the differing experiences of the genetic counseling process between the counselors and clients to better understand patients’ satisfaction and desires. Results demonstrated that clients were very satisfied with their genetic counseling experiences and felt they had a better understanding of genetic information than before their counseling experience.

The process of genetic testing can also be anxiety provoking, and genetic counseling can help reduce this anxiety through counseling and education. A study by Dinc and Terzioglu (2005) explored the psychological impact of genetic testing on 128 parents. Most parents (93.0%) reported higher than average levels of anxiety before genetic testing, but most (78.5%) also reported a desire for genetic counseling. And,
results of studies by Bernhardt et al. (2000), and Meiser et al. (2011) demonstrated that participants displayed reduced anxiety surrounding genetic testing after genetic counseling. While research regarding anxiety surrounding genetic testing has focused on testing for cancer genes, Huntington's disease, Alzheimer's, and carrier status, (Broadstock, Michie, & Marteau, 2000; Heshka, Palleschi, Howley, Wilson, & Wells, 2008) research on parental anxiety surrounding genetic testing is limited, especially in the case of WES.

Uncertainty surrounding genetic information

Sometimes genetic information and test results can be convoluted with numerous variants of unknown significance and rare or novel mutations being identified (Biesecker, 2012). These results can be fraught with uncertainty and difficult to understand for both genetics professionals and clients (Darilek et al., 2008; Lipinski, Lipinski, Biesecker, & Biesecker, 2006; Reiff et al., 2012). The concept of uncertainty has been found to play a considerable role in the illness experience. A study by Lipinski et al. (2006) examined parental perceived control over his or her child’s overall health in cases of rare chromosomal abnormalities (n=363). Results suggested that parents with high perceived uncertainty might have lower levels of perceived control, difficulties with psychological adaptation, and high levels of stress. Though uncertainty can be used as a coping mechanism for some, overall uncertainty has been perceived as negative. A study by Madeo, O’Brien, Bernhardt, and Biesecker (2012) was conducted with 266 parents of children with undiagnosed conditions. This study replicated the results of the Lipinski et
al. (2006) study, further demonstrating the relationship that high perceived uncertainty is associated with low perceived control and the use of less effective coping strategies. Madeo et al. (2012) also proposed that these parents might benefit from interventions aimed at diminishing feelings of uncertainty by focusing on areas where parents do have control. Just as this perceived uncertainty can be overwhelming for parents, WES results can be daunting as well. Uncertainty may arise surrounding the implications of a diagnosis, incidental findings, variants of unknown significance, and failure to receive a diagnosis after such an extensive test. However, there is no available research on patient and parent perceptions, knowledge, and understanding of WES results.

*Parental experiences raising a child with an undiagnosed condition*

Parents of a child with an undiagnosed condition of presumed genetic etiology may also have high levels of perceived uncertainty, which can increase the desire for a diagnosis. Lewis, Skirton, and Jones (2010) aimed to explore parental experiences of raising a child with an unknown medical condition by conducting qualitative interviews with 14 parents of children with undiagnosed conditions. The central theme that emerged was that the experience of having a child with an undiagnosed medical condition was a journey comprised of inner experiences involving emotions, and outer experiences involving interactions with society and medical professionals. Although experiences and the day-to-day issues of raising a child with an unknown medical condition were more related to the severity of symptoms than the lack of a known diagnosis, this unknown factor added additional stress and complexities to the intricate situation of raising a child
with medical issues. The authors found that an unknown diagnosis can be psychologically distressing for parents, especially in thinking about the child’s future and what may be expected (Lewis et al., 2010). They concluded that parents of children with an undiagnosed condition may have more “hoops to jump through” in order to receive special services for their children and may not know where to turn for social and psychological support. This study expanded on previous work of similar studies conducted by Graungaard and Skov (2006), and Rosenthal, Biesecker, and Biesecker (2001).

Research has also been conducted on the parental values and importance of receiving a specific diagnosis for their child’s symptoms. A study by Makela, Birch, Friedman, and Marra (2009) examined values and attitudes of 10 parents who had received a precise causal diagnosis for their children’s intellectual disabilities (ID) and 10 parents who were still searching for the cause of their child’s ID. This study involved qualitative interviews comparing the attitudes and values of parents who knew the diagnosis for their children’s ID and parents who did not have a known diagnosis for their children’s ID. Seven themes emerged regarding the value of having a specific diagnosis for the children's conditions, including validation, information, support, curiosity, early intervention, procuring services in the school system, and for prenatal diagnosis in future pregnancies. As these studies suggest, parents often want to find the cause for their child’s symptoms, and medical professionals bewildered by the individuals’ symptoms want to make a diagnosis; thus, these children may be primary candidates for WES.
Finally, it is important to examine the policies and procedures of the laboratories performing WES, as this impacts what information will or will not be available to clinicians and patients. Jamal et al (2013) conducted a comparison of six CLIA certified laboratories that perform clinical WES in the United States. This study looked at the differing policies for informed consent and reporting of results for WES. The results indicated that there are great discrepancies between laboratory policies regarding informed consent, data sharing, and managing results. Some laboratories do not report incidental findings of any kind, while other laboratories will confirm both potential disease-causing variants and incidental findings. Some may also report and confirm some variants of unknown significance if they are in a gene that could be the cause of symptoms (Jamal et al., 2013). Jamal and colleagues also point out that the ethical debate over how to return variants of unknown significance and incidental findings may contribute to the differing laboratory policies. This further complicates the ethical dilemma on how to maximize patient autonomy, limiting unnecessary stress and anxiety, and providing optimal patient care. WES is fairly new in the clinical setting, with Ambry Genetics being the first clinical laboratory to offer WES in fall of 2011 (Ambry Genetics, 2011). Since that time, laboratories have modified their policies regarding informed consent and results reporting for WES, and will likely change their policies in the future with increasing scientific advances and research on informed consent for WES and the impact of incidental findings (Jamal et al., 2013). Because of varying policies of the laboratories surrounding WES, individuals may have differing experiences based on the laboratory that is used and the results participants chose to receive. Little is known about
these experiences and it is important to take into account the particular laboratory and its policies to better understand individual experiences surrounding WES.

WES can be a useful tool in the clinical setting to identify a genetic etiology for an undiagnosed condition; however, this type of analysis is somewhat exploratory and can involve a lot of uncertainties for genetic professionals and patients alike. Because little is known about the experiences of individuals and parents undergoing WES for undiagnosed conditions, this collective case study aimed to explore parental experiences of WES, assess parents’ understanding of WES results, and analyze parents’ relationship with genetics providers. It is hoped that this information will aid in providing genetic counselors with a better understanding of the psychosocial issues surrounding their patients’ and families’ experiences with WES.
CHAPTER 4: Design and Methods

This research project utilized a collective case study methodology to investigate the WES process. Data from parental interviews, clinician interviews, and a chart review were used to investigate, describe, and analyze themes regarding the parental experience surrounding the process of WES, explore how results have impacted medical management for the child and the parents’ family planning, and to explore parental knowledge of their children’s WES results. A case study is an “in-depth description and analysis of a bounded system” (Merriam, 2009), in which the bounded system is the individual unit under investigation. In this study, the bounded system refers to the individual application of WES in pediatric patients, their family, and their health care provider(s) that took part in the WES process. A collective case study is a series of similar cases with thematic analysis across the cases. Thematic analysis is a commonly used method in qualitative research to identify and investigate patterns in data (Braun & Clark, 2006). As defined by Guest, MacQueen, and Namey (2012), “thematic analysis moves beyond counting explicit words or phrases and focus on identifying and describing both implicit and explicit ideas with in the data”. Analyzing multiple cases increases consistency, credibility, and transferability (Merriam, 2009). Multiple cases were also used in this study to demonstrate a variety of facets, psychosocial issues, and experiences of WES.

Yin (2008) considers a case study to be a research process used to investigate a phenomenon within a real life context. In this research study, the phenomenon under investigation was the process of WES, and the real life context involved having a child who had undergone WES.
According to Kavanaugh, Moro, & Savage (2010) “the goal of qualitative case study research is to seek an understanding of the case, particularly the complexity of its interactions within its contexts, as well as the interrelationships that exist among all cases.” This exploratory, qualitative, descriptive study involved semi-structured interviews with parents and clinicians, and a chart review. Three methods of data collection were used in this study and thus triangulation was employed. Triangulation is “comparing and cross-checking data” (Merriam, 2009) collected through multiple sources. Qualitative, collective case study methods are best suited for this study as it serves an exploratory function and because there is minimal data on experiences with WES and case studies often serve as a place to begin research. Case studies can involve descriptive narrative of the experiences of the participants thus providing a richer understanding of the process of WES. Other types of studies may not be able to provide the rich description necessary to explore a phenomenon from multiple angles and function as a starting point for future research.

Recruitment

Parents of children who had undergone WES at the Center for Human Genetics at University Hospitals Case Medical Center (UHCMC) in Cleveland, Ohio and Nationwide Children’s Hospital in Columbus, Ohio were invited to participate in the study. Both parents of each patient were asked to participate in individual interviews when possible. The study permitted parents to be interviewed together; however, this was not the preferred method because their opinions might have influenced each other and potentially served as a bias and limitation of the study. Participants must have been 18 years of age.
or older and have been the parent or legal guardian of a child who underwent WES. Participants did not need to have been present during the pre-test counseling session, but were permitted to answer questions based on their understanding of the pre-test counseling. Participants must have attended the post-test results session. There were no restrictions on when results were received, thus the amount of time that passed since results were given varied among participants with the earliest possible being in 2012 and latest possible being April of 2014. Participants who did not speak English were excluded, as the interviews were conducted over the phone and the interviewer was only fluent in English.

Potential participants were sent a research packet through the mail or given one at their results appointment by their genetics’ provider between October of 2013 and latest possible contact was April of 2014. A total of 55 families received research packets, 36 from Nationwide Children’s Hospital and 19 from UHCMC. The research packet included a cover letter from UHCMC or Nationwide Children’s Hospital which explained the purpose of the study and invited them to participate (Appendix 1 and 2), as well as a letter from the researcher at Case Western Reserve University which provided an overview of the study’s procedures, information regarding how to contact the student researcher via email or telephone to schedule an interview (Appendix 3) and an informed consent document (Appendix 4 and 5). The consent form described the purpose of the study, information regarding what was being asked of the participant and the potential risks and benefits of participating in the study.

If the parent wished to participate, the letter of invitation provided instructions on how to contact the researcher to schedule the interview and to sign and return the consent
form. At the time of each interview, all consent forms were reviewed orally and the participants were again given an opportunity to opt out of the study. Two follow-up reminder mailings were also sent to those that did not respond to the first packet.

The geneticists and genetic counselors involved in the care of the participating families were invited to participate in a semi-structured interview. Invitations were sent via email in November of 2014. Those who responded were given the consent form to review and a time was scheduled for the interview (Appendix 6 and 7). No follow-up was necessary for the clinician recruitment. The consent forms were reviewed with the participants before the interview.

IRB approval was obtained from University Hospitals Case Medical Center and Nationwide Children’s Hospital.

Data Collection: Parental Interviews

The first step in data collection was the parent interviews. A single researcher, using a semi-structured interview guide (Appendix 8), interviewed each participant. The interview guide for the parental interviews was developed by the primary researcher with expert review and feedback from thesis committee members, which included a genetic counselor, and a geneticist who are experienced in pre- and post-test counseling for WES, and a bioethicist. The interview guide was created to gather information about parental experiences of the WES process and explore the use of results for medical management and family planning. In accordance with the first aim of the study, the interviews focused on experiences with WES. For the second aim of the study, the participants were asked
questions about their options for results and their recollection of the meaning of the test results.

The interviews were conducted over the phone between December 2013 and September 2014 and were audio recorded and transcribed by a professional medical transcriptionist who has a history working with the Case Western Reserve University Department of Bioethics and is very familiar with qualitative research. The transcripts were carefully reviewed and edited for accuracy by the student researcher.

Data collection: chart review

A chart review was performed following the phone interview to complete the analysis of the second aim of the study to assess parents’ knowledge or memory of the test results. Charts contained data regarding specific information obtained during the WES consent process, WES results from the laboratory and the clinic notes from the consent and results appointments. Information collected included the name of the laboratory performing WES testing, which results the parents consented to receive, and whether any pathogenic mutations explaining the patient’s phenotype were identified. In addition, results were reviewed to determine whether incidental findings were reported, including variants of unknown significance, carrier status, and pathogenic mutations in genes not related to the patient’s phenotype (and recommendations made based on results). The chart review helped to account for the variability of results reported among clinical laboratories that perform WES because such variability—combined with differences in individual consent options—may influence parental experiences and understanding of results. The data from the chart review were triangulated with the data
collected in the parent interview(s) and clinician interview(s) by cross checking the data sources noting discrepancies and agreement. Information obtained during the parental interview was compared to the data recorded in the chart regarding how participants interpreted the results and what they remembered or considered meaningful. To limit researcher bias, the chart review was conducted after the parent interview. Each participant’s recollection of the specific mutation, gene, or number of findings was not documented in order to help maintain patient confidentiality and privacy. Also this information was not the main focus of this study; rather, the meaning the participants attached to WES results was compared to the information recorded in the clinic note by the genetic counselor and/or geneticist.

Data collection: clinician interviews

The third and final step in data collection was the clinician interviews. A single researcher, using the semi-structured interview guide, interviewed the geneticist and genetic counselor participants (Appendix 9). These participants were directly involved in the WES process for each of the parent participants. The interview guide was developed by the student researcher with expert review and feedback from thesis committee members. The interview guide was created to supplement the information about parental experience of the WES by gathering information from the perspective of the geneticist and genetic counselors and to assess the third aim of analyzing relationships between the genetics professionals and the parental participants.

The interviews were conducted over the telephone or in the geneticist or genetic counselor’s private office. The interviews were audio recorded and transcribed by a
professional medical transcriptionist who has experience working with the Case Western Reserve University Department of Bioethics and is very familiar with qualitative research. The transcripts were carefully reviewed and edited for accuracy by the student researcher.

