UNDERSTANDING PARENTAL OPINIONS ON WHOLE EXOME SEQUENCING IN THE PRENATAL SETTING

by

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B.S. in Biological Sciences, University of Pittsburgh, 2012

Submitted to the Graduate Faculty of

the Department of Human Genetics, Genetic Counseling

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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ABSTRACT

Whole exome sequencing is currently used for the diagnosis of genetic conditions in pediatric and adult patients. Prenatal genetic testing is commonplace, but clinical prenatal whole exome sequencing is currently not available by commercial laboratories. Controversy surrounds the ethical issues of knowing a fetus's genetic future and the implications it could have for termination and family planning. While ongoing discussion occurs whether prenatal whole exome sequencing should be offered, there are no studies assessing parental opinions of prenatal whole exome sequencing. A questionnaire focusing on this was distributed to individuals that were pursuing first trimester genetic screening. The results of the questionnaire were analyzed using descriptive statistics. Results showed that 83.1% of participants thought prenatal whole exome sequencing should be offered and 53.5% (with an additional 40.1% neutral) were interested in having prenatal whole exome sequencing for their fetus. Only 17.2% of participants responded that they would be willing to have amniocentesis in order to have prenatal whole exome sequencing, and 30.6% were neutral towards amniocentesis. The vast majority of participants were interested in receiving all types of results, including: conditions of childhood and adult onset that are treatable, non-treatable, and that may shorten lifespan. In regards to family planning, 60.1% of participants stated the results of prenatal whole exome sequencing

may affect their family planning if they are at risk to have a future child with a health problem, and 32.8% (with 20.2% neutral) stated that results of prenatal whole exome sequencing may affect their decision to continue the pregnancy. The majority of participants (59.7%) preferred a maximum turnaround time of three weeks or less for prenatal whole exome sequencing which is much shorter than currently reported turnaround times. Although interest is expressed for prenatal whole exome sequencing, the current available technologies for fetal DNA capture and whole exome sequencing turnaround time is not desirable for expectant parents. The public health significance of this study is that prenatal whole exome sequencing will likely become clinically available as technologies continue to improve. Understanding the public's views on the testing is important in order to predict uptake and any perceived barriers.

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PREFACE

I would like to take this opportunity to thank the individuals that helped me through this process. First, I would like to thank my family for their support during graduate school and throughout my entire life. I would also like to thank my fiancé for allowing me to pursue my dream and waiting patiently for me to finish schooling so that we can start our lives together.

I would like to thank the members of my committee for their critiques, suggestions, and encouragement for not only my thesis but also my manuscript of the study. In addition, I would like to thank Andrew Althouse, PhD for his assistance in the data analysis and teaching me some statistical processes. I could not have completed this project without the support of the genetic counselors and staff in the Medical Genetics Department at Magee-Womens Hospital and I thank them.

Lastly, I would like to thank Robin Grubs, PhD for her continuous support and encouragement throughout my time in the Genetic Counseling Program at the University of Pittsburgh. To my classmates, I could not have done this without you.

1.0 INTRODUCTION

Whole exome sequencing (WES) is a type of genetic test that helps provide a diagnosis to individuals with a likely genetic condition. WES is able to simultaneously sequence the coding regions of the human genes and detect variation in a gene's sequence.[1,2] WES technology is particularly useful in diagnosis of rare genetic disorders, in which other genetic testing has failed to reveal a unifying diagnosis for a patient's symptoms. With rare genetic conditions, single gene testing may not be available and WES becomes the best option to help determine a diagnosis. The diagnostic yield of WES has proved to be higher than other genetic testing options with on average 25% of results revealing a clear diagnosis.[3-6] WES is clinically offered to newborn, pediatric, and adult genetics patients. Prenatal WES is not currently available as a clinical test, but as technologies continue to improve it is likely that prenatal WES will become clinically available. The aim of this project was to analyze the responses given in a questionnaire regarding prenatal whole exome sequencing that was administered to expectant parents that were pursuing first trimester screening at Magee-Womens Hospital. The perceived interest in the testing was analyzed to help predict if there is interest in clinical prenatal WES and the implications it may have.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 OVERVIEW

2.1.1 Whole exome sequencing

Whole exome sequencing (WES) is currently the most comprehensive clinical genetic testing available. WES is able to simultaneously sequence the coding regions of all known protein-coding genes (exome) in the human genome.[1,7] The exome is estimated to comprise only 1% of the entire genome;[2,7] however, it is thought that about 85% of disease causing mutations are found in the exome.[2]

There are limitations of WES that must be considered when using WES as a clinical test. These limitations include: incomplete or low coverage of certain genes, lack of coverage of non-coding regions that may have a functional element, and inability to detect copy number variants translocations, and inversions.[1] Although there are several limitations to WES it still has many strengths. WES has an average diagnostic yield of 25%[3-6] which is higher than other clinical genetic testing options.

Some additional challenges arise with WES. Although cost of WES continues to decline it is still an expensive genetic test that is not always covered by health insurance plans.[8,9] The informed consent process for clinical WES can be lengthy due to the numerous topics that must be covered in order for a patient to be able to make an informed decision about testing.[10,11] Data handling is

another challenge due to shear amount of data that is generated by WES. It is estimated that 20,000 variants will be revealed in any WES analysis.[11] The issue of the returning of results of WES is another major challenge. There is much debate over which results should be returned as a part of a WES report. Mainly the debate focuses on the return of incidental findings and when they are appropriate to return.[9]

Current technologies are using next generation sequencing (NGS) platforms to perform WES. NGS allows for sequencing of different DNA sequences in a single reaction.[9] This allows for better coverage of the coding regions of the DNA and faster turnaround times.[2] Previously, Sanger sequencing was used as a platform which relies on a "shotgun method" and thus resulted in a lower coverage of the exome.[2]

2.1.2 Current prenatal genetic testing options

In current clinical practice, there are several prenatal genetic screening and testing options. Genetic screening options that are available to all pregnant women include: first trimester screening (increased risk for aneuploidies such as trisomy 18 and trisomy 21), quad screen (increased risk for aneuploidies trisomy 18, trisomy 21, and spina bifida), or maternal serum AFP (increased risk for spina bifida). For pregnancies that are considered high risk (e.g. advanced maternal age, abnormal ultrasound finding, etc.), there are additional prenatal genetic testing options such as cell free DNA (increased risk for trisomy 13, trisomy 18, trisomy 21, and sex chromosome aneuploidies), and chorionic villi sampling or amniocentesis for karyotype, microarray, or single gene/single site testing for a known familial mutation.

2.2 PRENATAL WHOLE EXOME SEQUENCING

2.2.1 The ACMG guidelines for whole exome sequencing

The American College of Medical Genetics and Genomics (ACMG) has released several policy statements regarding WES. In 2012, the ACMG first published guidelines for when to consider clinical genomic sequencing. This policy statement discusses prenatal WES saying it should be considered when a fetus is likely to have a genetic disorder but other genetic tests have not been able to determine a diagnosis.[7] This ACMG policy statement also recommends that WES should not be used for prenatal screening. In 2013, the ACMG published a list of a minimum of 57 genes which pathogenic or likely-pathogenic variants should be reported regardless of clinical indication for WES. This policy statement also declared that these incidental findings should be reported regardless the age of the patient.[12,13] In 2015, the ACMG revised their policy on reporting on incidental (secondary) findings with WES. In this updated policy statement, the ACMG recommended that patients and parents of patients should be able to opt out of secondary analysis and reporting with WES.[14]

An additional technical report was published by the ACMG in 2013, which focused on the ethical issues surrounding genetic testing of children. This report states that the ACMG does not support routine carrier testing for minors when there is no medical relevance for this testing. Additionally, this report supports the deferment of predictive testing of adult-onset conditions until adulthood, unless it is in the child's best medical interest to have the testing in childhood or adolescence.[15] WES may go against the suggestions of this ACMG technical report because information regarding a child's carrier status of certain conditions or a predisposition to an adult-onset condition as part of the primary or secondary findings. With WES in the prenatal settings,

individuals could use these findings to make reproductive decisions and could have more psychosocial implications than pediatric WES testing.

2.2.2 Ethical debate of prenatal whole exome sequencing

While the majority of debate for clinical WES surrounds the reporting of incidental (secondary) findings, additional ethical considerations must be taken into account for prenatal WES. One concern is that prenatal WES may violate the child's future right to not know their genetic information once born. While the goal of prenatal WES would be to help the parents make informed reproductive decisions, in reality it may create more confusion or anxiety. Prenatal WES would almost certainly reveal some variants of unknown significance which may complicate the decision making process. There are concerns that the results of prenatal WES would lead to an increased number of pregnancy terminations based on increased risk of the child to develop a condition at some point in their life or based on uncertain results.[16]

Another issues with prenatal WES is that the inclusion of incidental (secondary) findings with results may cross the line of diagnostic testing to a screening test.[17] With many of the reported genes with WES incidental (secondary) findings being related to adult-onset conditions, some have argued that those results seem more like screening for a risk for future disease than preforming a diagnostic test. Furthermore, there is concern for the psychosocial burden information about non-treatable or adult-onset conditions would create for the parents. There is also concern for stigmatization or discrimination of children that are born after the parents opted for prenatal WES and the result revealed a non-treatable condition or increased risk for an adult-onset condition.[17]

2.3 PROFESSIONAL OPINIONS OF WHOLE EXOME SEQUENCING

There have been several studies that assessed genetic professionals' views and experiences with genome sequencing. One study by Machini, *et al*. compared genetics professionals that have offered WES or whole genome sequencing (WGS) to professionals that have not yet offered WES/WGS. For the participants that stated they had not offered WES/WGS to patients, the main reasons for not offering the testing included: area of practice (e.g. prenatal), clinical utility, cost, interpretation challenges, insurance coverage, lack of guidelines, clinic or individual not ready to offer the testing, and novelty of the test. The genetics professionals that have offered WES/WGS to patients stated that challenges of the test included: insurance coverage/preauthorization, lack of training in result interpretation (e.g. variants of unknown significance), and the complexity of the informed consent process.[18] Another study by Nardini, *et al*. focused on views of genetic counselors of WES/WGS in the newborn period especially in regard to using this technology for newborn screening. The majority of participants in this study stated they did not feel prepared to counsel for WES/WGS results for newborn screening.[19] Some of the issues the genetic counselors that were surveyed for this study mentioned included: appropriateness of using WES/WGS as part of newborn screening, return of results and incidental (secondary) findings, and issues with the informed consent process.[19]

In regards to the return of incidental results of WES, a study by Yu, *et al*. the majority of genetics professionals (85%) thought that incidental findings should be offered to adult patients and 74% thought that incidental findings should offered to parents of a child that is having WES.[20] In this same study, 68% of genetics professionals thought results of the ACMG minimum gene list should be returned to individuals pursuing WES regardless of indication. A majority of participants thought that patient preference should be taken into account when considering which incidental findings to disclose.[20] In a second study by Grove, *et al*. the majority of genetics professionals

thought that patient autonomy and values should be the main determinant in deciding which results to return.[21]

2.4 PUBLIC OPINIONS OF WHOLE EXOME SEQUENCING

2.4.1 Opinions of WES in adult setting

There are two studies by Yu, *et al*. that surveyed individuals' opinions on WES/WGS and the return of results from these types of genetic testing. From these studies, approximately 70% of participants expressed interest in participating in a WGS study. Approximately, 25% of participants stated they would want all results from WGS and about 75% of participants said they would want at least one genetic result reported to them ranging from results for increased risk for common conditions such as cancer or Alzheimer's disease to conditions in which the person had a family history. A little less than 40% of participants indicated that there was at least one type of result they would not want to receive if tested. Many participants were interested in genetic testing results that are actionable, (i.e. has medical treatment or disease prevention). Some participants also indicated concerns for health and long-term care insurance that could limit their ability to follow-up if results revealed an increased risk to develop certain conditions.[22,23]

2.4.2 Opinions of WES in pediatric setting

A study by Sapp, *et al*. interviewed parents of children with rare genetic conditions to better understand the parents' preferences for the return of results with WES. The participants were enrolled into an exome sequencing study through the National Institute of Health and as part of the

consent agreed to receive any life-saving results of exome sequencing. The parents were able to opt to learn about any variants that were possibly related to their child's phenotype and variants that were related to human disease but not necessarily related to their child's phenotype. All participants in this study expressed interest in receiving WES incidental (or secondary) finding results for conditions that were treatable or preventable in childhood. The majority of participants' rationale for wanting these results was to be able to better guide their child's healthcare. About half of participants indicated at least some interest in receiving secondary results regarding non-treatable or unpreventable conditions in childhood (e.g. adult-onset conditions). Approximately three-quarters of the participants were also at least somewhat interested in receiving carrier status information for their children.[24] In two studies by Yu, *et al*., participants were less likely to be interested in having their child participate (about 50%) in a WGS study than their own participation (about 70%).[22,23]

2.4.3 Opinions of WES in newborn setting

Waisbren, *et al*. surveyed postpartum parents in the newborn unit to assess hypothetical interest in WES/WGS of their newborn. In this study, the majority of parents (82.7%) were at least somewhat interested in WES/WGS for their newborn. Individuals that reported a health concern for their newborn were less likely to express interest in WES/WGS than individuals whose newborn was reportedly healthy. Married couples were also somewhat less interested in WES/WGS for their newborn.[25]

Bombard, *et al*. analyzed public views on using WES/WGS for newborn screening. This study showed that a majority of the participants (79.6%) would participate in newborn screening if WES/WGS were used which was somewhat less than participants (94.4%) that stated they would participate in newborn screening with the current technologies.[26]

3.0 MATERIALS AND METHODS

3.1 SPECIFIC AIMS

Aim 1: To assess parental attitudes towards prenatal WES and their desire for the testing.

Aim 2: To analyze the results of the questionnaire to better understand parental preferences for return of results of prenatal WES.

Aim 3: To understand the impact on family planning and psychosocial effect prenatal WES may have if offered clinically.

3.2 QUESTIONNAIRE DESIGN

The study questionnaire design was a new design but used questionnaires previously reported in literature on whole exome sequencing as a reference.[26-28] The questionnaire first had a description of whole exome sequencing. This description included information on what WES is, when it is used, and what are the potential results or finding of WES. The questionnaire included questions to gauge parental receptiveness to prenatal WES, their willingness to undergo the necessary procedures in order to have prenatal WES, the types of results they would like to receive from

prenatal WES, and the impact the results would have on their family planning. The questionnaire also included questions regarding demographic information. The questionnaire was designed to be anonymous in nature, with no questions revealing identifying information. The questionnaire was assessed by a medical geneticist (Aleksandar Rajkovic), an obstetrician/gynecologist (Devereux N. Saller), a bioethicist (Lisa S. Parker), a pediatric genetic counselor who specializes in WES, and several prenatal genetic counselors from Magee-Womens Hospital for readability and relevancy of each question. The study and questionnaire were approved as an exempt study by the Institutional Review Board of the University of Pittsburgh (PRO#14050637).