Data analysis

The transcripts were summarized and analyzed for an in-depth description of each case. The transcripts were analyzed with thematic analysis in a four-step process including, familiarization with the data by means of reading and rereading the transcripts, inductive open coding of the data by marking units of data that appeared to be meaningful and analytical coding of data by interpretation and reflection on the meaning of the data (Richards, 2005; Merriam, 2009), sorting codes or units of data into similar themes or categories and refining the themes and naming the categories to be mutually exclusive for this research purpose (Merriam, 2009). Inductive coding is the process of identifying themes or trends in data by reading through each family experience as a single case and marking ideas and concepts that repeated or noted as being significant (Merriam 2009). The cases were first summarized with in-depth description, and analyzed individually using with-in case analysis. This type of analysis involves treating each individual case as a comprehensive unit of study in order to describe and summarize the parent’s experience with specific attention paid to the codes and connections within the case (Merriam, 2009). Each case is the bounded system of the application of WES for each family and therefore consisted of a parental interview or interviews, the corresponding chart review, and the geneticist and genetic counselor interview applying
to that family. Information from the chart review and the geneticist and genetic counselor interview was used to supplement each case. Reviewing the medical records from the WES process and the clinician interview helped in assessing the impact of the information available to parents after WES, and parental understanding of the information. The chart review was conducted by comparing the answers that participants provided to what was indicated in their medical record thus triangulating the data. The analysis included comparing the recollection of the type of results that the participants remembered (diagnostic, variants of unknown significance, etc.) to what results were documented in the chart and then assessed for agreement. Agreement was defined as reasonable and noticeable similarities between the two sources of information.

Additionally, participants’ understanding of findings was assessed by comparing their description of the significance of the mutation, incidental finding, or variants, to the description in the chart. Recollection of the specific mutation, gene, or number of findings was not assessed in this study. The geneticist and genetic counselor interviews helped to supplement this information by providing insight in to what the clinician felt was important to convey to the family throughout the process and what they felt the parents understood in the process. The data from the parental interview, the chart review, and the geneticist/genetic counselor interview were entered into a matrix, developed by the student researcher, so that data for each case could be organized and analyzed.

After within case analysis was conducted to provide a detailed experience of each case, cross–case analysis was conducted. Cross-case analysis involved a unified description of themes that emerged from the cases. For this analysis the data were entered into a matrix to display the thematically coded data from the parents, clinicians, and
counselors (Merriam, 2009). The within-case and cross-case analyses were performed to meet the aims of the study, including describing and analyzing parental experience of WES and exploring the use of results for medical management and family planning.
CHAPTER 5: Results

Participants

A total of four families consented to participate in this study. One family was from UHCMC and three families from Nationwide Children’s Hospital. One additional parent expressed interest in participating in the study and signed and returned a consent form but was unreachable on follow-up via phone or mail. At least one clinician for each case participated in this study (Table 1).
### Table 1: Study demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case1</th>
<th>Case2</th>
<th>Case3</th>
<th>Case4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender of parent</td>
<td>Female</td>
<td>Female, Male (separate interviews)</td>
<td>Female, Male (interviewed together)</td>
<td>Female</td>
</tr>
<tr>
<td>Education completed</td>
<td>Masters degree</td>
<td>High school, Some college</td>
<td>Bachelors degree, Some college</td>
<td>Some college</td>
</tr>
<tr>
<td>Age of parent at time of interview</td>
<td>32</td>
<td>27, 30</td>
<td>34, 35</td>
<td>34</td>
</tr>
<tr>
<td>Gender of child/children</td>
<td>Male</td>
<td>Female</td>
<td>Female and male</td>
<td>Male</td>
</tr>
<tr>
<td>Genetic diagnosis after WES</td>
<td>Unknown</td>
<td>Achieved by WES</td>
<td>Unknown for both children</td>
<td>Likely achieved by WES</td>
</tr>
<tr>
<td>Age of child at time of interview</td>
<td>4</td>
<td>4</td>
<td>9,7</td>
<td>3</td>
</tr>
<tr>
<td>Siblings of affected child</td>
<td>2 full, none with a similar disorder</td>
<td>2 full, none with a similar disorder</td>
<td>None (both children affected)</td>
<td>1 full, none with similar disorder</td>
</tr>
<tr>
<td>Clinicians involved in WES</td>
<td>2 genetic counselors and a geneticist</td>
<td>Genetic counselor and a geneticist (same genetic counselor and geneticist as case 4; geneticist did not participate in the study)</td>
<td>Geneticist</td>
<td>Genetic counselor and a geneticist (same genetic counselor and geneticist as case 2; geneticist did not participate in the study)</td>
</tr>
</tbody>
</table>
Case Analysis

Case 1

The first case involved a mother (Mother1) of a four-year-old boy who underwent WES to find a genetic diagnosis for his epilepsy and neurological symptoms. The family had been searching for a cause for their son’s symptoms since he was about 6 months old when he first developed infantile spasms. This patient’s geneticist as well as two genetic counselors, one involved in the consent for WES (genetic counselor1), and the other involved in the return of results for this patient (genetic counselor 2), also participated in this study. Mother1 reported that her son had numerous genetic tests before WES, all of which failed to find a genetic diagnosis, and he had been seen at a few different hospital systems along their diagnostic odyssey. Mother1 heard about WES from both a geneticist at another hospital system and online support groups. She was motivated to pursue WES to try to determine why her son had this condition and also for the possibility of better treatment options if a genetic cause was known. The participant’s major hope was that WES would find a diagnosis that had available treatments or a known prognosis; however she noted that the test “brings up more questions than answers, and the answers are not very definite right now because it’s fairly new, so I wasn’t really expecting to find an answer, but there was just always this little hope that we might.”

Genetic counselor1, who was involved in the consent process, said that Mother1 brought up the possibility of WES first. Genetic counselor1 questioned whether this was the appropriate test for this patient because there might be other testing options to pursue first; however, there were insurance limitations for other tests but WES was covered. The
geneticist hoped that WES would find a reason for the patient’s symptoms because there have been a few cases of individuals with similar symptoms who had an identifiable genetic mutation; however, realistically she expected that the cause of the symptoms was multifactorial in nature and that WES would not result in a diagnosis.

The pre-test counseling was conducted by genetic counselor1, and the geneticist was not directly involved in the consent process. Genetic counselor1 said she stressed the limitations and possible results that could arise in WES, including cancer predisposition syndromes and carrier status, but noted this family did not seem concerned about these possibilities and they really wanted as much information as possible. Mother1 said the consent process was helpful, stating:

“It’s good to know that you could end up learning something totally unrelated, that isn’t a good news kind of thing, that it’s good to know kind of all of the possible things you could learn. You have an idea of what you’re choosing when you choose it, that you may not just be looking for an answer to your question. You might be finding other things too, and that even if you get an answer, it might still be a fuzzy answer, and it’s just good to know that going in so that I did not have high expectations for what I would get out of it, and when we didn’t get the answer, I was not surprised.”

Mother1’s major concerns were that WES would find out “that he was at risk for something or that he was carrying something that our family was at risk for […] that we would then all of a sudden have this information that we would live in fear of.” Genetic counselor1’s major concerns were also about incidental findings, as well as gene coverage by WES. Genetic counselor1 said that in retrospect, she probably should have been more concerned about variants of unknown significance and put more effort into explaining what those were and what could come of them.
Mother1 reported that she had the option to receive results that were determined to be unrelated to her son’s condition. Even though these results could be frightening, or unexplainable, the family wanted to know, in case there were recommended screenings or treatments, or in case new information might be learned about the variants in the future. Genetic counselor1 and the genetics chart also reported these options and that the family consented to receive all possible information.

Mother1 said her experiences waiting for previous tests results helped her deal with WES. She reported that, in the beginning, when her child first had genetic testing, she felt much more anxious, and she wanted the results as soon as possible. Since she had previously gone through the experience of genetic testing, she had become more patient waiting for results, stating, “I’m used to having to wait for things and so I’m okay with waiting now.” However, she also stated that the time between when the results were returned to the geneticist and the time of the results appointment was stressful.

The results were reported in one appointment with the geneticist and genetic counselor2. Mother1 reported that WES did not find a genetic diagnosis for her son, but did find a few variants of unknown significance and carrier status for recessive disorders. Mother1 did not receive any information about test results over-the-phone. Information from the geneticist and the chart review was consistent with the parental report. Mother1 however, did not report any pharmacogenetic variants that were documented in the chart as well as by the geneticist.
Mother1 described herself as a visual person and explained that seeing the results was very important to her understanding of the information. She said:

“I really did need to be able to look at the charts and see what she was talking about when she was explaining it. If she’d tried to do it over the phone, it would not have worked. So I think the way she did it was the best way to do it. It’s just gonna be inevitable that those last couple of weeks are gonna be the hardest ones to wait for, but I don’t know that there’s any way to avoid that because I really don’t think it could’ve been done over the phone. I really needed to be able to look at the charts and all the different things she was talking about as she was saying it, ‘cause it’s a lot of information to try to take in.”

She suggested that some families might need multiple appointments for discussing WES results because it can involve complex information.

Mother1 felt that the results appointment was handled very well. She noted that it was important for her to see the results, and she appreciated the clinical notes from the geneticist and genetic counselor. She also appreciated seeing the time and effort that the health care providers had put into analyzing, investigating and explaining her son’s results. She did not describe any major confusion about the information.

Mother1 said some of the variants of unknown significance prompted additional investigation and doctors’ appointments. She said that this was probably the most stressful part of the experience because her child had variants of unknown significance in a few genes known to cause cardiac conditions, vision problems, and hearing problems. Due to these findings, the child was referred to a cardiologist for additional testing as well as given recommendations to follow-up with other physicians. She described this as “a necessary hassle.”
The geneticist said she had mixed feelings about disclosing and making recommendations about these variants of unknown significance due to “potentially increasing their anxiety and the burden of care on the family and on the system.” She noted that:

“it’s been my practice, which is for better or worse, to disclose that and to be proactive in screening about those things until we can determine if they are pathogenic or benign, and I know that’s not a universal practice, and we had counseled ahead of time about the possibility that the child may end up undergoing extra screening.”

The geneticist also felt it was important for the family to know that the variants were likely benign, and that the extra screening was just to be extra cautious. She also felt it was important for the family to know “the fact that the test was essentially negative for the diagnosis we were seeking does not mean it’s not genetic, and that this is not the last genetic test that the child will have.”

While medical management did not change for mother1’s son, aside from the additional screening recommendations from the geneticist and genetic counselor based on the variants of unknown significance, a recommendation was made for her son to wear sunscreen, as the results of WES suggested he was susceptible to skin cancer, though this recommendation was in the genetics chart but not reported by any of the clinicians during the interview. She noted that this information was a little surprising because it was previously unknown, although it did not have a dramatic impact on the family, and it was better to know this information just in case. Mother1 also said that no significant recommendations were made for the rest of the family, but she was told to keep track of family history information for cardiac issues. In addition, she was told that other relatives might be carriers for the same recessive diseases as her son. She said that she had
informed her relatives about her son’s carrier status, in case they wanted to be tested themselves, as many of her siblings were currently considering having children.

Mother1 did not mention pharmacogenetic variants; however, one was mentioned by the geneticist and reported in the genetics chart. This pharmacogenetic finding suggested that a medication change might be beneficial to the patient. While the information was given to the prescribing physician, no changes had been made, as the patient appeared to be doing well on his current dose.

Mother1 stated that some of her family members were relieved that no genetic diagnosis was made, because these relatives felt this decreased the risk for their own future children to have the same disorder. She also noted that WES did not impact how she felt about having additional children, because she and her husband had decided not to have any more children prior to WES. Mother1 added that because no diagnosis was made and the results of WES did not affect their lives, they did not feel like they had a significant adjustment process; and that the process did not have a significant effect on her relationship with her husband or their relationship as a family.
Mother1 said that this test lived up to her expectations because she had not expected to get an answer for her child’s condition, though she was still amazed that one could look at so much genetic information and still not have the answer. She also said “I was surprised by how relieved I was actually that they didn’t say ‘Yes, he has this neurodegenerative genetic disorder that is going to take this course and he’s going to have a limited life span.’” When asked how the test disappointed her, she said:

“I would love to know what is the cause of [patient 1’s] issues and symptoms and seizures and that sort of thing, and I would love to be able to treat it, but we had a lot of tests come back without answers, so we don’t really expect … It’s not as disappointing as it was early on, ‘cause we’re sort of expecting that now.”

She noted she has learned to deal with this disappointment and lower her expectations because he had a number of tests come back without an answer so they did not expect to get an answer, and this time it was not as disappointing as it was early on.

The geneticist and genetic counselor2 felt the family had a very good understanding of the information. They both were disappointed that they did not get an answer for the family and believed that the family was disappointed as well, but they said the family took the information in stride and had a very good understanding that WES does not find an answer for everyone.
Knowing what she knows now, Mother1 said she was happy her son had undergone WES. Mother1 said “I am very glad. I always would’ve wondered, if it could have given us answers, and unfortunately it didn’t, but I’m glad that I don’t ever have to wonder what I would’ve found out if I’d done it.” Genetic counselor 2 also stated:

“I think that the family would not have been comfortable leaving the option on the table and not pursuing it, so […] in the end, it didn’t change anything, but I think the family needed to kind of go through that. I think the family would’ve felt then they weren’t doing everything they could […] I think they felt that they needed to keep kind of opening these doors to see if they could find some things. So that’s why I’m glad that we did everything that we could for the family so that they, they have that peace that they checked all of these different places and kind of did what they could.”

Mother1 said that she would recommend WES to other families that were in the same position of trying to find a diagnosis for their child, due to the possibility of identifying a diagnosis. She did however note that she did not think the expense was worth the risks for people who were healthy to have their exome sequenced because—even though there was the possibility that it would reveal helpful health information—there were still a lot of variants that could not be explained. Finally, Mother1 stated that her son has since had additional panel based genetic testing and that they were waiting for these results at the time of this interview. She said the doctor recommended that if this test did not find a diagnosis, then the family should take a break from genetic testing for a few years and wait for future advances in technology. She noted that she and her husband agreed that this would be the best course of action.

On the topic of perspectives on how to best return results, Geneticist 1 said it was very important for her to give WES results in person due to the complexities of the information and to ensure that she has the patient or family’s undivided attention.
Case 1 analysis:

This case involves a highly motivated family seeking a diagnosis for their son’s condition. Mother1 was motivated out of a desire to find a diagnosis and for information to guide expectations and treatment. Previous research on parents with and without a known diagnosis for their child’s ID (Makela et al., 2009), found that curiosity and information were two themes that emerged as categories when parents valued a diagnosis. Makela et al (2009) reported that all families in their study preferred a diagnosis but the need for a diagnosis decreased as the child’s disability became clearer over time, though some families would always feel the need to know. Perhaps another aspect of this decrease in the “need to know” over time is the perception that all options to provide a diagnosis have been exhausted. Mother1 said she would love to know the cause of her son’s symptoms, but she had learned to deal with disappointment. This may indicate that she may not feel the need to know as strongly as she once did, not because of the way her son has grown and developed but because they have exhausted many options on this diagnostic odyssey and still have not found an answer. Mother1 also reported that she was unexpectedly relieved that WES did not diagnosis her son with a neurodegenerative disorder that would have seriously limited his life span. She mentioned she wanted answers, but what if the answer had been something with a known prognosis that would seriously limit his lifespan? Would she still have wanted to know this information?