3.3 QUESTIONNAIRE DISTRIBUTION

Questionnaires were distributed to expectant parents pursuing first trimester screening from June 2014 until October 2014. The prenatal genetic counselor that was on call each day at Magee-Womens Hospital would attach the questionnaire to the flow sheet of each woman pursuing first trimester screening. The flow sheet is used during the check-in process so the questionnaire was distributed to individuals pursuing first trimester screening by the staff at the front desk of the genetics ultrasound waiting area at Magee-Womens Hospital at the time of check-in. These individuals were also given a cover letter that explained the study and that it was voluntary to participate. Please see **Appendix A** for the cover letter and questionnaire. When the questionnaires were completed they were returned to the staff at the front desk or to an ultrasound tech. The questionnaires were kept in a confidential location until a genetic counselor collected them and returned them to the study team.

3.4 ANALYSIS OF RESULTS

Descriptive analysis was performed for all questions of the survey. Non-responders were not included in the analysis of each question with the exception of the demographic information.

Special consideration had to be taken into account for two questionnaires. A total of 184 questionnaires were returned and were at least partially completed. Two of the 184 questionnaires were completed by both the male and female partner on a single copy of the questionnaire instead of completing separate questionnaires. Both partners answered the questionnaires with the same answers to each question except for the following demographic information: gender, age, and education level. For the purpose of analysis, these questionnaires were counted twice (once for the male and once for the female) making the total number of questionnaires 186. An additional special consideration that had to be taken into account was for the question regarding the preferred individual to return the results of prenatal WES, which was supposed to be answered with one choice. Twenty-six participants misunderstood this question to be a select all that applied. For the analysis, this question was analyzed as a select all that applied and counted each selected answer individually.

4.0 RESULTS

Table 1 shown below describes the demographic information of the 186 participants in the study. The overall response rate of the questionnaire was 23.0% (186/808). Refer to **Appendix A** for a copy of the questionnaire. Of the 186 respondents, the sample was predominantly female (90.9%), white (70.4%), and college-educated (57% had Bachelor's degree or greater). The median age the participants was 29 years old. Of all participants, 33.9% reported that this was their first pregnancy, 18.3% reported having prior genetic counseling, and 16.7% reported a family history of congenital anomaly or genetic condition.

Table 1. Demographic Summary of Participants

	Total (n=186)	
	n	%
Sex		
Female	169	90.9
Male	5	2.7
Did Not Answer	12	6.5
Age		
<20	9	4.8
20-29	80	43.0
30-39	82	44.1
40+	3	1.6
Did Not Answer	12	6.5
Race		
White	131	70.4
Black	25	13.4
Asian	10	5.4
Other	6	3.2
Did Not Answer	14	7.5
Education		
Less than High School Diploma	4	2.3
High School Diploma/GED	32	17.2
Some College	34	18.2
Bachelor's Degree	38	20.4
Some Graduate Level	10	5.4
Graduate Degree or Beyond	58	31.2
Did Not Answer	10	5.4
First Pregnancy		
Yes	63	33.9
No	113	60.8
Did Not Answer	10	5.4
Prior Genetic Counseling		
Yes	34	18.3
No	140	75.3
Did Not Answer	12	6.5
Family/Pregnancy History of Congenital Anomaly		
Yes	31	16.7
No	146	78.5
Did Not Answer	9	4.8

Table 2 describes the expectant parents' desire to have prenatal WES and the willingness to undergo necessary procedures in order to have prenatal WES. If participants did not respond to the question, the non-response was not included in the analysis of that particular question. The number of responses for each question is listed in the table.

Most responders (83.1%) agreed that prenatal WES should be offered, 14.8% of participants were neutral to this notion, and while 2.2% were opposed to prenatal WES. About half (53.3%) indicated that they would want prenatal WES for their fetus with an additional 40.1% of participants expressing a neutral feeling of having prenatal WES for their fetus. A significant minority (34.6%) of participants expressed the desire for prenatal WES even if there was no indication of a medical problem and 30.2% were neutral that they would want WES in the absence of a medical indication. Only 17.2% of participants reported willingness to have an invasive procedure, such as amniocentesis, for prenatal WES, with an additional 30.6% of participant expressed a neutral attitude toward this notion. Over half (52.2%) of participants expressed unwillingness to have amniocentesis in order to have prenatal WES. There was a significant minority (44.2%) of participants who agreed they would want prenatal WES only if amniocentesis was not required and 30.6% of participants expressed a neutral opinion towards desiring prenatal WES only if amniocentesis was not required. Only 16.6% of participants disagreed that they would want prenatal WES only if amniocentesis was not required.

Table 2. Parental desire and willingness to have prenatal whole exome sequencing (WES)

	Number of Responders	Agree	Neutral	Disagree
If my baby is born with a birth defect or medical problem, I want to know the cause.	183	170 (92.9%)	10 (5.5%)	3 (1.6%)
If my baby has a birth defect or medical problem, I would do any available genetic test to help determine a possible cause.	183	126 (68.9%)	48 (26.2%)	9 (4.9%)
If my baby has a birth defect or medical problem, it is important for me to know the cause while the baby is in the womb.	183	101 (55.2%)	60 (32.8%)	22 (12.0%)
WES should be offered to pregnant women for their baby if there is a problem identified by ultrasound or other means.	183	152 (83.1%)	27 (14.8%)	4 (2.2%)
I would want my baby to have WES while in the womb if it was available.	182	97 (53.3%)	73 (40.1%)	12 (6.6%)
Even if my baby has no indication of a birth defect or genetic condition, I would want my baby to have WES while in the womb to learn about his/her other genetic risks.	182	63 (34.6%)	55 (30.2%)	64 (35.2%)
I would have amniocentesis in order to have WES for my baby.	180	31 (17.2%)	55 (30.6%)	94 (52.2%)
I would want to have WES for my baby while in the womb only if I did not have to have amniocentesis.	181	80 (44.2%)	71 (39.2%)	30 (16.6%)

Table 3 shown below summarizes the participants' opinions for the return of results of prenatal WES. Table 3 in particular focuses on the types of incidental (secondary) findings the expectant parents would want to receive as part of prenatal WES. Only 9.3% of participants stated they would want prenatal WES only if incidental findings were not reported and 22.5% of participants indicated they would want prenatal WES only if they could choose which incidental are reported to them. The vast majority of participants agreed that they would want to know about both treatable childhood conditions (96.2%) and non-treatable childhood conditions (86.3%). Most participants also agreed for treatable adult-onset (76.0%) and non-treatable adult-onset conditions (74.3%). However, 70.2% reported that an increased risk for adult-onset conditions would cause them anxiety and 71.4% reported that a variant of unknown significance would cause them anxiety. Participants indicated that WES findings could influence future family planning, with 60.1% of participants agreeing it would influence it, 26% expressing neutral feelings, and only 14% disagreeing that WES results would influence family planning. In regards to reproductive decisions, 32.8% indicated that results of prenatal WES may affect their decision to continue the pregnancy and 47.0% of participants disagree that results of prenatal WES would affect their decision to continue the pregnancy.

Table 3. Parental opinions regarding results of whole exome sequencing (WES)

	Number of Responders	Agree	Neutral	Disagree
I would want my baby to have WES while in the womb only if any incidental findings are not reported.	183	17 (9.3%)	82 (44.8%)	84 (45.9%)
I would want my baby to have WES while in the womb only if I can choose which incidental findings are reported to me.	182	41 (22.5%)	65 (35.7%)	76 (41.8%)
I would want to know if my baby has a childhood onset disorder that could be treated before symptoms occur.	182	175 (96.2%)	7 (3.8%)	20 (11.0%)
I would want to know if my baby has a childhood onset disorder that has no treatment or cure.	182	157 (86.3%)	17 (9.3%)	8 (4.4%)
I would want to know if my baby had an increased risk for a disorder that could not be treated until adulthood.	183	139 (76.0%)	27 (14.8%)	17 (9.3%)
I would want to know if my baby has an increased risk for disorder of adulthood that has no treatment or cure.	183	136 (74.3%)	26 (14.2%)	21 (11.5%)
Finding out my baby is at an increased risk for a disorder of adulthood would cause me anxiety.	181	127 (70.2%)	41 (22.7%)	13 (7.2%)
It would cause me anxiety if my baby had a “variant of unknown significance” as part of his/her WES results.	182	130 (71.4%)	34 (18.9%)	18 (9.9%)
WES may reveal that the pregnancy has a different father than expected (non-paternity). I would want that result reported.	177	119 (67.2%)	45 (25.4%)	13 (7.3%)
The results of WES would affect my decision about having more children in the future if the results show I am at risk to have other children with health problems.	178	107 (60.1%)	46 (25.8%)	25 (14.0%)
If my baby has a birth defect or medical problem, knowing the cause may affect my decision to continue the pregnancy.	183	60 (32.8%)	37 (20.2%)	86 (47.0%)
A patient should discuss the possible results of whole exome sequencing with a medical professional before having the test.	177	171 (96.6%)	5 (2.8%)	1 (0.6%)

Figure 1 and **figure 2** depict the parental desire for the types of childhood onset conditions they would want to be reported with prenatal WES. Figure 1 shows the total percentage of responders that would want various types of childhood onset conditions reported. The majority of participants stated they would want results regarding conditions of childhood that are treatable (91.8%), non-treatable (81.4%), and conditions that may shorten lifespan (82.5%).

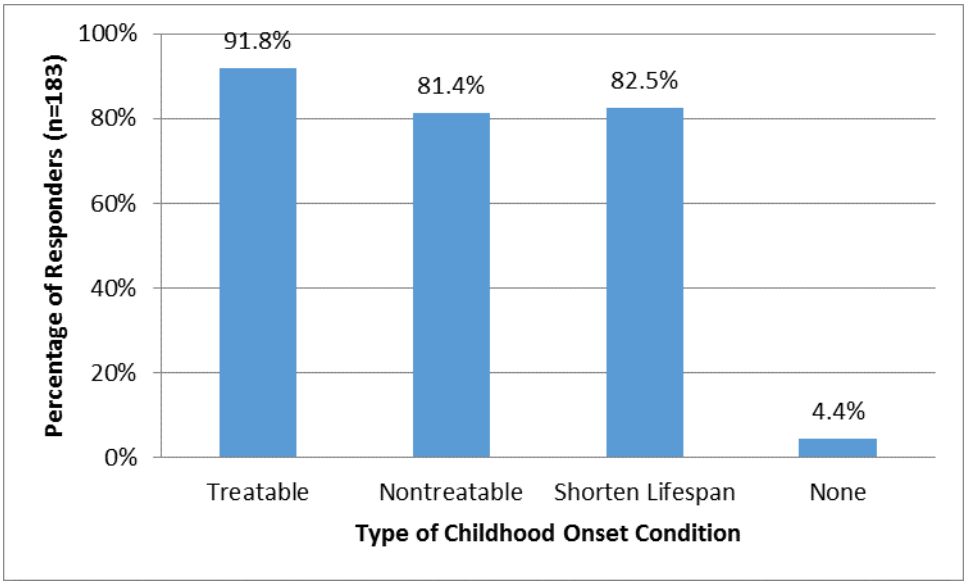

Figure 1. Types of results participants would want to be reported with prenatal whole exome sequencing regarding childhood onset conditions (n=183).

Figure 2 describes the combinations of types of childhood onset conditions expectant parents would want to be reported with prenatal WES. The majority of participants (76.5%) indicated that they would want to know about all types of results for childhood conditions (treatable conditions, non-treatable condition, and conditions that shorten lifespan). Only 4.4% of participants stated that they would not want any results relating to childhood onset conditions reported to them.

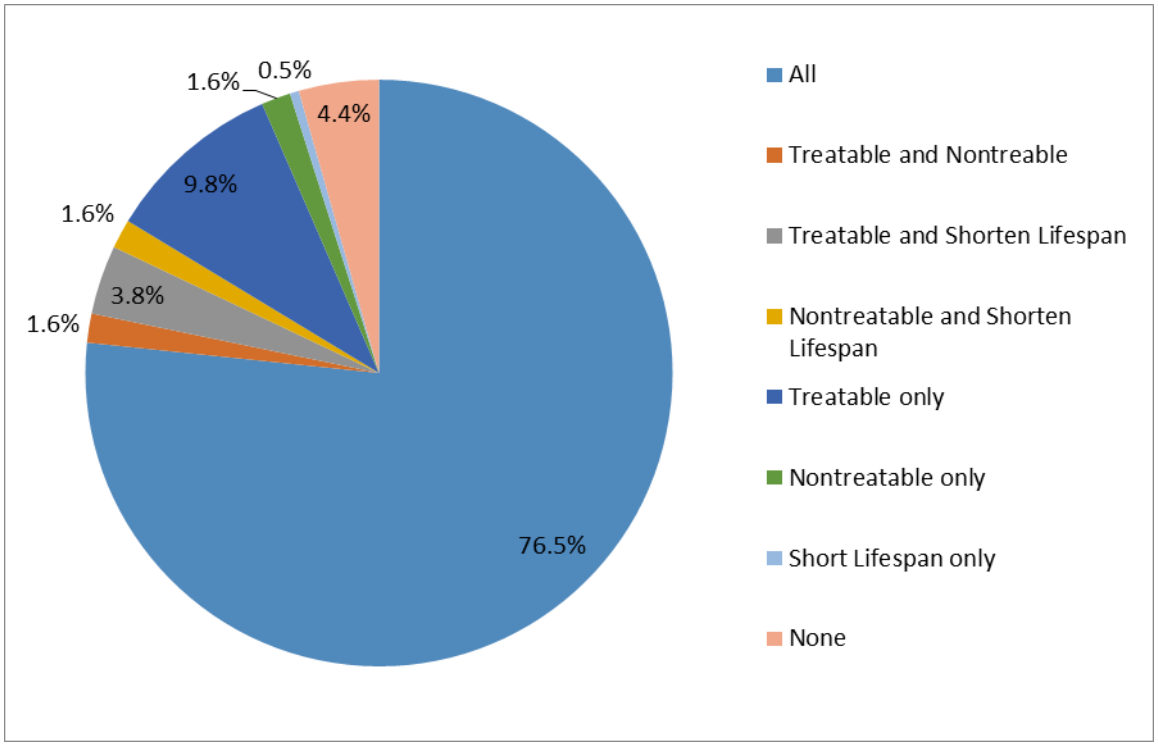

Figure 2. Types of childhood onset conditions participants would want to be reported with prenatal whole exome sequencing (n=183).

Figure 3 and **figure 4** depict the parental desire for the types of adult onset conditions they would want to be reported with prenatal WES. Figure 3 shows the total percentage of responders that would want various types of adult onset conditions reported. The majority of participants stated they would want results regarding adult onset conditions that are treatable (86.8%), non-treatable (76.9%), and conditions that may shorten lifespan (79.1%).