Another interesting aspect of this case is how Mother1’s siblings and her husband’s siblings reacted to some of the information. Mother1 said that their relatives were very interested in learning that the results had not found a specific genetic diagnosis
as they felt it lowered the risks for their future children. However, just because WES did not find a diagnosis does not mean that the cause is not genetic, but simply that WES technology was not capable of finding the cause for the condition. Mother1 seemed to understand this fact because they had pursued additional genetic testing after WES, but their relatives may not have this same understanding.

Previous research and bioethical literature on WES has described how variants of unknown significance could affect patient care and possibly cause unnecessary stress. Although there are no recommendations on best practices in returning or managing these types of variants, the geneticist in this case noted that she tended to approach variants with caution when they are in genes with a known significant clinical impact, have efficient screening capabilities, and may not have apparent symptoms. Mother1 reported that the information about variants and the extra screening recommendations were the most stressful parts of this process, but called it a “necessary hassle.” Perhaps her concern was because she was worried about her son’s health, but she expected unknown information, so it was not a surprise. She seemed to feel that extra screening, although stressful, was just part of the process that she had accepted.

Mother1 believed the genetic counseling and consent process was very important for this type of test because it helped her balance her expectations and understand what they were getting themselves into. She understood the limitations of this test, so when they did not get an answer for the condition but found lots of other information, she was not surprised or confused.
Mother1 had recalled most of the types of variants reported in the medical record, and she remembered the meanings of the results, including variants of unknown significance, the recommendations for additional screening, and carrier status and how it could affect other relatives. The genetics providers felt that the family also had a very good understanding of the information. The only information that was not reported by Mother1 was the pharmacogenetic variant, which could affect the metabolism of a medication that her son was taking. She may have forgotten this information, did not find it important, or perhaps she saw it as something for her son’s doctors to deal with. According to previous research (Kaphingst et al. 2012; Michie et al., 1997; Meiser et al. 2011; Reiff et al. 2012; Visser & Bleiker, 1997) people tend to remember information that they find important. Perhaps she did not find the pharmacogenetic variant to be important, because due to her son’s response to his current medication, no changes needed to be made, or perhaps she saw it as something for his physicians to deal with, and not important for the family to worry about.

Although the family, the geneticist, and genetic counselor 2 reported disappointment in the lack of a diagnosis from WES, no one was particularly surprised. Mother1 said she was satisfied overall with the process because she felt well prepared for it, thought everything was clearly explained to her, and appreciated the care and attention the genetic professionals put into analyzing and explaining the WES. Most of all, she needed to feel like she was doing everything in her power to help her son. Satisfaction was not based around the results in this case but the effort in obtaining the results and engaging in the process.
Case 2:

Case 2 involved both the mother and father (Mother2 and Father2) of a four-year-old girl who underwent WES. Each parent participated in a separate interview, as well as the genetic counselor involved in this case. Mother2 reported they had been searching for a diagnosis for their daughter’s significant motor delay since she was about six months old, when they realized she was not meeting her developmental milestones. Both parents reported that their daughter had numerous genetic tests before WES, all of which failed to find a diagnosis. The counselor said that the major motivation for offering WES was the possibility of finding a genetic diagnosis for the child’s phenotype, because all previous testing had failed to find a diagnosis, and the family was motivated to find an underlying genetic cause. On the topic of understanding the nature of the test and decisions to undergo WES, Father2 said:

“We always thought it was a pretty complex test, which we were fine with. We just thought it was the ‘next level,’ and we were encouraged by the geneticist that this could find something we hadn’t found, so we started looking into it.”

Both parents indicated that their major motivations in pursuing WES was the possibility of finding a diagnosis for their daughter’s condition and their confidence in the physician’s and genetic counselor’s recommendations of this test. Mother2 hoped:

“WES would find answers to explain things, just what was going on with her so that we could know just what to do, if there was anything we needed to be doing differently therapy-wise, [and] if there was anything we could expect in the future.”

However, Mother2 approached WES with an open mind and was aware that they might not receive a diagnosis or answers for the future. Father2 also noted that he did not expect
a diagnosis from WES because they had already had a lot of genetic testing that did not find an answer, and he understood that this test does not find a diagnosis for everyone. The genetic counselor had the same hopes and expectations as the family.

In pre-test counseling, the genetic counselor felt it was important for the family to know the limitations of the test, including that the test might not find a genetic cause, that a diagnosis did not guarantee prognostic information or management information, and that there was a possibility of incidental findings and variants. The genetic counselor’s major concerns included “finding an incidental secondary finding … or something difficult to explain that ends up being more questions than answers.” Both Mother2 and Father2 reported that they felt comfortable with the counseling process prior to WES. Father2 elaborated on this counseling process stating “our experience with the genetic counselor was very thorough, and we understood what we were up against I think before we did exome sequencing.”

Mother2 and Father2 both remembered that they had been presented with a few options about the types of results that they would receive, and they decided to receive all possible results. Father2 reported WES “could’ve uncovered things about us…as well as our daughter, things that may not even be related to what her symptoms were…I think we were given the option if we wanted to or didn’t want to know.” He also reported that he found some of these options to be a little scary, but that both he and his wife decided that they would rather have this information, in case there was something they could do about it. The genetic counselor described the family as well-educated and information-seeking, and said that the family seemed to understand the test and wanted all the information they could get from the test. The chart review confirmed that the family had the options to
receive various amounts of secondary information and variants of unknown significance and that the family chose to receive all possible results.

Mother2’s biggest fear about WES was that it would reveal that their daughter had something with a “terrible prognosis,” and not knowing whether there would be anything they could do about it. Mother2 also reported testing fatigue, saying that she had been worn out from all of the testing that had been done and that she was ready for a “go-big-or-go-home” approach. Both parents referenced their experience with previous genetic testing as preparation for WES and for the amount of time it would take for this test to be completed. Mother2 said, “by this point I had been able to practice patience with testing.”

Mother2 reported significant anxiety in the situation that surrounded the return of the results. She noted that their “usual” genetic counselor was out of the office when the results had come back, and another genetic counselor had called her to inform her that the test results had been received. She reported that this was very difficult for her because “I was so used to him helping me and explaining everything. So the way she explained it was really scary for me.” Mother2 also reported that over the phone she was told that the test had found a diagnosis, and she was given the name of the disorder including some brief information about it, and told to schedule an appointment. She said this was also difficult for her because she felt the name of the disorder did not adequately describe her daughter’s features, and she was not able to find much information online that she could understand. Learning about the test results in this manner provoked anxiety because she felt confused and overwhelmed, and had to wait for the appointment to learn any
information about this disorder. Neither Father2 nor the genetic counselor reported a similar experience.

The WES results were given in one session with the geneticist and genetic counselor. Both parents found the session to be very helpful. Mother2 added “it was really nice to sit face-to-face with the doctor and not feel rushed, and felt like you know the time was open for us to just discuss anything we needed.” They appreciated having the extra time and the ability to have all of the important information written out and explained to them. Father2 said “sitting down with the doctor face-to-face, getting an explanation, as well as being able to ask him any questions we want and having the access to the Geneticist was really important at that point to understand what exactly the results were.”

Both parents reported that WES found a mutation that explained their daughter’s symptoms. They also remembered that WES found a few secondary findings including variants of unknown significance, but this information was not concerning or important to them. In regards to variants of unknown significance and focusing on the diagnosis, Father2 said “none of it was active and none of it was anything that’s considered to be a concern for the future and we just moved on with what was relevant and what was active.” The genetic counselor and the medical chart also confirmed that WES found a primary cause for the child’s phenotype as well as some additional variants of unknown significance and pharmacogenetic variants, although the family did not report the pharmacogenetic variants. The genetic counselor thought that the family had a good understanding of the information and added that they “keyed in on the primary reason for the result, and they felt anything else was sort of ancillary.” The genetic counselor
reported feeling excited to give these results to the family. This was one of the genetic counselor’s first cases of WES and he felt very happy to get such a clear-cut answer.

After the results appointment, the diagnosis made much more sense to Mother2, as the disorder’s features and name were explained to her in more detail. For this family, the diagnostic odyssey had changed from trying to “figure out the cause” of their daughter’s symptoms to learning more about the disorder. Father2 reported satisfaction in knowing that his daughter’s information could be added to the body of information about the disorder for future research. He also mentioned that it was somewhat satisfying to know that there were individuals who are adults with the same genetic mutation as their daughter. The genetic counselor believed that the parents were excited to have an answer but still want to learn more about the diagnosis and it is a very rare condition. The genetic counselor believed that the family had been relieved of some of the burden associated with the diagnostic odyssey. When asked about stress in the WES process, Father2 said he did not feel the process of WES was stressful. He said one reason why the battle of trying to find a diagnosis and raising a child with a genetic condition is stressful “because a lot of times [in] genetic[s], my understanding is it can’t really be fixed.”

Mother2, Father2, and the genetic counselor reported that no changes were made to medical management based on the WES results because symptomatic management that they had already been doing was sufficient in this case. In addition, results did not change care or implications for other members of the family, thus no results needed to be shared with more extended family members. This was in agreement with the findings in the chart review, including no major changes to medical management or recommendations that were significantly different from what the family reported. The only comment from
the chart review, which was not mentioned in any of the interviews but appeared to be a tentative recommendation, was a possible brain MRI.

Both parents agreed that WES did not directly impact how they felt about having additional children. Mother2 reported:

“Even though they said you know that our chances were very low of that happening again, my husband and I, with the care that she requires just fear that if we were to have another child with this or with any other disability, it would be very unfair to her and our other children to you know put them through that and just take away more attention from them.”

This concern was not directly related to WES but to having another child with a medical condition.

Father2 reported that WES exceeded his expectations, as he did not really expect to receive a diagnosis. Mother2 also said that genetic counseling was extremely important. She said being able to communicate and have that relationship with the counselor and have someone to explain things on their level helped her get through this process. Both parents reported that they are happy they went through the WES process. Mother2 said:

“It’s [brought] us a lot of closure because we were spending months and months and months of appointments trying to just figure out what was going on with her, and I know it took a lot of time away from our family, so just having the closure of knowing there’s no more tests to be done, you know, we’re not chasing something anymore. It’s just a waiting game to try to figure out what this means, but we know now that we don’t have to pursue any more tests as of now, and it’s brought a lot of closure to us. We’ve been able to just relax and be a family.”

Both parents also said they would recommend WES to other families who had nowhere else to go and had exhausted all other testing options. Father2 said:
“as a parent you’d probably want to do this test first, you know, because it’s the most powerful and it’s the biggest and the strongest, but I feel like you have to have a Geneticist that would do what ours did, and that is start where they’re supposed to start and you know do the appropriate tests and then eventually get the exome sequencing if it’s necessary.”

*Case 2 analysis:*

Case 2 is an example of where WES achieved a diagnosis for the child’s phenotype. As noted in the literature, a genetic diagnosis is achieved in approximately 25% of cases; (Yang et al., 2014) however, many of these conditions are very rare. Although a genetic mutation can explain a phenotype, genetic professionals cannot always provide information regarding prognosis or management recommendations. Due to the rarity of these disorders, this information may not exist. Families with a child with a rare diagnosis such as Family2 may then be forced into a new area of their medical odyssey: while they may no longer have to pursue genetic testing to find a diagnosis, they now have to wait for the medical community to learn more about the condition at hand. Overall, this family was very happy to receive a diagnosis and experienced satisfaction and closure, but due to the rarity of the condition that their daughter has, they found they did not have a lot of information about the condition and experienced uncertainty regarding the prognosis for their child. This feeling of closure mixed with feelings of uncertainty regarding prognosis and expectation has been previously reported. Many parents who have a child with a rare condition diagnosed by chromosomal microarray reported that they felt closure in the search for a genetic diagnosis, but uncertainty regarding prognosis and what the future would hold for their child (Reiff et al., 2012).
Mother2 reported significant anxiety surrounding the return of the results because the genetic counselor that they had previously worked with was unavailable and she was given some result information by another genetic counselor whom she had never met. This was very difficult for Mother2 as she had not established a relationship with this counselor. It can take a number of months for WES results to be returned, thus changes in faculty and staff can occur or individuals may not be available, as in this case. Mother2 did not seem to be aware that this was a possibility and appeared to be caught off guard. Perhaps it would be wise for genetics professionals to address this during the pre-test counseling session. Father2 did not bring up this issue; however, he did not personally receive the call about the results, so he did not share in this experience with Mother2, nor did he mention in the interview that his wife had struggled with this event. Perhaps he was unaware of how much anxiety it had caused. During the results appointment, Mother2 felt much more comfortable as she was meeting with the geneticist and the genetic counselor with whom she had built a relationship and appreciated the time that was taken to explain all of the aspects of the results.

The parents reported similar findings to each other and to the chart review, and the meanings of the findings were consistent with the report and clinic note. The only results discrepancy was the pharmacogenetic variant that the parents did not report. There was also a recommendation in the clinic note to possibly follow up with a brain MRI. This recommendation appeared to be somewhat tentative and not of immediate concern, which may have been the reason it was not mentioned by anyone. This family did not seem very concerned with the incidental findings and other variants. In this case, no
additional screening recommendations were made based on the incidental findings or variants of unknown significance that were identified.

Both parents cited the explanations from the genetic professionals as helpful in their understanding of the results and Mother2 found genetic counseling to be crucial. Parents of children who had chromosomal microarrays also found that genetics professionals helped them to understand the result information (Reiff et al., 2012) and parents often desire genetic counseling with genetic testing. (Dinc & Terzioglu 2005)
Case 3

The third case involved both the mother and father (Mother3 and Father3) of two children, a nine-year-old girl and seven-year-old boy with the same phenotype including developmental delay, epilepsy, and movement abnormalities, who had WES. Full WES was performed for their daughter and partial sequencing was performed for their son, based on their daughter’s test results. Mother3 and Father3 participated in the same interview. The geneticist who ordered WES also participated in an interview. A genetic counselor was not directly involved in the WES process for this family.

Mother3 and Father3 had been searching for a diagnosis for their children’s condition for about nine years, and they had undergone numerous genetic tests for both children prior to WES. The geneticist had been following this family for about six years. Father3 said that the main reason they decided to pursue WES was that “it was basically the next test in the line of testing. Basically they told us that they had pretty much exhausted everything they could think of and this would be the next logical step.” The geneticist offered WES because extensive genetic testing had already been performed and he thought WES was the next reasonable step to try to find a diagnosis. The family was very motivated to find a diagnosis because they felt something genetic must have cause the children’s phenotype. Mother3 said she hoped WES would yield “some type of results that might give us an idea of why our kids are the way they are.” Both parents hoped for, and expected, an answer from WES. The geneticist also reported feeling very hopeful and expected to find a diagnosis for this family, stating, “they had two affected children, both parents available, and we thought it would be a fairly straightforward one to find a diagnosis.”
The geneticist described being very thorough and meticulous in the pre-test counseling for WES so that the family would really understand the risks and benefits of the test. The family agreed and felt the counseling was thorough and transparent, and they valued these aspects of pre-test counseling. They were aware that the test could come back with unexplainable results or that it might not find a reason for the children’s condition. However, Mother3 and Father3 did not recall having options about what information would be returned. Mother3 stated, “What the lab was going to send back was what they were going to send back.” There may have been a misunderstanding about the question that was asked, or they may not have remembered these options. However, it was evident in the chart review that they did have options about receiving incidental findings and variants of unknown significance, and that they consented to receive all available information. The information discussed with the geneticist during the interview was consistent with the chart review.