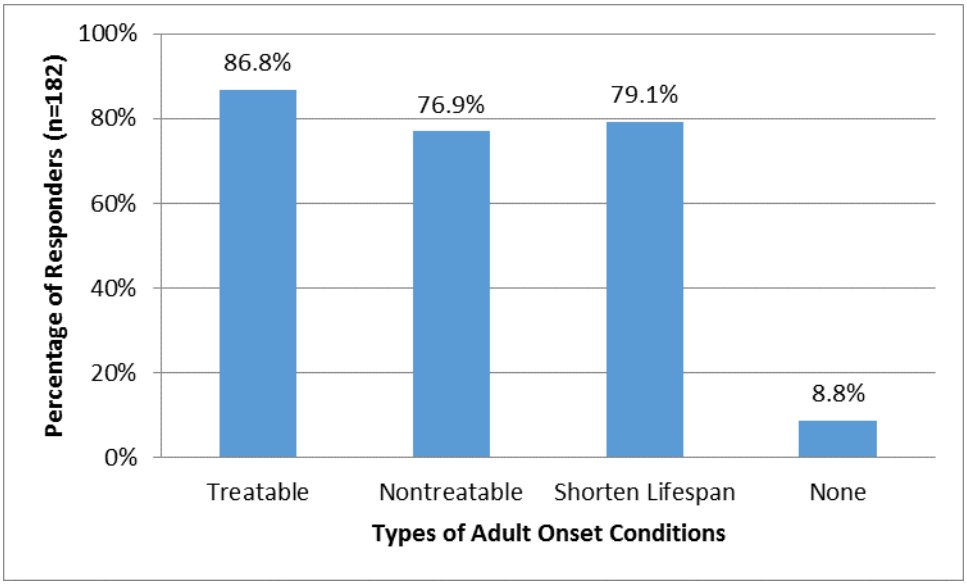

Figure 3. Types of results participants would want to be reported with prenatal whole exome sequencing regarding adult onset conditions (n=182).

Figure 4 describes the combinations of types of adult onset conditions expectant parents would want to be reported with prenatal WES. The majority of participants (72.5%) indicated that they would want to know about all types of results for childhood conditions (treatable conditions, non-treatable condition, and conditions that shorten lifespan). Only 8.8% of participants stated that they would not want any results relating to childhood onset conditions reported to them.

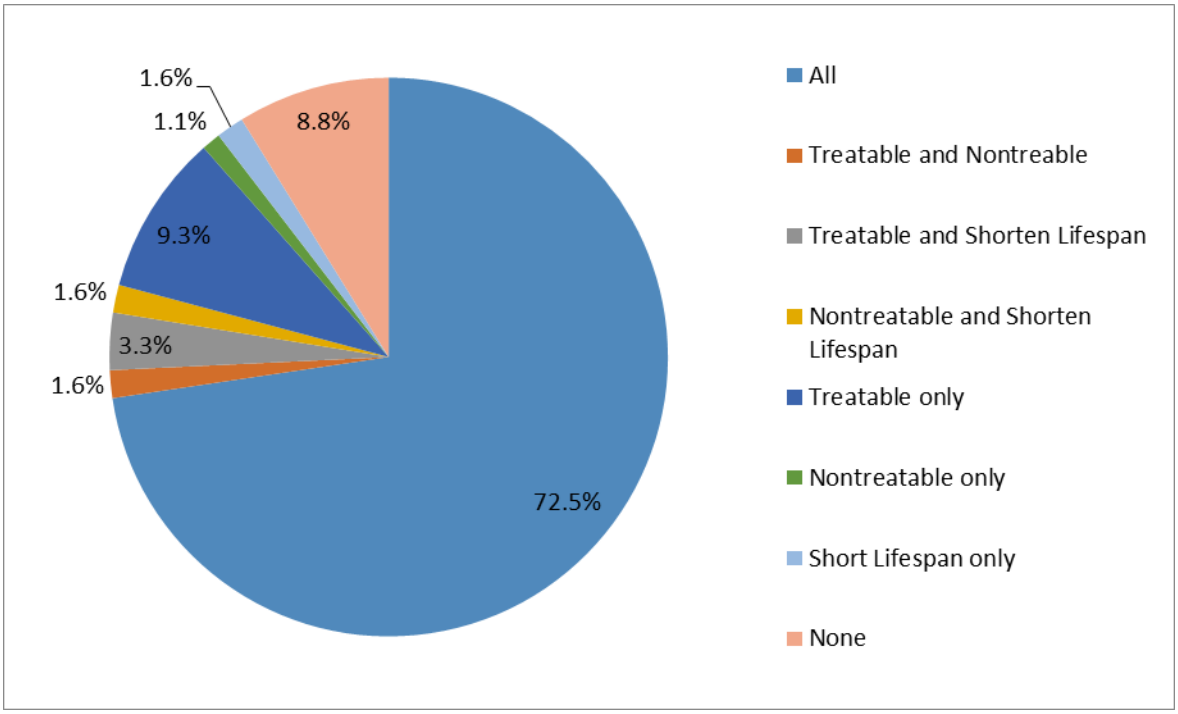

Figure 4. Types of adult onset conditions participants would want to be reported with prenatal whole exome sequencing (n=182).

Figure 5 describes how participants responded to the question "How much did you know about whole exome sequencing before this study?" Over 75% of participants indicated that they did not know what WES was prior to this questionnaire. A total of 24% of participants expressed that they at least know WES was a type of genetic testing. There was one person that responded "Other" and commented that they were not sure if this was the type of testing their doctor had talked to them about.

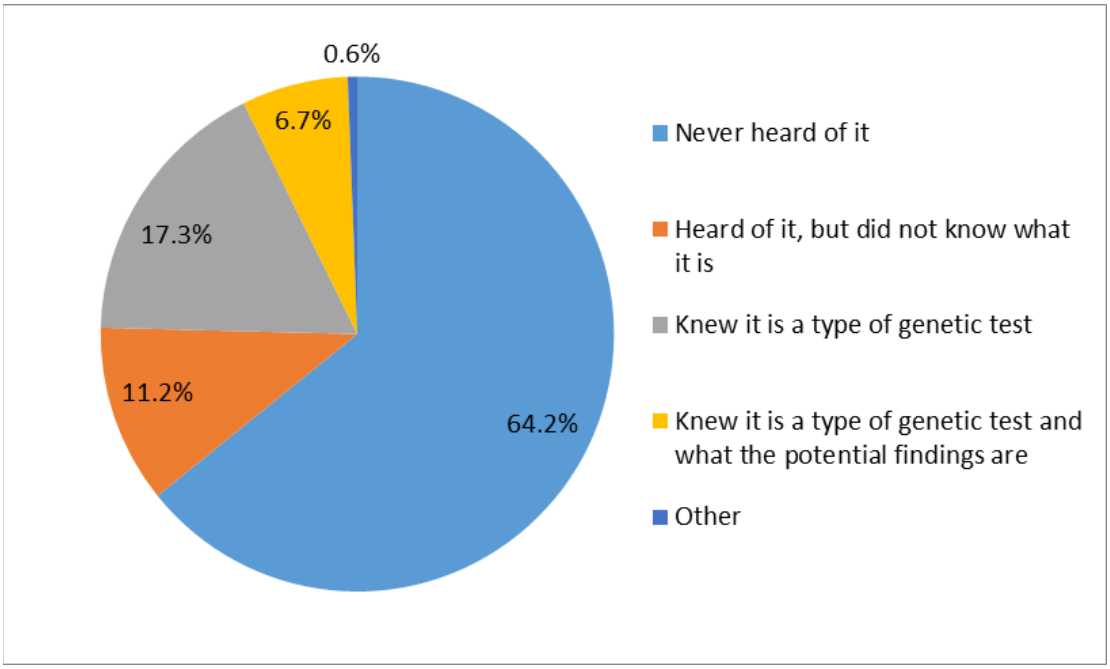

Figure 5. Prior knowledge of participants on whole exome sequencing (n=179).