Mother3 and Father3 did not report any major concerns about the test. Father3 said:

“I didn’t really have any major concerns. We just figured if it did come back with something, then we would just start addressing [it] in the treatment plan as necessary. So I wouldn’t really say we had any problems with it.”

While the parents did not report any concerns related to incidental findings, the geneticist did report that interpreting and reporting unexpected findings had been his main concern. However, the geneticist also said that they are a very strong couple that had a good grasp of the situation for their children, and that they would be able to handle any results that came their way.
The parents reported that they felt impatient and excited while waiting for results because they felt WES had a good chance of uncovering the genetic cause of their children’s symptoms. They were given brief preliminary results over the phone, which included that the results did not find a diagnosis for their children, and were told to come in for a full appointment to discuss the results. Mother3 said knowing that WES did not find a diagnosis beforehand “helped us to be more realistic about how we were going to feel when we were looking at the results.”

The family and the geneticist reported that they did not learn very much from WES. WES did not determine a genetic diagnosis and there were few variants of unknown significance, but none in genes that would be related to the phenotype. This was surprising and disappointing to everyone involved. The family said the most stressful part of the process was that WES did not find a genetic diagnosis and that they were “at the end of the road” with possible testing without an answer and with nothing to focus on. The family did report that the test uncovered pharmacogenetic variants, and Mother3 said learning about the pharmacogenetic variants was helpful because they now knew to address this increased sensitivity in case such medication is prescribed to anyone in the family in the future. The chart review confirmed these pharmacogenetic variants that the family reported; however, the geneticist did not mention them when asked about variants or unrelated findings.

The family felt the geneticist spoke with simplicity, transparency and honestly about the results and that these were as the most important factors in helping them understand the results. The geneticist felt the family had a very good understanding of the results as well, and said that these parents seemed to accept the results for what they
were, though there may have been disappointment that they did not have an answer. The family, the geneticist and the chart review all agreed that WES did not change medical management for their children or anyone else in the family aside from the knowledge of the pharmacogenetic variants.

On the topic of family planning, there were some discrepancies between the geneticist and the parents in this case. The geneticist spoke a lot about how the family wanted more children and wanted WES in part to help determine recurrence risks for their family planning. The family said that by the time they got to WES they had already decided not to have more children due to the level of care that their existing children require.

This family expressed frustration over the fact that full WES was performed on their daughter while the laboratory only did comparative partial testing on their son. They felt that if the lab had done full testing on both kids, they might have found a reason for their disorder. They explained that the testing was done this way was because it was cheaper to do testing on only one child and then compare results.

Despite the disappointment they experienced after such hope for a diagnosis with WES, the family was generally happy that they went through the process because they now had done everything possible to find a diagnosis.
Case 3 analysis:

Case 3 is a unique case detailing parents of two children with the same phenotype but WES failed to identify a genetic diagnosis. The family and the geneticist both hoped and expected to find an answer; however, they also understood that it was possible they would not have a diagnosis.

Mother3 and Father3 did not recall discussing options about the different types of information that they could receive. The chart review, however, noted that options regarding which information the family would like to receive, i.e., carrier status, extended report of variants and/or choosing to receive all possible information, were discussed. In addition, the parents chose the option of receiving all possible information on the consent form. Perhaps they misunderstood the researcher’s question about options or simply did not remember them. Either way, they seemed to have a good understanding of what they were dealing with and knew that they could receive many different types of possible results.

These parents remembered all of the result information reported in the genetics chart, although there was not a lot of accessory information aside from the pharmacogenetic variants. They recalled the variants and thought that they were important for their family to know because if anyone were to need the medication in the future, they could be proactive and tell their physician that they may respond differently to that medication. Previous studies on recollection of genetic information report that people tend to remember information that they found important (Kaphingst et al. 2012; Michie et al., 1997; Meiser et al. 2011; Reiff et al. 2012; Visser & Bleiker, 1997).
Mother3 and Father3 may have focused on this information, as it was one of the few results that was specific or that “they could hold on to.” Previous studies report that parents have lower perceived uncertainty when they have higher perceived control. Perhaps these parents focused on this area of control to relieve some of their uncertainty regarding the lack of a diagnosis for their children (Lipinski et al., 2006).

The geneticist and the family reported different information about a desire for more children. While the geneticist repeatedly mentioned that the family was in part seeking WES for future family planning, the parents firmly reported that they were not interested in having more children. It could be that the parents had changed their minds about future children during their time working with the geneticist and that the geneticist did not realize the family’s sentiments had changed.

While the parents did not express regret about the WES process, they did remain concerned about the fact that their son’s exomes were only partially sequenced for the purpose of filtering variants against his sister’s full sequencing results. Because the family had exhausted all other genetic testing options, they might have still wondered whether more information could have been uncovered if their son’s exome had been fully sequenced. In cases of siblings with the same disorder, it is more beneficial to look for similarities between the two rather than to look at each sibling independently because the siblings share the same phenotype and thus should share the same genetic diagnosis, regardless of which sibling was fully sequenced. These complexities of the testing approach may be difficult for families to understand and difficult for geneticists and genetic counselors to articulate. In this case, it seemed the family may have believed that, with all other testing options exhausted, perhaps sequencing their son’s full exome could
have yielded a diagnosis. Family3 did not seem to fully understand the reasoning behind the way the testing was performed and believed that cost was the primary reason that their son’s exomes were not fully sequenced. If the parents were distressed by this testing method, it would reason that they would report lower satisfaction with the process. However, this family reported that they were satisfied with the process and felt that their geneticist had done his due diligence. Perhaps they recognized that testing was performed this way for reasons beyond cost efficiency but did not fully grasp this concept and so still wanted to hang on to the hope of finding a diagnosis with the testing methods currently available.
Case 4:

The fourth case involves the mother (Mother4) of a three-year-old boy who had WES. The genetic counselor involved in the WES process also participated in this study. The family had been searching for a diagnosis since their child was about a year old, when he was not reaching his developmental milestones. He continued to have developmental delay and cerebral palsy–like symptoms. Mother4 described this process of trying to find a diagnosis as long and emotional, because they did not have any answers. Mother4 reported, “once we got to genetics, we felt like something would come out of it, good, bad, whatever.” Their son’s previous genetic testing had not identified a diagnosis, and the geneticist and genetic counselor offered WES because the family was still motivated to find an answer after all other reasonable testing had been performed. The main motivation was to find a genetic diagnosis for their child’s condition. Mother4 said “We just wanted answers because we wanted to help him, like any knowledge […] is helpful.” The genetic counselor stated that this family was hoping to find a diagnosis and very interested in information about prognosis and recurrence risks.

In regard to pre-test counseling, Mother4 reported that she felt very comfortable with the genetic counseling process and with the geneticist and genetic counselor who worked with the family. The genetic counselor said that it was important for the patients to understand the benefits and limitations of the test. Mother4 seemed to be very aware of the possible outcomes, including a lack of diagnosis, and unexplainable variants. She explained that her expectations were not always consistent and throughout the process she often felt WES would find a diagnosis even though they were very aware that this test might not find answers. Overall, she felt “the chances of maybe finding out something is
better than us not knowing anything at all. So [...] for my family, it was best that we try to figure out something.”

Mother4 reported that they had been presented with options about the amount of information that could be reported, including the incidental findings. Mother4 spoke about feeling very uncertain at first about whether or not she wanted to know accessory information, she said, “Do I want to live knowing that, or am I better off not knowing?” She mentioned her husband wanted to know everything from the beginning, but she needed some time to think about it. She finally decided she wanted to know everything as well, partly because, if they were going to go ahead with the test and its financial costs, she wanted to get everything that she could out of it. The genetic counselor was concerned with incidental findings as well for this family with the possibility that “the family would essentially be biting off more than they could chew and finding some more unanswered questions than trying to get more clarity to their situation.” Mother4’s biggest concern about the test was that it might not find anything at all.

Mother4 felt anxious while waiting for the results to be returned. She said that some weeks would go by without thinking about the test, and other times she would be preoccupied with concern about the results. She first learned about the results in a phone call from her genetic counselor. The counselor gave her some brief information over the phone, and they scheduled an appointment to review the results. The geneticist and genetic counselor needed some time to review the results in their entirety and to have the information organized in order to answer the family’s questions.
Mother4 reported mixed feelings about receiving some information over the phone first. She said she felt very confused at first about the information regarding her son’s conditions. The results were not very clear to her at first, partially because she did not have any information in front of her to look at. She wanted more details about what the test had found, which the genetic counselor was not prepared to provide, as the counselor and geneticist needed to do more research into the complicated results. She said she was somewhat glad she received some information over the phone because if the test had found something terminal, she would not want to have broken down in front of the geneticist and genetic counselor and she would have needed time before she was ready to discuss those results.

Mother4 said that the appointment to discuss the results of WES with the geneticist and genetic counselor was extremely helpful. She said they knew what her questions would be even before she asked them, and she had the results in front of her. The full explanation of the details cleared up a lot of her confusion about the results. Mother4 found that looking at the report and being guided through it step-by-step was helpful. She also said that reading information about the gene and the only other known individual with the same condition and genetic mutation as her son was also helpful.

She said that the most stressful part of learning about the results was moving forward, figuring out what to do with the information and waiting for more information about this gene and this condition to be discovered. The genetic counselor also reported that moving forward with the information was difficult in this case because the diagnosis is not that clear cut and there is limited information about it. Mother4 reported that WES found a cause for their child’s condition but it is still something very rare that cannot be
fully explained. She said there is still a lot of uncertainty about his condition but felt relieved to have something concrete proving a genetic change that explains her son’s symptoms, even though they do not know exactly what the change means or what to do with the information. The genetic counselor also reported this de novo mutation; however, he phrased the mutation as the “likely” explanation of the child’s symptoms because even though the symptoms are consistent, only one other case has been reported in medical literature. Test results and the clinic note in the chart review also described the mutation as a “likely” explanation of symptoms.

Other results that Mother4 reported included carrier status for a recessive disorder, and some changes that she called “cancer cells.” She said no one knows what these “cancer cells” are or what they mean. Mother4 thought the incidental findings related to cancer were confusing and at the time of the interview she said it is something that she still worries about and doesn’t quite make sense to her. The “cancer cells” that she was referring to were likely variants of unknown significance in cancer predisposition genes seen in the chart review. Mother4 reported that she discussed these findings with the genetic counselor, but they did not go in great detail about them. She also did not ask a lot of questions about these results because she knew they were unrelated to her son’s medical condition and unrelated to the reason they were doing the test. The genetic counselor was aware of the family’s concern about these results and tried to help put these results in context for them as variants of unknown significance.

Despite her concerns about the cancer variants, Mother4 said that WES was a positive experience and exceeded her expectations in some ways. She said “there’s hope with this test.” Because this test is becoming more popular and widely available, she has
hope that more information will come out about the genetic change that her son has. One stressful part of WES was discussing so many different things that she had never heard of before and trying to take in all the new information throughout the process.

Mother4 said she expected lots of different types of results from WES and she knew she may not have clear answers so nothing particularly surprised her about the results. She also said that she felt well prepared for the uncertainty of the results and what they were getting into with the test because of the support from the geneticist and the genetic counselor as well as support groups with members who have gone through similar experiences with their children. Mother4 reported that the results did not drastically change the care for her son because they were already involved in the necessary therapies based on his symptoms, but they now had a better idea of which areas to focus on.

Mother4 said the results did not change medical care for anyone else in the family but changed care in a very different way. She said that she realized the family now pays more attention to their other child than they did before. They were preoccupied with their affected son’s therapies and finding a diagnosis, and now that they have not had this sort of preoccupation, they are giving their children more equal attention. They are also more open and willing to talk about their affected child’s condition with other family members and other people because now they can explain what is likely causing their son’s issues instead of not having any answers. No information in regard to genetic information needed to be told to other individuals in the family.
Mother4 got very emotional about how the process has affected their family life. Nothing seemed directly related to the process of WES but rather the process of raising a child with medical issues and developmental issues and all of the tests and financial constraints that accompany them. Mother4 reported she was definitely happy they chose to proceed with WES because now they have some information to go on and have a better understanding of their son. Also, having a genetic explanation helped her realize that her son’s condition was not her fault. She said she would recommend it to other people but to definitely research it and learn as much as possible about the test from other individuals including the geneticist, genetic counselors and other parents who have been through the process. She said that the parents should make the decision that is right for the family, going into the process knowing the risks and limits.

Case 4 analysis:

Case 4 involves a number of complex issues that can arise in the process of WES, including receiving a diagnosis that had only been reported once in the literature. Mother4 phrased this as the “known” diagnosis for her son’s condition while the genetic counselor used “likely” diagnosis due to the extreme rarity of the diagnosis. Mother4 wanted an answer and decided to believe in this result. The scientific community may feel less inclined to jump to this conclusion about such a rare phenomenon. The danger of believing in such a diagnosis is that if it were refuted in the future, it may be difficult for Mother4 to cope with any new, contradicting information. Reiff et al. (2012) also reported that some parents reported a variant of unknown significance on a chromosomal
micro array as the known cause of the child’s condition likely because novel and rare variants may be reclassified as pathogenic as more becomes known about the condition and more people are found with similar genetic changes.

Mother4 also said that the results showed that her son had some cancer cells, when in fact the chart review did not mention cancer cells, but did mention variants of unknown significance in cancer predisposition genes. It is likely that this is what Mother4 was referring to when she mentioned “cancer cells.” As with any counseling on cancer predisposition genes, it is important to make sure the patient understands the difference in terminology and severity. In this case, the geneticist recalled downplaying these findings as variants of unknown significance, but because Mother4 reported still worrying about these findings, it could be that they moved past them too quickly in the post-test counseling. Perhaps a referral to cancer genetics in cases such as this would be an appropriate step.

Mother4 had difficulties receiving results over the phone. Previous studies on parental understanding of chromosomal microarrays (Reiff et al., 2012) also suggest that many parents have difficulties receiving and understanding this information over the phone, and that visual material, only available in person, helps to facilitate comprehension. However, Mother4 said she definitely would have wanted this information over the phone first if it were result saying her son had a terminal condition so that she could have time to process this information before the appointment.

According to Makela et al. (2009), families with rare diagnoses tend to have similar experiences to families without a diagnosis because they have little information
and may not have access to support groups that fit their specific needs. This case could be considered to be somewhere between the two, and this family also reported the desire to connect with other individuals and families affected by the same condition and to receive that sort of support. Mother4 stated she wished she could talk to the one other family with the same diagnosis as her son to have that support from others going through the same thing.
CHAPTER 6: Discussion

The specific aims of the study were to explore parental perspectives on WES testing, assess parental knowledge and understanding of their child’s WES, and analyze similarities and differences between the clinicians’ and parents’ perspectives regarding the WES process.

The collective case study approach was used because there is limited information on parents’ perspectives of WES, thus this methodology provides a place to explore and gather initial data. Despite each family’s different situation and testing results, common themes emerged surrounding motivation to end the diagnostic odyssey, learning through previous genetic testing, WES counseling, return of results, and empowerment.

Motivation

The first theme was the motivation to end a diagnostic journey, taking every step they could in order to find an answer (ideally, a diagnosis). Each family wanted an answer to explain their child’s condition. Previous studies (Reiff et al., 2012; Lipinski et al., 2006; Madeo, et al., 2012, and Makela et al., 2009) have cited the motivation to end the diagnostic odyssey. Many of these studies also reported that the desire for a diagnosis changes over time and differs between families, with some reporting that the desire is strongest in the beginning of the diagnostic odyssey and decreases over time. Others reported that at first families did not want to find a diagnosis because they had a sense of denial over their child’s condition; however, over time they came to terms with the
condition and desired an answer. At the time of their respective interviews, the families in the current study reported that they wanted to know the cause of their child’s phenotype.

In this present study, families 1, 2, and 4 also hoped that WES testing could provide some information that would aid in treatment or management and provide prognostic information if a genetic diagnosis were to be found. The families in this study realized that having a genetic diagnosis did not go hand and hand with finding a cure, improved treatments, or available prognostic information. While they hoped that with a diagnosis, this information would also be available, they realized it might not be the case. Family3 reported the hope and expectation of a genetic diagnosis for their children’s phenotype but did not mention the hope for better treatments or detailed prognostic information. This may be because this family had been searching for a diagnosis for their children for a longer period of time than the other families in this study. They had been searching for approximately nine years, while the remaining families had been searching for approximately two to four years. Family3 may be at the point in their diagnostic journey where they feel treatment and management will not change for their children and just want to know why both their children have the same phenotype. The geneticists and genetic counselors in this study also had similar motivations for offering WES. The genetics providers mentioned the main reason to pursue WES was to try to find an underlying genetic diagnosis for the phenotype and also cited the parents’ motivation to find a diagnosis as part of the reason why the test was offered. They also reported that in the event of a genetic diagnosis, it might be possible to give information on recurrence risk, prognosis, and possible management recommendations.
The families in this study also reported that they felt the possibility of finding a diagnosis outweighed the risks and limitations of WES. They reported that they understood WES testing does not provide a diagnosis in most cases and that there was the potential for incidental findings and variants of unknown significance. Realizing WES could bring about more questions than answers, these risks were not seen as major deterrents to this process, but rather a risk that they would accept. The families in this study decided to proceed with the process of WES testing. It is unknown what families who have been offered WES and have declined testing understand and perceive about WES.

Learning through experience

The second theme to emerge involved learning through previous experiences with genetic testing. Mother1, Mother2 and Father2 each independently reported that their experiences with waiting for previous genetic test results to be returned was invaluable practice when waiting for WES results to be returned. These families not only discussed the familiarity with the complexities of genetics but also noted they had lower expectations for finding a diagnosis based on previous genetic testing, which had not revealed a diagnosis. Nevertheless, Mother3, Father3, and Mother4 felt, as they waited for results, that WES really might be the test that would bring a diagnosis because of the amount of genetic information that was being analyzed. All four families had undergone previous genetic testing but the families differed in their optimism about results. This suggests that parental experience in previous genetic tests is helpful when mentally
preparing for the process of WES, but does not necessarily affect families’ confidence about WES. During the interview, parents often mentioned growing accustomed to disappointment due to past experiences with the medical community and genetics as they failed to find a cause for their child’s phenotype. Parents reported that failure to find a diagnosis became less disappointing over time.

Parents in this study reported that they believed WES should be offered to similar families who had been searching for a diagnosis for their child’s condition without success in finding a diagnosis. Father2 also reported it was important to start with other genetic tests and follow the advice of their doctors in “working up to” WES if necessary. In the future WES is likely to be offered to more individuals and earlier in the process of trying to find a genetic diagnosis, as the cost of WES decreases with the technological advances. Families undergoing WES in the future may not have the “learned experience” that the families in this study had. How families with limited experience with genetics professionals and genetic testing experience WES is not understood, but the evidence from this study suggests that those families with limited experience with genetics may have more confusion, misunderstanding, or dissatisfaction with the process of WES. These families may then need more education about genetics and genetic testing, and more thorough consent processes as they may be learning information about genetics for the first time.
Parental needs from WES counseling

The third theme revolved around parents’ needs from WES counseling. WES is a complex genetic test that involves numerous unique facets including possibilities for unexplainable information, variants of unknown significance, incidental findings, information about carrier status, etc. Previous literature has discussed the numerous challenges that go into providing informed consent and useful information for WES (Merrill, Vaidya, & Pyeritz, 2013). In the four cases analyzed in this study, parents reported that they felt comfortable with the consent and pre-test counseling process because they felt the geneticist and/or genetic counselor was transparent and honest about the risks, benefits, and limitations of WES. The parents, geneticists, and genetic counselors also often agreed on what information was important to know about the test. Both the parents and clinicians in this study reported it was important to know that WES does not find a diagnosis for everyone, and that the possibility for identifying variants of unknown significance and numerous types of incidental findings was a real possibility. Parents reported that they understood what they were pursuing by undergoing this test. Because the information was thoroughly explained during pre-test counseling, they knew that they might simultaneously receive “more than what they had bargained for”, yet still not receive the answers they originally sought. Through triangulation of the chart review, parental interviews, and clinician interviews, it was noted that families 1, 2, and 4 accurately reported that they had some options about the types of results that they would receive from WES. These families decided to receive all possible information because they would “rather know than not know.” Family 3 mentioned that they did not have options about the types of results they could receive; however, their geneticist and the
chart review proved otherwise. This family did have options discussed with them about the types of results they could receive from WES and consented to receive all possible information. This family may have misunderstood the researcher’s question, forgotten about these options, or may not have understood that they had these options even though they consented to receive all possible information. Family3 reported that they were aware that they could receive information unrelated to the phenotype including some of the information that they consented to receive but they did not report the options. When the results were returned, no significant surprises were reported in any of the four cases. All families felt they had a good understanding of their results following their post-test counseling appointments. At the time of the interviews for this study, relatively few discrepancies in the results were noted between the parental reports and their respective genetic charts and clinician interviews. The families in this study also reported satisfaction with the process of WES testing and their pre- and post- test counseling, noting their counseling about the test and the investment of time and effort from their clinicians as major factors contributing to their satisfaction.

Method of returning results

The method of returning results emerged as the fourth theme. Parents in Cases 2 and 4, who received some results information over the phone that included a specific diagnosis or likely diagnosis, reported significant anxiety in receiving these partial results over the phone, as well as how stressful it was waiting to come in to discuss the remainder of the results. However, after the in-person post-test counseling appointment,
the families in both of these cases reported that they felt more comfortable with the results. Mother2 mentioned that some of her anxiety stemmed from the fact that a genetic counselor she had never met had delivered preliminary results to her over the phone. She did not seem to be aware that it was possible for someone besides their primary genetic counselor to give them the results. Mother 2 also mentioned that she wanted more information about the results and the implications about the results as soon as she received them, which also caused anxiety. Mother4 also reported anxiety when receiving results via the telephone because she wanted more information about her son’s results than what was available in that first phone call. All parents reported that having a face-to-face results appointment with a geneticist and/or genetic counselor had been extremely important to the WES process, and that seeing the results and the work each genetic professional put into their children’s results aided in their overall comprehension and satisfaction with the process. The results of the current study are similar to those from the Reiff et al. (2012) study on parental experiences with chromosomal microarrays, in which many parents also reported significant difficulties when receiving results information over the phone but higher understanding and satisfaction when results were delivered in person. Family 3 was told over-the-phone that WES testing did not find a genetic reason for their children’s phenotype and were told to schedule an appointment to discuss the results. This family did not report anxiety in this process but felt receiving this information over-the-phone helped prepare them to be realistic about the results during the appointment. It is likely they did not report anxiety from receiving results over-the-phone because they did not have any new or complex information to learn in this manner. However, when reporting negative results over-the-phone that require in-person follow-
up, there is a risk that the family would not return to receive more detailed information in clinic once they learn the results were negative. Mother 1 received all the results in person and did not report significant anxiety in receiving the results but did report that the time between being told that results were in and having the results appointment was the hardest time to wait. Geneticist 1 commented on her perspectives in returning results stating that she felt it was important to give WES results in person due to the complex nature of the results and the need to have the family’s undivided attention.

Empowerment

The final theme involved empowerment. This theme emerged many times throughout the interviews and surrounded many different facets of the process. Along with the desire to end the diagnostic odyssey, it seemed that parents also wanted to feel like they were doing everything in their power to find a diagnosis for their child. All four families also reported satisfaction with the process of WES, regardless of whether or not WES found a diagnosis. Pursuing every possible option to try to end the diagnostic odyssey may be where parents perceive that they have control, thus decreasing their perceived uncertainty, and increasing the overall satisfaction with the process. Parents were empowered by having the option of WES and learning about the test in order to decide whether it was something they wanted to pursue for their child. All parents reported that if they had not pursued WES, they would be wondering whether WES would have given them an answer. These parents seemed to feel satisfaction in knowing
that they had done everything in their power to find a diagnosis and that the genetics professionals helped them engage in this process.

Study limitations:

As a collective case study, this research involved 4 different families who went through the process of WES. One limitation of this study is that results cannot be generalized to a larger population due to the small sample size, and nature of this qualitative methodological approach. However, as a qualitative study the goal was not to make generalizations but rather to explore the process of WES and perceptions of the families in this process. This study adds narrative and description of the parental experience to a body of research that has previously focused on technological advances and professional opinion pieces.

Another limitation is ascertainment bias. Recruitment material indicated participants would be asked about their experience with WES. The individuals who agreed to participate may have been those who already had more interest in sharing their experiences. Some families who may have felt overwhelmed with the experience may not have wanted to participate, as they may not have wanted to engage any further in this process. The recruitment process also required families to reach out and contact the researcher if interested in participating. This puts a lot of responsibility on the participants to engage in the research. Some families may not have had time or were willing to participate in an interview. Perhaps more easily accessible such as a survey would have engaged more families.
This study was also limited by the nature of the qualitative study, which used a semi-structured interview guide. The interview guide was reviewed by the thesis committee to avoid leading questions; however, the nature of some of the questions could have solicited response bias or lead parents to think about something that they had not considered prior to the interview. This methodology also involves researcher bias, as one student researcher was responsible for all interviews and analysis of the interviews. Case studies inherently have some researcher bias because this bias cannot be eliminated; however, using one researcher in this type of analysis does have the advantage of consistency.

Recollection of the results and the WES process is also subject to recall bias as the participants received WES at different times in the past. The amount of time spent searching for a diagnosis, the child’s phenotype, age of the parents and the children, and the number of children with a specific phenotype also varied between the families in this study. These differences may have played a role in the perceptions of the process and understanding of the results.
CHAPTER 7: Conclusion and Implications for Genetic Counseling

WES testing is a new type of genetic analysis, sequencing the coding regions of DNA in attempt to determine a genetic diagnosis for a specific phenotype. WES involves many complicated issues due to the possibility for variants of unknown significance and incidental findings, while only achieving a 25% diagnostic yield. While most previous research centered on the ability of WES to detect mutations, ways to improve the technology, and clinician perspectives on handling results, there is minimal research from the patient perspective. This collective case study shed light on many important aspects of the WES process from the perspectives of four different families and their genetics providers.

The major implications for genetic counseling for WES include the importance of thorough and transparent counseling, empowering the family, and methods of returning results. Families valued counseling about WES, felt their counseling was detailed and honest, reported feeling prepared for the process, and felt that there were no major surprises about WES results because the families knew what to expect. The specific results were somewhat surprising at times simply because they were previously unknown, but the families were aware of the possibilities. Previous studies (Kaphingst et al., 2012; Meiser et al., 2011; and Reiff et al., 2012) have also demonstrated that genetic counseling increases knowledge and understanding of genetic information.

WES is a complex test requiring detailed informed consent, and geneticists and genetic counselors may be best suited for handling consent for WES because they tend to have more experience explaining genetic testing to families. Even if genetics
professionals have not previously ordered WES, they have experience with counseling and consenting for other types of genetic tests, which can help prepare them for introducing WES, just as previous genetic testing helped prepare the families for the WES process. Other medical professionals may not have the experience and background necessary to adequately counsel and consent WES patients. Previous studies (Baars, Henneman, & Ten Kate, 2005; Greendale & Pyeritz, 2001; Bensend, McCarthy Veach, & Niedorf, 2014; Carroll et al., 2009) have demonstrated that health care providers who do not specialize in genetic medicine and counseling often lack the necessary knowledge to provide genetics services.

This case study demonstrated how genetic testing can be empowering regardless of the results. Previous other studies have also demonstrated how genetic testing and genetic counseling can be empowering by helping patients feel in control of their situation (Bernhardt, Biesecker, & Mastromarino, 2000; McAllister et al., 2008). It is important for clinicians ordering and consenting for WES to be aware that parents may find the availability and option of WES to be empowering, and patients may be driven to pursue WES because of the possibility of finding an answer for their child’s condition, trying to do everything in their power to reach that answer for their child. Geneticists and genetic counselors can foster empowerment by explaining testing options and facilitating decision making. Geneticists and genetic counselors can also address the parents’ drive to do everything in their power to find a diagnosis, especially if WES may not be the next best testing option for the family, or if the family has major concerns about WES but feels compelled to do the test anyway because of the possibility of identifying a diagnosis.
Previous studies have been conducted regarding the return of genetic testing results over the phone, versus returning all results in person. Most of these studies have focused on testing for a specific disorder (such as hereditary breast and ovarian cancer) and have found that the method of returning results had little impact on patient understanding of those results (Jenkins, et al., 2007). In these studies, patient understanding was measured either after receiving all results in person or receiving all results on the phone. In the current study, the patients in three cases received preliminary results over the phone and then had an in-person appointment to receive the full information and counseling.