Figure 6 describes the participants preferred turnaround time for prenatal WES. More than half of participants expressed preference for a turnaround time from the collection of sample to the reporting of results of less than 3 weeks (with 11.7% preferring <1 week and an additional 48.0% referring 1-3 weeks).

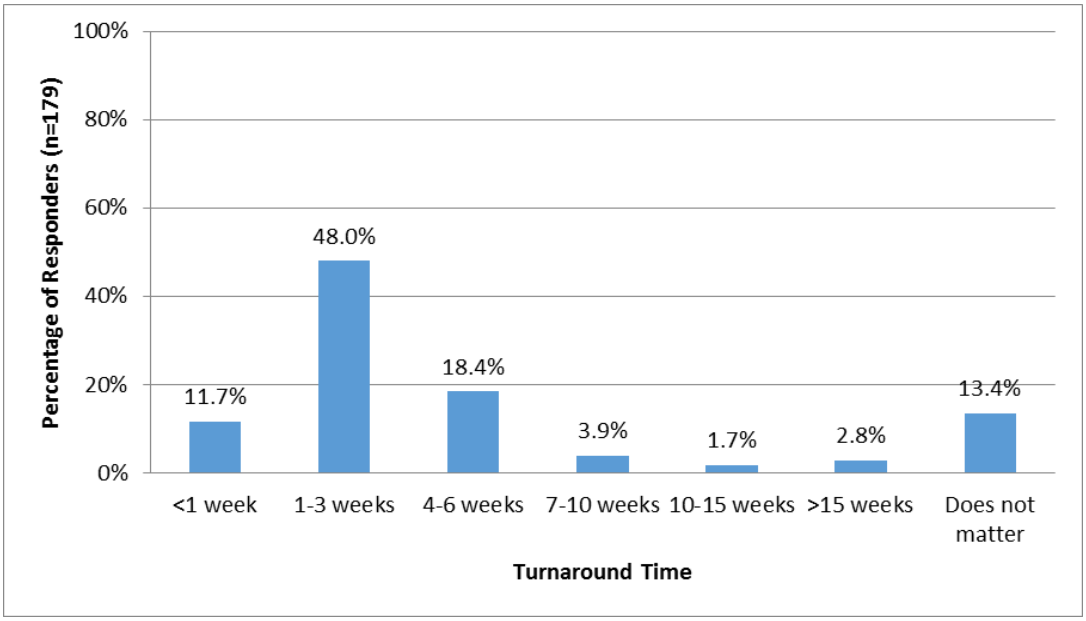

Figure 6. Parental preferences for whole exome sequencing (WES) turnaround time (n=179).

Figure 7 describes the participants preferred professional to return results of prenatal WES. The majority of participants expressed a desire to receive WES results from a genetics professional (62.0%). Many participants were also willing to receive results from their OB/GYN (48.6%). Few participants indicated a desire to receive prenatal WES results from their primary care provider (5.6%) or pediatrician (6.1%).

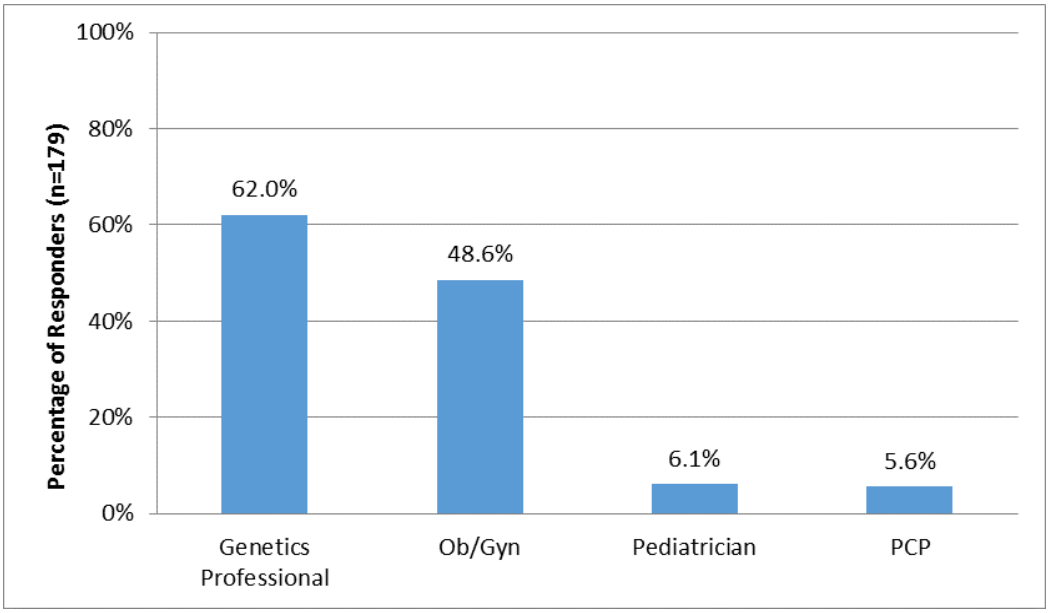

Figure 7. Parental preferences for individual to return whole exome sequencing (WES) results (n=179).

5.0 DISCUSSION

5.1 ANALYSIS OF QUESTIONNAIRE

The data from **Table 2** showed that a majority of participants (83.1%) felt that prenatal WES should be offered. Additionally, over half of participants (53.3%) expressed that they would want to have prenatal WES for their fetus with an additional 40.1% that were neutral towards prenatal WES. A significant minority of participants (34.6%) thought prenatal WES should be offered even if there was no medical indication identified. There was much interest expressed in prenatal WES by the participants. Several participants commented on their personal desire for prenatal WES stating, “I want to be able to have any test needed for me to have a healthy pregnancy,” and “Better to know than not to know.” One participant who was educated on WES stated, “I read a few journal articles about whole exome sequencing and wish it were available to me and covered by insurance. Another important reason to do whole exome sequencing would be to contribute to research on risk for identified variants (conditions that may develop from them) to better identify environmental (biopsychosocial) risk for developing a condition.”

Although, there was interest in prenatal WES, the participants knew little about WES prior to this study, with 75.3% of participants having never heard of it or did not know what it. This must be taken into consideration when assessing hypothetical interest and actual uptake of the testing if offered. When individuals are better explained the testing, types of results, implications the results

may have on future medical management, and psychosocial implications, they may have differing attitudes regarding prenatal WES than were expressed in this questionnaire.

Other factors that may affect hypothetical interest in prenatal WES versus actual uptake are the current turnaround time for WES and the need for an invasive procedure, such as amniocentesis, in order to have prenatal WES. The majority of participants (59.7%) stated that the preferred turnaround time for prenatal WES results is three weeks or less. This is much shorter than the current advertised turnaround time of 8 – 15 weeks by various testing laboratories.[29-31] Current WES technologies would require an invasive procedure, such as chorionic villi sampling or amniocentesis, in order to be able to perform prenatal WES. A little less than half of participants (44.2%) stated that they would want prenatal WES only if amniocentesis did not have to be performed. A non-invasive option for prenatal WES may be preferred over an invasive procedure. A couple of participants even commented on their concerns of the safety of the test. One participant wrote, “Is it safe for me and the baby where I would not miscarry?” Another participant commented, “I would be for the sequencing if it was of little to no risk to the baby.”