With more complicated genetic testing, patients can become confused by partial results delivered via the phone. Reiff, et al. (2012) found that patients reported anxiety and confusion when receiving results from chromosomal microarrays over the phone. Similarly, returning results from WES is also complicated because there are so many possible outcomes (Bamshad et al., 2011; Ng et al., 2010b; Ng, Nickerson, Bamshad, & Shendure, 2010c). In this study, Mother 2 and Mother 4, who received initial WES test results via phone, were confused, anxious, and immediately wanted more information. Mother1, who did not receive results via phone, did not report this anxiety, nor did Mother3 and Father3, who were told over the phone that WES had not found a diagnosis but to schedule an appointment to discuss the results.

There are some benefits to giving preliminary WES results via phone before a patient’s in-person appointment. In a busy genetics clinic and when parents may be traveling from long distances, appointments may need to be scheduled several weeks in advance, so some families may find it advantageous to receive some information as soon
as possible via phone, rather than waiting for their scheduled appointment. Giving some basic information over the phone may also help families prepare for their follow-up appointments, giving them more opportunity to think of questions and concerns beforehand so that appointments can be more productive. Families may need time to adjust to the initial shock of results, so delivering some information via phone can reduce the need for additional in-person appointments just to discuss the results, and can avoid the economic burden these additional appointments would have for some families (Jenkins, et al., 2007).

Conversely, providing results exclusively in person can decrease confusion and anxiety about the results by facilitating a full discussion. When discussing the results in person, the geneticist and/or genetic counselor can visually show the patient their test results, which were considered by the parents in this study to be helpful to their understanding of their results. Another benefit of delivering results exclusively in person is that it does not put families in the position of receiving partial results over the phone several weeks before their in-person appointments, thus reducing the anxiety of having received incomplete information and then waiting to receive any additional information about the results. In addition, delivering results in-person may ensure follow-up to the genetics clinic. If results are given via phone there is the possibility that some families may be less likely to follow up, even though important information may still need to be addressed.

Reiff et al. (2012) recommended that patients have the option of whether to receive chromosomal microarray results over the phone or in person. This may also be a reasonable recommendation for WES; however, future studies would be necessary to see
how patients and families respond to these options. Reiff et al. (2012) also advised “post-test genetic counseling should be available soon after results are delivered to address the medical and psychosocial implications.” Some of the anxiety in receiving the results on the phone before discussing them in detail in person was reported to be due to the amount of time that would pass between the results phone call and the results appointment, and realizing they would have to wait weeks before learning anything more about their child’s condition. In the case of WES, there is a wide window of time in which laboratories may return results, making it difficult to estimate when a patient should schedule a results appointment. If the preliminary results phone call could take place more closely before the in-person meeting, then this could relieve some anxiety and would make returning preliminary results via phone more consistently appropriate for patients than it currently is. However, the ideal specific length of time between receiving a results phone call and discussing results in person is not known.

Until genetic counselors and geneticists have a better understanding of the preferences in returning results, findings in the current study suggest that it may be in everyone’s best interest to provide WES results exclusively in person, due to the significant anxiety and confusion surrounding receiving WES results via phone, and due to the satisfaction and understanding that were reported when results were returned in person. In addition, the method of returning results and who may possibly give the results to the patient should be discussed during pre-test counseling. Hopefully this type of information would allow patients and families to mentally prepare themselves to receive the results knowing that a great deal of complicated information may be discussed and the family may receive bad news at that appointment. Sharing these expectations with
families before the testing process begins would increase perceived control of the situation, thereby decreasing their perceived uncertainty, as previously discussed.

Further studies on receiving clinical WES results with a larger study population would be appropriate in order to make more sound recommendations on how to best manage WES results.

Genetics providers may need to provide anticipatory guidance that WES may be a long process of learning about the results. Follow-up visits to discuss results and incidental findings may take numerous appointments. Ambiguous results may potentially become clearer with advances in technology and learning more about the human genome. Mother4 reported confusion over the variants of unknown significance in the cancer genes; however she stated that she did not ask as many questions about these variants as she realized that they were not the reason for doing the testing. Thus further results appointments may be necessary to discuss these incidental findings. WES testing may not only require a lengthy consent process but a discussion of the commitment to the process.

*Future Directions*

Moving forward with WES in the clinical setting, more research will be needed to understand the process of WES from the perspectives of the patients and their families and the clinicians ordering the testing. This research study provides initial insights into the process of WES from parents’ perspectives. The descriptions and narratives from these parents may help geneticists and genetic counselors focus on important factors in the process of WES.
This research was a case study analysis, which does not aim to build theories or allow for generalization, but serves as a place to begin and guide future research. Further studies on parental perspectives could be performed by controlling for different aspects of the process and comparing the perspectives. One example may be to compare the perspectives of families with a diagnosis to those without a known diagnosis to better understand satisfaction or possible regrets with the process. Does the lack of a diagnosis cause families to be discouraged and less engaged with their genetics providers in the long term? Future research needs to be undertaken to understand how to best handle the return of results from WES.

Larger qualitative studies could also be performed to build theories on the subject of parental experiences with WES. Grounded theory and other methods of theory building can be employed for more representation of this process. Larger qualitative studies with more participants and theory building would aid in development of future studies to focus on individual aspects of the process such as the consent process or the results process to better understand the needs of individuals and families undergoing testing at each step.
APPENDIX 1: Letter from the Director, Center for Human Genetics, University Hospitals Case Medical Center

University Hospitals
Case Medical Center

Dear Patient or Parent/Guardian,

The Department of Genetics and Genome Sciences at Case Western Reserve University is conducting a research study to investigate parental experiences with whole exome sequencing. Your participation in the research study is entirely voluntary. There is little to no information regarding a patient or family’s experiences with whole exome sequencing, and this study is important for obtaining that information. The researchers hope to use the information obtained from this study to provide genetics professionals and other healthcare providers with insights to improve the care of patients and families undergoing this type of testing. I support this study to be carried out at the University Hospitals Center for Human Genetics locations. The Institutional Review Board of the University Hospitals Case Medical Center has reviewed and approved this study.

The Center for Human Genetics has agreed to offer the opportunity to participate in this study to its patients. Should you agree to participate, please contact the student researcher as instructed on the following pages. If you would prefer not to participate, please discard this packet.

Thank you for your consideration,

Shawn E. McCandless, MD
Director Center for Human Genetics
University Hospitals

Among the nation’s leading academic medical centers, University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a nationally recognized leader in medical research and education.
APPENDIX 2: Letter from the Molecular and Human Genetics Center, Nationwide Children’s Hospital

Dear Parent/Guardian,

We are contacting you about a research study being done in partnership with the Department of Genetics and Genome Sciences at Case Western Reserve University. The study is part of a Master’s thesis and its aims are to better understand parents’ experiences with a genetic test called whole exome sequencing. There is little to no information regarding a patient or family’s experiences with whole exome sequencing and this study is important for obtaining that information. The researchers hope to use the information obtained from this study to provide genetics professionals and other healthcare providers improve the care of patients and families undergoing this type of testing.

As a site that offers whole exome sequencing, we have volunteered to provide packets to the parents of children who have had whole exome sequencing. Researchers at Case Western Reserve University do not have access to any names or addresses of our patients. Your participation in the research study is entirely voluntary.

Should you wish to participate, please contact the student researcher as instructed on the following pages. If you would prefer not to participate, please discard.

If you have any questions, do not hesitate to contact us at 614-722-2465 or 614-722-3535.

Sincerely,

Matthew Pastore, MS, LGC
Licensed Genetic Counselor
Clinical Assistant Professor of Pediatrics
The Ohio State University

Scott Hickey, MD
Clinical Assistant Professor of Pediatrics
The Ohio State University
Division of Human and Molecular Genetics
APPENDIX 3: Invitation to Participate

Dear Parents,

We are writing to invite you to participate in a study about parents’ experiences with a type of genetic test called whole exome sequencing. You have been invited to participate because you have a child who had whole exome sequencing and you have received the results of this test.

The goal of this study is to learn more about parents’ experiences, perceptions, and feelings about going through the whole exome sequencing process with your child from your decision to pursue this test through receiving the results. We are also interested in learning about parents’ knowledge and perceptions of the results. We hope that this information will provide us with a better understanding of the parent’s experience and what parents liked or disliked about the process in order to improve the experience for families in the future. This study is being conducted by Danielle Mouhlas, a genetic counseling graduate student at Case Western Reserve University as part of a master’s degree thesis project.

The study will consist of a telephone, audio recorded interview with parents of children who have had whole exome sequencing. Questions will include information about your experiences with this test and your knowledge of your child’s results. The interview is expected to take approximately one hour. One or both parents may participate in the study and interviews will be conducted separately. The study will also consist of a chart review of your child’s whole exome sequencing records and clinic notes relevant to the whole exome sequencing process. No other information will be obtained from your child’s chart and the chart will not leave its secure location in the hospital. Information from the chart will only be used for this research study.

Some of the questions may make you feel uncomfortable and bring up feelings that may be upsetting to you. You will have the opportunity to decline to answer any questions, or end the interview at any point, for any reason. While there are no direct benefits to you, your participation in this study may help medical and genetics professionals involved with the whole exome sequencing process, by identifying the concerns that are most important to families of individuals who undergo this test. There is no cost to you for participating in this study and you will not be paid for participation.

Should you decide to participate in this study, your entire interview will be kept confidential. Your responses will only be shared with the researchers in this study.
Please note that this packet also includes the 3 copies of the consent to participate form. There are 2 copies available if both parents would like to participate, one for each parent. If you are interested in participating in this study we ask that you read and sign this form. Please return the form in the addressed, stamped envelope provided. We have also enclosed a copy of the consent form for you to keep.

If you would like more information about the study or have any questions, please contact Danielle Mouhlas at dem39@case.edu or call her at (440) 590-5650. If you send an email or leave a voice mail message, please include a current working telephone number, as well as the best time to reach you. Your contact information will not be used for any additional reasons. You may also contact Michelle Merrill at michelle.merrill@uhhospitals.org or (216)-844-7238 or Dr. Anne Matthews if you have any additional questions at alm14@case.edu or (216) 368-1821.

While we would greatly appreciate your participation, participating in this study is your choice. Choosing not to participate will not affect the care and support your child and family receives.

Thank you for considering participating in this research study. We appreciate your time.

Sincerely,

Danielle Mouhlas
Graduate Student
Genetic Counseling Training Center
Case Western Reserve University

Michelle Merrill, MS, CGC
Instructor, Dept Genetics & Genome Sciences
Case Western Reserve University
Center for Human Genetics
University Hospitals Case Medical Center

Anne L. Matthews, PhD
Professor, Dept. Genetics & Genome Sciences
Director, Genetic Counseling Training Program
Case Western Reserve University
APPENDIX 4: University Hospitals Case Medical Center Parent Consent Form

UNIVERSITY HOSPITALS
CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 11.2012)

Project Title: Parental Experiences with Whole Exome Sequencing
Principal Investigator: Michelle Merrill

Introduction/Purpose
You are being asked to participate in a study to better understand parents’ feelings and experiences about a genetic test known as whole exome sequencing (WES). You are being asked to participate in this study because you have a child who has had WES at Center for Human Genetics, University Hospitals Case Medical Center or Nationwide Children’s Hospital and you have received the results of this test.

The purpose of this research is to better understand how parents feel about their journey in pursuing WES for their child and their understanding of WES results. This study will ask questions about your experiences with genetic professionals, the knowledge you gained from this experience, how satisfied you are with the WES process overall, your understanding of results and some general demographic information.

You will be one of about 30 participants enrolled in this research study at the following genetics clinics: University Hospitals Case Medical Center and Nationwide Children’s Hospital.

Study Procedures
As a participant in this study, you will be asked to participate in a phone interview with the primary researcher and graduate genetic counseling student, Danielle Moulias. The interview will take approximately 1 hour. This interview will be recorded and transcribed into a text document. Any identifying information will be removed from the recording before it is transcribed. As a participant we are also asking that you allow the researcher to look at your child’s WES test results and clinic notes from your appointment. No other medical information will be obtained and the information obtained will only be used for this research purpose. The information obtained from the chart review will be coded and matched up with your interview.

Screening
You must be 18 years of age or older to participate in this study and have a child who has had WES testing and you must have attended the appointment where you received the results.

Risks
Your participation in this study does not involve any physical risks to you. At any point you feel uncomfortable or to not wish to answer a question during the interview, you may skip it and go to the next question.
UNIVERSITY HOSPITALS
CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 11.2012)

Project Title: Parental Experiences with Whole Exome Sequencing

Principal Investigator: Michelle Merrill

Benefits
There will be no direct benefit to you for participating in this study. Your participation in this study may help in our understanding of parents’ experiences with WES and understanding results.

Alternatives to Study Participation
Because of the nature of this research the only alternative is to not participate in this study.

Financial Information
There is no cost to you or your insurance for participation in this study. You will be responsible for the cost of phone call as determined by your service provider. You will not be paid for your participation in this study.

Confidentiality
Your information will be kept confidential and we will do our best to make sure that all of the information collected will be kept private. All interview recordings and transcriptions will be coded with an ID number and kept on a password-protected computer and destroyed 1 year after completion of this study. Your name will not appear on the transcript. All consent forms will be kept in a locked cabinet in the researcher’s locked office. Information from the medical chart will not leave the clinical area (University Hospitals Case Medical Center or Nationwide Children’s Hospital) and will also be coded with your ID number. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Privacy of Protected Health Information
The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of University Hospitals. This Authorization form is specifically for a research study entitled “Parental Experiences with Whole Exome Sequencing” and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your PHI and in what ways they can use the information. In order for the Principal Investigator, Michelle Merrill and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, you may not join this study. Your decision to allow the use and disclosure of your PHI is voluntary and will have no impact on your treatment at University Hospitals. By signing this form, you are allowing the researchers for this study to use and disclose your PHI in the manner described below.
UNIVERSITY HOSPITALS
CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 11.2012)

Project Title: Parental Experiences with Whole Exome Sequencing

Principal Investigator: Michelle Merrill

Generally the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that you are in a research study and will see and use your PHI. The researchers working on this study will collect the following PHI about you: your name and age, your child’s name and age, your address, and your child’s personal whole exome sequencing test results and the interpretation of the results. This PHI will be used to assess parents’ experiences with WES. Your access to your PHI may be limited during the study to protect the study results.

Your PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: the student researcher, a graduate student in the genetic counseling training program; Danielle Mouhlas; the thesis research committee members: Drs. Anne Matthews, Laura Konczal, Michelle McGowan, and certified genetic counselor Michelle Merrill; and Matthew Pastore, a certified genetic counselor at Nationwide Children’s Hospital; other staff from the Principal Investigator’s medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Your permission to use and disclose your PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization you may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to Michelle Merrill, MS, CGC, Center for Human Genetics, 1500 Lakeside University Hospitals Case Medical Center, 11100 Euclid Ave. Cleveland, OH 44106-6055. If you have a complaint or concerns about the privacy of your health information, you may also write to the UH Privacy Officer, Management Service Center, 3605 Warrensville Center, MSC 9105, Shaker Heights, OH 44122 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office of Civil Rights, US Department of Health and Human Services Government Center, JF Kennedy Federal Building, Room 1875, Boston, MA 02203. Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect your health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. University Hospitals is committed to protecting your confidentiality. Please understand that once your PHI has been disclosed to anyone outside of University Hospitals, there is a risk that your PHI may no longer be protected; however other Federal and State laws may provide continued protection of your information.
UNIVERSITY HOSPITALS
CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 11.2012)

Project Title: Parental Experiences with Whole Exome Sequencing

Principal Investigator: Michelle Merrill

Summary of your rights as a participant in a research study
Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Case Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of your study records
Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Case Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed your identity could become known.

Contact information
Danielle Mouhlas has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator Michelle Merrill can also be contacted at 216-844-7238. If you have any questions, concerns or complaints about the study in the future, you may also contact them later.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about any of the following: concerns regarding the study; research participant’s rights; research-related injury; or other human subject issues, please call the University Hospitals Case Medical Center’s Research Subject Rights phone line at (216) 983-4979 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.
**Project Title:** Parental Experiences with Whole Exome Sequencing

**Principal Investigator:** Michelle Merrill

**Signature**
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

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| [X] | Printed Name of Participant |

**Study personnel (only individuals designated on the checklist may obtain consent)**

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| [X] | Printed name of person obtaining informed consent |

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<tr>
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<th>Signature of Principal Investigator</th>
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| [X] | Printed name of Principal Investigator |

Version date 11.2012

Page 5 of 5
APPENDIX 5: Nationwide Children’s Hospital Parent Consent Form

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

STUDY TITLE: Parental Experiences with Whole Exome Sequencing

PRINCIPAL INVESTIGATOR: Scott Hickey, MD

CONTACT TELEPHONE NUMBER: 614-722-3535

STUDY SPONSOR: University Hospitals Case Medical Center, Cleveland, Ohio

SUBJECT’S NAME: __________________________ DATE OF BIRTH: __________________________

NOTE: The words “you” and “your” are used in this consent form. These words refer to the study volunteer whether a child or an adult.

1) INTRODUCTION

We invite you to be in this research because you have a child who has had whole exome sequencing (WES) at Center for Human Genetics, University Hospitals Case Medical Center or Nationwide Children’s Hospital and you have received the results of this test.

Participation is voluntary. Using this form as a guide, we will explain the study to you. If you have any questions about the study, please ask. Once you understand this study, we will ask you to decide whether you would like to participate or not. By signing this form, you agree to be in this study. If you do not want to be involved with this study, all regular and standard medical care will still be available to you here or at another institution. You also have the right to leave this study at any time, even if you agree to join now.

You will be given a signed and dated copy of the consent form.

2) WHY ARE WE DOING THIS RESEARCH STUDY?

This is a study to better understand how parents feel about their journey in pursuing WES for their child and their understanding of WES results. This study will ask questions about your experiences with genetic professionals, the knowledge you gained from this experience, how satisfied you are with the WES process overall, your understanding of results and some general demographic information.

3) WHERE WILL THE STUDY BE DONE AND HOW MANY SUBJECTS WILL TAKE PART?
This study will be done at several sites, including Nationwide Children’s Hospital. Overall 30 participants will take part in this study. We hope to enroll 15 participants here at Nationwide Children’s Hospital.

4) **WHAT WILL HAPPEN DURING THE STUDY AND HOW LONG WILL IT LAST?**

As a participant in this study, you will be asked to participate in a phone interview with the primary researcher and graduate genetic counseling student, Danielle Moulias. The interview will take approximately 1 hour. This interview will be recorded and transcribed into a text document. Any identifying information will be removed from the recording before it is transcribed. As a participant we are also asking that you allow the researcher to look at your child’s WES test results and clinic notes from your appointment. No other medical information will be obtained and the information obtained will only be used for this research purpose. The information obtained from the chart review will be coded and matched up with your interview.

You must be 18 years of age or older to participate in this study and have a child who has had WES testing and you must have attended the appointment where you received the results.

5) **WHAT ARE THE RISKS OF BEING IN THIS STUDY?**

We believe that there is very little chance that bad things will happen as a result of being in this study. It is possible that you could feel upset when answering questions about your diagnosis or medical treatment, but it may be more likely that you find the questions or feedback process a little boring. If you do find any of the questions upsetting or don’t want to answer a question, you don’t have to, and the study coordinator will be available to discuss this with you further.

Your participation in this study does not involve any physical risks to you. At any point you feel uncomfortable or to not wish to answer a question during the interview, you may skip it and go to the next question. You may also stop the interview at any time. You may revoke your permission to participate in the study at any time. To revoke your permission, you must do so in writing by sending a letter to Scott Hickey, MD, Nationwide Children’s Hospital, 700 Children’s Drive, Columbus, OH 43205.

6) **ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

Although there will be no benefit to you from being in this study, we hope to learn something that could help others in our understanding of parents’ experiences with WES and understanding results.

7) **WHAT ARE THE COSTS AND REIMBURSEMENTS?**

There is no cost to you or your insurance for participation in this study. You will be responsible for the cost of phone call as determined by your service provider. You will not be paid for your participation in this study.

8) **WHAT HAPPENS IF BEING IN THIS STUDY CAUSES INJURIES?**

We believe that there is very little chance that injuries will happen as a result of being in this study.
9) **WHAT HAPPENS IF I DO NOT FINISH THIS STUDY?**

It is your choice to be in this study. You may decide to stop being in this study at any time. If you decide to stop being in this study you must call the Principal Investigator or the study coordinator to see if there are any medical issues about stopping. If you stop being in the study, there will not be a penalty or loss of benefits to which you are otherwise entitled.

10) **OTHER IMPORTANT INFORMATION**

If you are an employee of Nationwide Children’s Hospital or the Research Institute at Nationwide Children’s Hospital, your job or performance appraisal will not be affected in any way if you decline to participate or withdraw your consent to participate in this study.

Nationwide Children’s Hospital is a teaching hospital and we are committed to doing research. Doing research will enable us to learn and provide the best care for our patients and families. You may be asked to participate in other research studies in the future. You have the right to decide to participate or decline to participate in any future studies. We will not share your contact information with researchers outside Nationwide Children’s Hospital.

11) **HOW WILL MY STUDY INFORMATION BE KEPT PRIVATE?**

Information collected for this study may include information that can identify you. This is called “protected health information” or PHI. By agreeing to be in this study, you are giving permission to Scott Hickey and the study staff to collect, use, and disclose your PHI for this research study unless otherwise allowed by applicable laws. Information collected is the property of Scott Hickey.

The reason why this PHI is collected, and what information will be used is listed below. The PHI will only be shared with the groups listed, but if you have a bad outcome or adverse event from being in this study, the Principal Investigator and staff or other health care providers may need to look at your entire medical records. In the event of any publication regarding this study, your identity will not be revealed.

The PHI collected or created under this research study will be used or disclosed as needed until the end of the study. The records of this study will be kept for an indefinite period of time and your authorization to use or disclose your PHI will not expire.

**PHI that may be used or disclosed:** Names (individual and parents); Address (including city, state, ZIP code and county); Birth Date; Medical Record Numbers; clinic visit summary, pedigree (family history), whole exome sequencing results.

**People or Companies authorized to use, disclose, and receive PHI collected or created by this research study:**

- PI and study staff
- The Nationwide Children’s Hospital Institutional Review Board (the committee that reviews all human subject research)
- Nationwide Children’s Hospital internal auditors
• The Office for Human Research Protections (OHRP) (the federal government office that oversees human subject research)
• University Hospitals Case Medical Center

Because of the need to give information to these people, absolute confidentiality cannot be guaranteed. Information given to these people may no longer be protected by federal privacy rules.

Reason(s) why the use or disclosure is being made: to locate medical charts, to make initial contact with you, to contact you in the future if additional information is needed.

You may decide not to authorize the use and disclosure of your PHI. However, if it is needed for this study, you will not be able to be in this study. If you agree to be in this study and later decide to withdraw your participation, you may withdraw your authorization to use your PHI. This request must be made in writing to the Principal Investigator at Scott Hickey, MD, Nationwide Children’s Hospital, 700 Children’s Drive, Columbus, OH 43205. If you withdraw your authorization, no new PHI may be collected and the PHI already collected may not be used unless it has already been used or is needed to complete the study analysis and reports.

12) WHOM SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions about anything while on this study or you have been injured by the research, you may contact the Principal Investigator at 614-722-3535, Monday – Friday, between 8:00 am and 4:30 pm.

If you have questions, concerns, or complaints about the research; if you have questions about your rights as a research volunteer; if you cannot reach the Principal Investigator; or if you want to call someone else - please call (614) 722-2708, Nationwide Children’s Hospital Institutional Review Board, (IRB, the committee that reviews all research involving human subjects at Nationwide Children’s Hospital).
Subject’s Name __________________________ Date of Birth ____________________

**SUBJECT or SUBJECT’S PARENT OR PERSON AUTHORIZED TO CONSENT ON BEHALF OF THE CHILD (SUBJECT TO THE SUBJECT’S GENERAL MEDICAL CARE)**

I have read this consent form and I have had an opportunity to ask questions about this research study. These questions have been answered to my satisfaction. If I have more questions about participating in this study or a research-related injury, I may contact the Principal Investigator. By signing this consent form, I certify that all health information I have given is true and correct to the best of my knowledge.

I have been given a copy of the Nationwide Children's Hospital Notice of Privacy Practices. It allowed by law, I understand that my right to any information that is created or collected by Nationwide Children's Hospital for this study can be temporarily suspended if necessary for the purposes of this research project. I also understand that my right to access to this information from this study will be reinstated upon completion of this research unless I have been told by the Principal Investigator that I will not receive study results.

I agree to participate in this study or I give permission for my child to participate in this study. I will be given a copy of this consent form with all the signatures for my own records.

**CONSENT SIGNATURES**

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<th>SUBJECT or SUBJECT’S LEGAL REPRESENTATIVE</th>
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Permission of the second parent not obtained because (select all that apply):

- [ ] Not required by the IRB (risk level 1 or 2).
- [ ] Other parent is deceased.
- [ ] Other parent is unknown.
- [ ] Other parent is not reasonably available.
- [ ] Only one parent has legal responsibility for the care and custody of subject.

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I certify that I have explained the research, its purposes, and the procedures to the subject or the subject’s legal representatives before requesting their signatures.

IRB Rev. 3/1/12 Page 5 of 5 Initials ________
APPENDIX 6: University Hospitals Case Medical Center Clinician Consent Form

UNIVERSITY HOSPITALS CASE MEDICAL CENTER CONSENT FOR INVESTIGATIONAL STUDIES (v. 11.2012)

Project Title: PARENTAL EXPERIENCES WITH WHOLE EXOME SEQUENCING
Principal Investigator: MICHELLE MERRILL

Introduction/Purpose
You are being asked to participate in an interview about your experiences with whole exome sequencing (WES). You were selected as a possible participant because you ordered WES for one of your patients whose parent or parents has participated in the Parental Experiences of WES study.

Please read this form and ask any questions that you may have before agreeing to participate in this research.

Researchers from the department of Genetics and Genome Sciences at Case Western Reserve University are conducting this study. The researchers conducting this study are Danielle Mouftah, Michelle Merrill, Dr. Michelle McGowan, Dr. Laura Konczal and Dr. Anne Matthews.

The purpose of this research is to learn more about the experiences that clinicians and genetic counselors have when ordering WES and returning results to a family. Six clinicians and/or genetic counselors are being invited to participate in this interview.

Study Procedures
If you agree to be a participant in this research, we would ask you to do the following things:

1. You will participate in one interview that will last approximately thirty minutes. The interview will take place in your private office at the Center for Human Genetics at University Hospitals Case Medical Center, in your private office at Nationwide Children’s Hospital or over the phone. During the interview you will be asked a number of questions about your experience with WES for one of your patients. These questions will include, but limited to: 1) why you decided to offer WES to the patient/family; 2) perceptions of the pre-test counseling process and informed consent process; 3) perceptions of the follow-up session when results were given, including what was emphasized for your patient, what results you thought were important, and your perceptions of the family’s understanding of the WES results.

2. Because your opinions are important to us, the interview will be audio-taped. Tape recording the interview will help researchers to correctly document your opinions and experiences.

3. Your participation in this part of the study will be limited to the interview.

Version date July 15th 2014
UNIVERSITY HOSPITALS  
CASE MEDICAL CENTER  
CONSENT FOR INVESTIGATIONAL STUDIES  
(v. 11.2012)

Project Title: PARENTAL EXPERIENCES WITH WHOLE EXOME SEQUENCING  
Principal Investigator: MICHELLE MERRILL

Risks  
This research has the following risks: During the interview some questions may cause discomfort. You do not have to answer any questions if you do not want to. Individuals may request that the audio-tape be turned off for their responses to some of the questions. In this case, the recorder will be turned off.

Benefits  
There are no direct benefits for participants in this study. However, there is a potential benefit of contributing to our understanding of counseling for WES in the clinical setting.

Alternatives to Study Participation  
Because of the nature of this research the only alternative is to not participate in this study.

Financial Information  
You will not receive any compensation for this interview.

Confidentiality  
The records of this research will be kept private. Publications from this research will not include any information that will make it possible to identify a participant or a patient.

Audio tape recordings of the interview will be assigned a Case Number. These tapes will be stored in a locked file. Only members of the research team will have access to the audiotapes. Audiotapes will be transcribed.

Your name will not appear in the transcription of the interview in order to protect your confidentiality. Audio-tapes will be destroyed after they have been transcribed (typed) and reviewed for accuracy.

Transcriptions will be stored electronically on a password-protected computer.

Version date July 15th 2014  
Page 2 of 4
UNIVERSITY HOSPITALS
CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 11.2012)

Project Title: PARENTAL EXPERIENCES WITH WHOLE EXOME SEQUENCING

Principal Investigator: MICHELLE MERRILL

Consent forms will be stored in a locked office in the Biomedical Research Building at Case Western Reserve University.

Summary of your rights as a participant in a research study
Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Case Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of your study records
Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Case Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed your identity could become known.

Contact information
Danielle Mouhlas has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator Michelle Merrill can also be contacted at 216-844-7238. If you have any questions, concerns or complaints about the study in the future, you may also contact them later.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about; concerns regarding the study; research participant’s rights; research- related injury; or other human subject issues, please call the University Hospitals Case Medical Center’s Research Subject Rights phone line at (216) 983-4979 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

Version date July 15th 2014
**Project Title:** PARENTAL EXPERIENCES WITH WHOLE EXOME SEQUENCING

**Principal Investigator:** MICHELLE MERRILL

### Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

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### Study personnel (only individuals designated on the checklist may obtain consent)

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CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

STUDY TITLE: Parental Experiences with Whole Exome Sequencing

PRINCIPAL INVESTIGATOR: Scott Hickey, MD

CONTACT TELEPHONE NUMBER: 614-722-3535

STUDY SPONSOR: University Hospitals Case Medical Center, Cleveland, Ohio

SUBJECT’S NAME: ______________________ DATE OF BIRTH: _____________

NOTE: The words “you” and “your” are used in this consent form. These words refer to the study volunteer whether a child or an adult.