Incidental (secondary) findings of WES continue to be center of debate among professionals. There has been much discussion over which type of incidental findings should be reported with WES and if individuals should be able to opt-out of receiving any of these findings. Participants in this study had strong interest in receiving all types of incidental (secondary) findings, with the majority of participants wanting to know about childhood onset and adult-onset conditions that are treatable, non-treatable, or may shorten lifespan even though over 70% of participants stated that finding out their fetus was at an increased risk for an adult onset condition would cause them anxiety. Additionally, 71.4% of participants agreed that a variant of unknown significance would cause them anxiety, but participants still had a desire to receive all results of prenatal WES. One participant commented on the anxiety that may be created through prenatal WES commenting,

"I'd be happy to get testing done if it was definitive, not if there is a chance of a disorder and if there were false positives. Only 100% definitive results. I don't want to know about adulthood. That would cause great anxiety for decades down the road although this sounds like a great idea initially it makes me wonder if it is going against nature or ethics by looking into the genetics that much. I found myself very torn."

In terms of reproductive and family planning, the opinions of the expectant parents were somewhat more divided. When asked if knowing the cause of a health problem in the fetus would affect their decision to continue the pregnancy, 32.8% of participants agreed and 20.2% were neutral. Furthermore, 60.1% of participants expressed that if prenatal WES results indicated that they were at risk to have a future child with health problems it would affect their decision to have more children. One participant even commented on the concern for how prenatal WES may affect reproductive decisions stating, "I understand the usefulness of genetic testing but there should be a limit. We don't need to know everything before it happens. I fear the amount of abortions that would occur due to 'risk' for certain conditions."

5.2 LIMITATIONS OF STUDY AND FUTURE DIRECTIONS

There were several limitations to this study. The response rate of the study was 23.0% (186/808). Due to the nature of this anonymous study, it is impossible to know if there was a significant difference between responders and non-responders. Comparing the study population's demographics to the demographics of Allegheny County[32], there were some obvious differences. According to Allegheny County census data from 2008-2012, 35.1% of residents age 25 or older have a Bachelor's degree or higher compared to the study population which 57% of individuals had

at least a Bachelor's degree. The higher rate of college educated individuals that participated in the study may have introduced some bias in that they were more likely to participate in the research study and the results are not reflective of the general population's opinions, but it is difficult to predict if this is a meaningful comparison because the Allegheny County data includes individuals that are older than child bearing years and may have been less likely to pursue a higher degree. Census data from 2013, 51.9% of residents of Allegheny County are female which is much lower than the 91.0% of female participants in the study population. When considering the lack of male participation (2.7%), it can be hypothesized that male participation was low due to disinterest in participating in research, lack of involvement in the appointment, or were unaware of the study. Racial background of participants in the study was similar to Allegheny County. Racial summary of the study cohort compared to Allegheny County are as follows: white- 70.4% versus 79.9%, black- 13.4% versus 13.3%, Asian- 5.4% versus 3.2%, and all other races- 3.2% versus 3.2%. In the study cohort, 7.5% of participants did not respond to this question so the actual racial summary may be different than what was reported.

Another limitation to this study was the limited amount of information provided to the participants about WES before having them form an opinion. As a whole, the study cohort was rather uneducated on prenatal WES. If individuals were better educated on the subject matter they may have different opinions than what they expressed in the study. One study participant even noted her confusion on the study subject stating, "I understand some of these questions but still a little confused by a lot of it."

Future directions of this study would be to expand the study population in several ways. First, it would be important to have more expectant fathers participate in order to eliminate any bias that may arise from having a majority of women participants. Additionally, the study could be expanded to include expectant parents from varying gestational ages, and varying levels of testing,

such as no prenatal testing or screening, first trimester screen, non-invasive prenatal testing, and chromosome analysis through amniocentesis or chorionic villi sampling. The study would also benefit by giving participants a more detailed description of WES and explaining in detail ethical questions surrounding prenatal WES with a longer time frame for reflection on the issue. This would help to assess if parental opinions of prenatal WES change as they become more informed on the subject.

5.3 PUBLIC HEALTH SIGNIFICANCE

Currently, commercial genetic testing laboratories do not offer prenatal WES even though the ACMG guidelines state that WES may be considered if the fetus likely has a genetic condition. These guidelines also state that WES should not be used as a prenatal screening method.[7] As the WES testing technology improves and more in known about the human genes and genome, it is inevitable that prenatal WES will be offered more readily to the public. Knowing if there is interest from the public in this type genetic testing is important before making it available as it require many valuable resources that could otherwise be used elsewhere.

Over time prenatal WES may become more available as a prenatal genetic testing option. As this study showed, the majority of participants did not know anything about WES prior to the questionnaire. In order for WES to be a prenatal testing option, public education should take place so that there is a better understanding of the test before it is performed.

5.4 CONCLUSIONS

Parental opinions regarding prenatal WES was studied, specifically in regards to desire for testing, willingness to have necessary procedures in order to have prenatal WES, types of results parents would want reported, and implications results may have on psychosocial effect and family planning. Demographic information was collected to help determine if bias was introduced into the study. The answers to the study questionnaire were analyzed using descriptive summaries. The majority of participants thought that prenatal WES should be offered and a little over half of the participants stated that they would want the test if available. The majority of participants were also interested in receiving all types of results even though the results may provoke anxiety.

These results are helpful to predict the uptake of prenatal WES by expectant parents if made clinically available. While there is interest from expectant parents, the current technologies may not meet their expectations in regards to fetal DNA capture and turnaround times for results. Additionally, some concerns were expressed on how this testing may affect reproductive decisions and the psychological burden it may create by knowing so much genetic information before a child is even born.

APPENDIX A: PRENATAL WHOLE EXOME SEQUENCING QUESTIONNAIRE

A.1 COVER LETTER

Study Title: Understanding Parental Opinions on Whole Exome Sequencing in the Prenatal Setting

The purpose of this questionnaire is to assess parent's feelings on whole exome sequencing performed on babies while still in the womb. For this reason, we will be surveying pregnant women and their partner at Magee-Womens Hospital and ask them to complete a brief (approximately 15 minutes) questionnaire. All participants of this research study must be 18 years or older in age. If you are willing to participate, the questionnaire will ask you about background (e.g. gender, race, age, education, pregnancy history), as well as about your feelings on whole exome sequencing performed on babies while still in the womb. This genetic technique is currently not offered for babies that are still in the womb. There are no anticipated risks associated with this study, nor any direct benefits to you. Please read the explanation of whole exome sequencing and complete the questionnaire. This questionnaire is entirely anonymous, your responses will be kept strictly confidential, and results will be kept under lock and key. Your participation is voluntary and you may choose to stop filling out the questionnaire after you have begun and not submit it. This study is being conducted by Eve Kalynchuk, who can be reached at kalynchuke2@mwri.magee.edu or 412-641-7547, if you have any questions. ***Please complete this questionnaire only one time.*** When you complete your questionnaire, please return it to the sonographer or ultrasound tech. Thank you!

A.2 COMPREHENSIVE QUESTIONNAIRE

WHAT IS WHOLE EXOME SEQUENCING?