1) INTRODUCTION

You are being asked to participate in an interview about your experiences with whole exome sequencing (WES). You were selected as a possible participant because you ordered WES for one of your patients whose parent or parents has participated in the Parental Experiences of WES study.

Please read this form and ask any questions that you may have before agreeing to participate in this research.

Researchers from the department of Genetics and Genome Sciences at Case Western Reserve University and from the Section of Human and Molecular Genetics at Nationwide Children’s Hospital are conducting this study. The researchers conducting this study are Danielle Moulias, Michelle Merrill, Dr. Michelle McGowan, Dr. Laura Konczal, Dr. Anne Matthews, Matthew Pastore, and Dr. Scott Hickey.

Participation is voluntary. Using this form as a guide, we will explain the study to you. If you have any questions about the study, please ask. Once you understand this study, we will ask you to decide whether you would like to participate or not. By signing this form, you agree to be in this study. If you do not want to be involved with this study, all regular and standard medical care will still be available to you here or at another institution. You also have the right to leave this study at any time, even if you agree to join now.

You will be given a signed and dated copy of the consent form.

2) WHY ARE WE DOING THIS RESEARCH STUDY?

The purpose of this research is to learn more about the experiences that clinicians and genetic counselors have when ordering WES and returning results to a family.
3) WHERE WILL THE STUDY BE DONE AND HOW MANY SUBJECTS WILL TAKE PART?
This study will be done at several sites, including Nationwide Children’s Hospital. Overall, six clinicians and/or genetic counselors are being invited to participate in this interview. We hope to enroll three participants here at Nationwide Children’s Hospital.

4) WHAT WILL HAPPEN DURING THE STUDY AND HOW LONG WILL IT LAST?
If you agree to be a participant in this research, we would ask you to do the following things:

1. You will participate in one interview that will last approximately thirty minutes. The interview will take place in your private office at the Center for Human Genetics at University Hospitals Case Medical Center, in your private office at Nationwide Children’s Hospital or over the phone. During the interview you will be asked a number of questions about your experience with WES for one of your patients. These questions will include, but limited to: 1) why you decided to offer WES to the patient/family; 2) perceptions of the pre-test counseling process and informed consent process; 3) perceptions of the follow-up session when results were given, including what was emphasized for your patient, what results you thought were important, and your perceptions of the family’s understanding of the WES results.

2. Because your opinions are important to us, the interview will be audio-taped. Tape recording the interview will help researchers to correctly document your opinions and experiences.

3. Your participation in this part of the study will be limited to the interview.

5) WHAT ARE THE RISKS OF BEING IN THIS STUDY?
We believe that there is very little chance that bad things will happen as a result of being in this study.

6) ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
There are no direct benefits for participants in this study. However, there is a potential benefit of contributing to our understanding of counseling for WES in the clinical setting.

7) WHAT ARE THE COSTS AND REIMBURSEMENTS?
You will not receive any compensation for this interview.

8) WHAT HAPPENS IF BEING IN THIS STUDY CAUSES INJURIES?
We believe that there is very little chance that injuries will happen as a result of being in this study.

9) WHAT HAPPENS IF I DO NOT FINISH THIS STUDY?
It is your choice to be in this study. You may decide to stop being in this study at any time.
10) OTHER IMPORTANT INFORMATION

If you are an employee of Nationwide Children’s Hospital or the Research Institute at Nationwide Children’s Hospital, your job or performance appraisal will not be affected in any way if you decline to participate or withdraw your consent to participate in this study.

Nationwide Children’s Hospital is a teaching hospital and we are committed to doing research. Doing research will enable us to learn and provide the best care for our patients and families. You may be asked to participate in other research studies in the future. You have the right to decide to participate or decline to participate in any future studies. We will not share your contact information with researchers outside Nationwide Children’s Hospital.

11) HOW WILL MY STUDY INFORMATION BE KEPT PRIVATE?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances when this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law. Your records may be reviewed by the following groups (as applicable to the research):

- PI and study staff
- The Nationwide Children’s Hospital Institutional Review Board (the committee that reviews all human subject research)
- Nationwide Children’s Hospital internal auditors
- Sponsor University Hospitals Case Medical Center, Cleveland, Ohio

The records of this research will be kept private. Publications from this research will not include any information that will make it possible to identify a participant or a patient.

Audio tape recordings of the interview will be assigned a Case Number. These tapes will be stored in a locked file. Only members of the research team will have access to the audiotapes. Audio-tapes will be transcribed.

Your name will not appear in the transcription of the interview in order to protect your confidentiality. Audio-tapes will be destroyed after they have been transcribed (typed) and reviewed for accuracy.

Transcriptions will be stored electronically on a password-protected computer.

12) WHOM SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions about anything while on this study or you have been injured by the research, you may contact the Principal Investigator at 614-722-3535, Monday – Friday, between 8:00 am - 4:30 pm.

If you have questions, concerns, or complaints about the research; if you have questions about your rights as a research volunteer; if you cannot reach the Principal Investigator; or if you want to call someone else - please call (614) 722-2708, Nationwide Children's Hospital Institutional Review Board, (IRB, the committee that reviews all research involving human subjects at Nationwide Children’s Hospital).
Subject's Name ______________________________ Date of Birth ______________________________

SUBJECT or SUBJECT'S PARENT OR PERSON AUTHORIZED TO CONSENT ON BEHALF OF
THE CHILD (SUBJECT TO THE SUBJECT'S GENERAL MEDICAL CARE)

I have read this consent form and I have had an opportunity to ask questions about this research study. These questions have been answered to my satisfaction. If I have more questions about participating in this study or a research-related injury, I may contact the Principal Investigator. By signing this consent form, I certify that all health information I have given is true and correct to the best of my knowledge.

I agree to participate in this study or I give permission for my child to participate in this study. I will be given a copy of this consent form with all the signatures for my own records.

CONSENT SIGNATURES

SUBJECT or SUBJECT’S LEGAL REPRESENTATIVE DATE & TIME AM/PM

SUBJECT or SUBJECT’S LEGAL REPRESENTATIVE DATE & TIME AM/PM

Permission of the second parent not obtained because (select all that apply):

☐ Not required by the IRB (risk level 1 or 2).
☐ Other parent is deceased.
☐ Other parent is unknown.
☐ Other parent is not reasonably available.
☐ Only one parent has legal responsibility for the care and custody of subject.

PERSON OBTAINING CONSENT DATE & TIME AM/PM

I certify that I have explained the research, its purposes, and the procedures to the subject or the subject’s legal representatives before requesting their signatures.
APPENDIX 8: Parent Interview Script

Interview Guide

Script

I want to thank you for taking time to talk to me today. My name is Danielle Mouhas and I am a graduate student in genetic counseling at Case Western Reserve University. I would like to talk to you about whole exome sequencing and to ask you some questions about your experiences with genetic testing for your child. I am most interested in your reactions as a parent. I will not be asking questions about the actual, specific test results and scientific information, also I am not going to ask about specific symptoms or medical information.

This interview is expected to last approximately one hour. I will be tape recording the interview so that I do not miss any of your responses. This interview will be confidential and no one will know who you are from your responses. Your decision to participate in this study is completely voluntary and you may choose to end the interview at any time. Before the interview begins and I turn on the tape recorder, I need to go over some specific information about the study.

Informed consent:

Review consent, audio consent, and HIPAA forms orally.

[Continue if consent is obtained]

Thank you for agreeing to participate in this study. Are you ready for me to turn on the tape recorder and begin the interview?

[Continue when ready]

Pre-interview demographic questions

1. How are you related to the child who had WES? [If guardian, ask how long have you cared for this child?]
2. Is your child a boy or a girl?
3. How old is your child who underwent WES?
4. Does this child have any siblings? Full or half?
5. Were you present for the counseling discussion and consent for WES?

Interview

1. What were your experiences with geneticists or genetic counselors prior to having WES?
a. Did you see a genetic counselor or a geneticist prior to consenting [or having blood drawn] for WES?
b. Were any genetic tests performed on your child before WES was done? Do you remember what those tests were?
c. How long have you been searching for a diagnosis? Tell me about this process.

2. How did you first learn about WES? [probes: from a doctor, online, friend, etc.]

3. What factors led you to decide to have WES for your child? [Emphasize parental experience]

4. What did you hope to learn from WES? What did you expect to learn from WES?

5. How did you feel about the counseling process prior to having the WES?
   a. What do you remember about the consent process? Do you remember if you had choices about what results you would get? How did you feel about these options?
   b. What were your major concerns about the test? Were any of your questions about the test left unanswered?

6. How did you feel while waiting for results to be returned?

7. How did you learn about the results?
   a. Were all results presented in one session? Over the phone? Did you learn about results at a number of different appointments? How did you feel about this? Would you have preferred a different method?

8. What information did you learn about your child’s condition from WES?
   a. Did the test find an answer for your child’s condition?
   b. What results do you remember talking about with the genetics doctor or genetic counselor? [change in a specific gene, variants].
   c. How did you feel about these results?

9. How did you feel about the visit to discuss your child’s results?

10. What did you find helpful in regard to understanding the test results?
    a. What did you find stressful in regard to understanding the test results?

11. Did you get any results that confused you? [IF YES THEN] What did you find confusing? Were your confusions cleared up? [IF YES THEN] By whom? [IF NO FOR EITHER PART THEN GO TO QUESTION 12]

12. How did the test live up to your expectations? What disappointed you about the testing? Why or why not?
    a. Was there anything that you were not expecting? [IF YES THEN]
       What?
13. Did the results change your child’s care in any way? Did they change care for anyone else in the family? [IF YES THEN] How so? Are you concerned about other family members based on the results?

14. Did the doctor or genetic counselor make any recommendations based on the results of the WES? [Recommendations for prenatal care, siblings, other family members, further testing etc.]

15. Were there any results that needed to be shared with more extended family members? Do/did you feel comfortable enough to share the results? [IF HAVE NOT SHARED RESULTS THEN] Do you plan on sharing the results?

16. Did WES impact how you feel about having additional children? If so, how?

17. Since you have found out the results for WES, how have you been able to adapt to the information? How have the results impacted your child’s life? And your family’s life?

18. Knowing what you know now, are you glad you went through the process and had WES for your child? Would you recommend this to other people? [FOR PARENTS WHO DID NOT HAVE A DIAGNOSIS] What do you think about repeating the test in the future?

Other probes may be necessary to elicit a complete response.

**Demographic questions**

How old are you?

What is the highest level of education you have completed?

What is your occupation?
APPENDIX 9: Clinician Interview Script

Interview

1. How long have you been following this patient?
2. What factors led you to order WES to this family?
3. What did you hope to learn from WES? What did you expect to learn from WES?
4. Was this the first patient you ordered WES for? How many times before this patient did you order WES?
5. What do you recall about the pre-test counseling and informed consent process of WES for this family?
   a. What information about did you think was important to give this family?
   b. Do you remember what questions the family asked
   c. What were your major concerns about the test? Do you remember if the parents voiced any concerns?
   d. What options did the patients have about types of results to be returned?
6. Did you have any contact with the family between ordering the test and waiting for the results to be returned? Why?
7. What information did you learn about the child’s condition from WES?
   a. Did the test find an answer for the child’s condition?
   b. What results do you remember talking about with the patient’s family?
   c. How did you feel about giving these results?
   d. What information did you think was important for them to know?
8. How did the test live up to your expectations? What disappointed you about the testing? Why or why not?
   a. Was there anything that you were not expecting? [IF YES THEN] What?
9. In your opinion, what were the important aspects of the result?
   a. What did you try to convey to the family about the results.
10. How did you feel the parents responded to the results.
    a. Did you feel they were confused, upset, anxious, happy?
    b. How did they react to the results.
    c. What results did you think were important?
    d. What did you think they found to be important?
    e. How well do you think the family understood the results?
11. Did the results change your patient’s medical management in any way? Did the results change the care for anyone else in the family? [IF YES THEN] How so? Are you concerned about other family members based on the results?
12. Were there any results that needed to be shared with more extended family members?

13. How do you think the results of WES have impacted the family? Bonding, family life, etc.

14. Knowing what you know now, are you glad you recommended WES for the family. Did this experience impact how you feel about ordering WES for other individuals?

Other probes may be necessary to elicit a complete response.
APPENDIX 10: IRB Approval

IRB APPROVAL NOTIFICATION

The University Hospitals Institutional Review Board (IRB) has reviewed the following submission:

Principal Investigator: Michelle Merrill
Protocol Title: Parental experience of whole exome sequencing
UHCMC IRB number: 07-13-19

Submission Type: UH IRB Continuing Review
Changes to Protocol, Submission of an additional Consent/Assent form, Addition of or revisions to a Questionnaire

Review Type: Full Board
Date of Committee Review: 06/26/2014

As such, the UHCMC IRB has determined that with respect to the rights and welfare of the individuals, the appropriateness of the methods used to obtain informed consent and the risks and potential medical benefits of the investigation, the current submission is acceptable under Federal Human Subject Protection regulations promulgated under 45 CFR 46 and 21 CFR 50 and 56.

Date of Approval: 08/26/2014
The current expiration date for this study is: 08/25/2015
(The expiration date is the last day that a protocol has IRB approval)

- Per Federal regulation, changes MAY NOT be made to any element of the current research without prior IRB approval, except to eliminate an immediate and apparent hazard to subjects enrolled in the trial.
- Per Federal regulation, the research may not continue without IRB approval. You must submit a request for continuation at least 6-8 weeks prior to the expiration date noted above. Once the study is complete, the IRB requires prompt notification of study closure.
- Failure to retain current IRB approval may result in archiving of the current study and human subjects non-compliance allegations.

Documents reviewed and/or approved as part of this submission:

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clinic consent IRB updated 8.11 | Version 1.0 | 06/12/2014  

**Human Risk:** [Risk for adults] Not Greater Than Minimal Risk  
**Vulnerable populations approved for inclusion:** NONE. No Vulnerable Populations will be enrolled in this study.

**Funding Source:** Center for Genetic Research Ethics and Law, Department of Bioethics

**Other information:** Waiver of informed consent [45 CFR 46.116/21 CFR 56.108], waiver of HIPAA [45 CFR 160 and 45 CFR 164].

**Approval Signature:**

[Signature]

UHCMC IRB Chairperson  
(Signature was applied by the IRB Administration Office)
REFERENCES


Baars, M.J., Henneman, L., & Ten Kate L.P. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. Genetics in Medicine, 7(9). 605-610.


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