Whole exome sequencing is a new type of genetic test that has been shown to help find a genetic explanation for a patient's medical problems. This test works by reading portions of a person's DNA, which is in every cell of the body. The test looks for changes in the DNA sequence that are not detected by many of the other genetic techniques that are currently used. If there is a change in the DNA sequence, it could potentially cause health problems. Whole exome sequencing, in addition to finding disease causing changes, has been shown to identify other variations in the DNA. The following table describes the types of changes in the DNA sequence that can be reported from whole exome sequencing:

Type of Results	What it means
Disease Causing Variant	Change in a gene that causes disease or defect
Benign Variant	Change in a gene that does not cause disease or defect
Variant of unknown significance	Change in a gene that the effect is unknown at this time
Incidental finding*	Change in a gene that is associated with risk for developing a disease that may not be related to current condition

**Example of an incidental finding*: A baby may have whole exome sequencing in attempt to find the genetic cause for a birth defect, but it may discover that the baby has a change in the DNA sequence that can increase a person's lifetime risk for breast cancer, ovarian cancer, and/or other types of cancer.

Based on the information above please answer the following questions.

1. Whole exome sequencing may reveal something about your baby, which may also reveal information about your own health. For example, your baby may have a change in their DNA that causes a condition of adulthood and you could potentially have the same change in your DNA. Would this possibility influence your decision to have your baby tested using whole exome sequencing? [ ] Yes [ ] No

2. There are several different types of incidental findings that could be reported from whole exome sequencing regarding increased risks for conditions that develop in childhood. What type of these findings would you want reported if your baby had whole exome sequencing? *Please select all that apply.*

   [ ] Treatable conditions [ ] Conditions that may shorten lifespan

   [ ] Non-treatable conditions [ ] None

3. There are several different types of incidental findings that could be reported from whole exome sequencing regarding increased risks for conditions that develop in adulthood. What type of these findings would you want reported if your baby had whole exome sequencing? *Please select all that apply.*

   [ ] Treatable conditions [ ] Conditions that may shorten lifespan

   [ ] Non-treatable conditions [ ] None

4. If you chose to have whole exome sequencing while your baby is still in the womb, who should report the results to you? *Please select one.*

[ ] OB/GYN (Obstetrician/gynecologist) [ ] Pediatrician

[ ] Primary care physician [ ] Other: _____

[ ] Genetics Professional

5. The length of time it takes to get results of genetic testing varies from a couple days to several weeks depending on the test. How long do you feel is an acceptable amount of time to wait for whole exome sequencing results for your baby while still in the womb? *Please select one.*

[ ] Less than 1 week [ ] 7-10 weeks

[ ] 1-3 weeks [ ] 10-15 weeks

[ ] 4-6 weeks [ ] Over 15 weeks

[ ] It does not matter as long as it is before the baby is born

Please circle one option for each of the following statements to best describe how you feel.

1. If my baby is born with a birth defect or medical problem, I want to know the cause.	Agree	Neutral	Disagree
2. If my baby has a birth defect or medical problem, I would do any available genetic test to help determine a possible cause.	Agree	Neutral	Disagree
3. If my baby has a birth defect or medical problem, it is important for me to know the cause while the baby is in the womb.	Agree	Neutral	Disagree
4. If my baby has a birth defect or medical problem, knowing the cause may affect my decision to continue the pregnancy.	Agree	Neutral	Disagree
5. Whole exome sequencing should be offered to pregnant women for their baby if there is a problem identified by ultrasound or other means.	Agree	Neutral	Disagree
6. I would want my baby to have whole exome sequencing while in the womb if it was	Agree	Neutral	Disagree

available.

7. Even if my baby has no indication of a birth defect or genetic condition, I would want my baby to have whole exome sequencing while in the womb to learn about his/her other genetic risks.	Agree	Neutral	Disagree
8. I would want my baby to have whole exome sequencing while in the womb ***only if*** any incidental findings are ***not*** reported.	Agree	Neutral	Disagree
9. I would want my baby to have whole exome sequencing while in the womb ***only if*** I can choose which incidental findings are reported to me.	Agree	Neutral	Disagree
10. I would have amniocentesis (a genetic testing procedure used to test babies still in the womb with a 1:1000 risk of miscarriage) in order to have whole exome sequencing for my baby.	Agree	Neutral	Disagree
11. I would want to have whole exome	Agree	Neutral	Disagree

sequencing for my baby while in the womb ***only if*** I did not have to have amniocentesis.

12. It would cause me anxiety if my baby had a "variant of unknown significance" as part of his/her whole exome sequencing results.	Agree	Neutral	Disagree
13. Finding out my baby is at an increased risk for a disorder of adulthood would cause me anxiety.	Agree	Neutral	Disagree
14. I would want to know if my baby had an increased risk for a disorder that could not be treated until adulthood.	Agree	Neutral	Disagree
15. I would want to know if my baby has an increased risk for disorder of adulthood that has no treatment or cure.	Agree	Neutral	Disagree
16. I would want to know if my baby has a childhood onset disorder that could be treated before symptoms occur.	Agree	Neutral	Disagree
17. I would want to know if my baby has a	Agree	Neutral	Disagree

childhood onset disorder that has no treatment or cure.

18. I would want to have whole exome sequencing on my baby if treatment for any identified problem was available for my baby while still in the womb.	Agree	Neutral	Disagree
19. The results of whole exome sequencing would affect my decision about having more children in the future if the results show I am at risk to have other children with health problems.	Agree	Neutral	Disagree
20. Whole exome sequencing may reveal that the pregnancy has a different father than expected (non-paternity). I would want that result reported.	Agree	Neutral	Disagree
21. A patient should discuss the possible results of whole exome sequencing with a medical professional before having the test.	Agree	Neutral	Disagree

How much did you know about whole exome sequencing before this study? *Please select one.*

[ ] I never heard of it.

[ ] I heard of it, but did not know what it is.

[ ] I knew it is a type of genetic testing.

[ ] I knew it is a type of genetic testing and what the potential findings are.

[ ] Other: _____

Additional Comments:

_____

_____

_____

_____

DEMOGRAPHIC INFORMATION

Gender: _____

Race: _____

Age: _____

Highest level of education completed:

[ ] Less than high school

[ ] High school/ GED

[ ] Some college

[ ] Bachelor's degree

[ ] Some graduate level

[ ] Graduate degree or beyond

How far along are you in your current pregnancy? _____ Weeks _____ Days

Is this your first pregnancy? [ ] Yes [ ] No

Have you ever had genetic counseling? [ ] Yes [ ] No

Has the baby of this pregnancy been diagnosed with a birth defect or medical problem?

[ ] Yes [ ] No *If yes*, please describe: _____

Have you ever had a pregnancy in which the baby had a birth defect or medical problem?

[ ] Yes [ ] No *If yes*, please describe: _____

Was anyone in your family born with a birth defect or genetic condition?

[ ] Yes [ ] No *If yes*, please describe: _____

Thank you!

APPENDIX B: IRB APPROVAL FORM

IRB Approval form

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Eve Kalynchuk

From: Christopher Ryan, PhD, Vice Chair

Date: 6/10/2014

IRB#: PRO14050637

Subject: Understanding Parental Opinions on Whole Exome Sequencing in the Prenatal Setting

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The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section

45 CFR 46.101(b)(2).

Please note the following information:

- Investigators should consult with the IRB whenever questions arise about whether planned changes to an exempt study might alter the exempt status. Use the "**Send Comments to IRB Staff**" link displayed on study workspace to request a review to ensure it continues to meet the exempt category.
- It is important to close your study when finished by using the "**Study Completed**" link displayed on the study workspace.
- Exempt studies will be archived after 3 years unless you choose to extend the study. If your study is archived, you can continue conducting research activities as the IRB has made the determination that your project met one of the required exempt categories. The only caveat is that no changes can be made to the application. If a change is needed, you will need to submit a NEW Exempt application.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

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