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ORIGINAL RESEARCH

Not the End of the Odyssey: Parental Perceptions of Whole Exome Sequencing (WES) in Pediatric Undiagnosed Disorders

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Abstract Due to the lack of empirical information on parental perceptions of primary results of whole exome sequencing (WES), we conducted a retrospective semi-structured interview with 19 parents of children who had undergone WES. Perceptions explored during the interview included factors that would contribute to parental empowerment such as: parental expectations, understanding of the WES and results, utilization of the WES information, and communication of findings to health/educational professionals and family members. Results of the WES had previously been communicated to families within a novel framework of clinical diagnostic categories: 5/19 had Definite diagnoses, 6/19 had Likely diagnoses, 3/19 had Possible diagnosis and 5/19 had No diagnosis. All parents interviewed expressed a sense of duty to pursue the WES in search of a diagnosis; however, their expectations were tempered by previous experiences with negative genetic testing results. Approximately half the parents worried that a primary diagnosis that would be lethal might be identified; however, the hope of a diagnosis outweighed this concern. Parents were accurately able to summarize their child's WES findings, understood the implications for recurrence risks, and were able to communicate these findings to family and medical/educational providers. The majority of those with a Definite/Likely diagnosis felt that their child's medical care was more focused, or there was a reduction in worry, despite the lack of a specific treatment. Irrespective of diagnostic outcome, parents recommended that follow-up visits be built into the process. Several parents expressed a desire to have all variants of unknown significance (VUS) reported to them so that they could investigate these themselves. Finally, for some families whose children had a Definite/Likely diagnosis, there was remaining frustration and a sense of isolation, due to the limited information that was available about the diagnosed rare disorders and the inability to connect to other families, suggesting that for families with rare genetic disorders, the diagnostic odyssey does not necessarily end with a diagnosis. Qualitative interviewing served a meaningful role in eliciting new information about parental motivations, expectations, and knowledge of WES. Our findings highlight a need for continued communication with families as we navigate the new landscape of genomic sequencing.

Keywords Whole exome sequencing · Genetic counseling · Empowerment · Parental perspectives

Introduction

Approximately 50 % of children who are seen in a clinical genetics setting remain without a diagnosis with the standard approach of a clinical evaluation followed by targeted genetic testing (Shashi et al. 2013). Whole exome sequencing (WES) is increasingly being utilized as a diagnostic tool for these children with undiagnosed disorders. The benefits of WES include a diagnosis in 20–50 % of patients, identification of new disease-causing genes, insight into the phenotypic and allelic heterogeneity of Mendelian disorders, an

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understanding of the importance of *de novo* mutations in pediatric rare disorders, better awareness of disease pathogenesis and, in some instances, new treatments (Enns et al. 2014; Gilissen et al. 2011; Lee et al. 2014; Mikati et al. 2015; Shashi et al. 2015a, b; Yang et al. 2013; Yang et al. 2014; Zhu et al. 2015). Despite the diagnostic utility of WES in pediatric undiagnosed disorders, little is known about the parental perceptions of the process and the primary results that are generated by WES. Information prior to the availability of WES indicates that 30–60 % of parents who received a genetic diagnosis for their child from targeted genetic testing expressed confusion about medical terminology used by the professionals, the perception that they as parents were passive rather than active participants in the process, and felt that they were not provided emotional support from the medical team (Ashtiani et al. 2014). Such feelings are likely to be magnified with WES, in part because the disorders diagnosed are frequently rarer than those diagnosed by conventional methods, with little information available to the families, and the analyses may yield multiple gene variants that complicate the results interpretation. Further, variants of unknown significance (VUS) require ongoing evaluation and the choices and results surrounding secondary/incidental findings increase the complexity of decision making. These factors may result in feelings of uncertainty and frustration about the process and outcome of WES, but have not been systematically explored.

A proposed key outcome measure for assessing the effectiveness of clinical genetic services has been the construct of empowerment (McAllister et al. 2007, 2008a). Empowerment has been defined as the complex belief that one can: a) make important life decisions in an informed way (i.e., decisional control); b) has sufficient information about the condition, including risks to oneself and one's relatives, and any treatment, prevention and support available (i.e., cognitive control); c) can make effective use of the health and social care systems for the benefit of the whole family (i.e., behavioral control); d) can manage one's feelings about having a genetic condition in the family (i.e., emotional regulation); and e) can look to the future having hope for a fulfilling family life (i.e., hope) (McAllister et al. 2011). The process of empowerment involves steps leading to self-efficacy through acquisition of knowledge and skills, utilization of resources, and involvement with similar others with the goal of enhancing family outcomes and developing positive coping strategies (McConkie-Rosell and Sullivan 1999). For WES in children with undiagnosed disorders, studying parental expectations, understanding, utilization of results and communication to others could inform us on factors that contribute to empowerment.

While prior empirical data have indicated that empowerment may lead to more informed decisions and a more positive outcome for families seeking genetic services (McAllister et al. 2008a, b), there are no data on parental empowerment as related to WES. The need for such data has been emphasized as a crucial step to effectively implement WES in undiagnosed disorders (Facio et al. 2014). Thus far, however, publications on parental/patient perspectives on WES have mostly focused on secondary/incidental findings (Abdul-Karim et al. 2013; Bergner et al. 2014; Clayton and McGuire 2012; Clift et al. 2015; Green et al. 2013; Hegde et al. 2015; Jarvik et al. 2014). The few studies that have examined parental perceptions of the primary WES results in childhood undiagnosed disorders reported that parents expressed a sense of responsibility in needing to pursue the WES and had positive expectations about learning the results (Krabbenborg et al. 2016; Sapp et al. 2014). When exploring the experience of whole genome sequencing (WGS) with parents and adult siblings in families with children with Miller syndrome Tabor et al. found that they had difficulty explaining whole genome sequencing, indicating the complexity of the information related to sequencing (Tabor et al. 2012).

It is to be noted that none of these studies comprehensively examined the parental perceptions of the primary results from WES on their children (e.g., reservations regarding the primary results, how they would utilize the results, how they would communicate the results to others). In order for genetic counselors, medical geneticists and other health professionals to partner with families and work towards the outcome of enhancing empowerment for families undergoing WES, it is important to explore parents' experience of the process. We conducted a retrospective study with the aim of exploring key factors contributing to the process of empowerment, in parents of children who had undergone WES for an undiagnosed disorder.

Materials and Methods

Sample

We recruited parents of children with undiagnosed disorders seen in the Duke Genome Sequencing Clinic, which performs trio WES on a research basis, in conjunction with a clinical evaluation by medical geneticists and pre- and post-WES genetic counseling. Pretest and post-test genetic counseling was provided by one of two certified genetic counselors. The Genome research clinic mirrors a traditional medical genetics clinic with families being seen by a team including a medical geneticist and a genetic counselor. The same team followed the family through the consenting, pre-test genetic counseling, results and post-test genetic counseling. Parents were provided with the study genetic counselors' as well as the medical geneticists' contact information and encouraged to contact their team with any questions or concerns. The study genetic counselor for each family contacted a total of 24 parents who had received the WES results and invited them to participate in this sub-study. Parents had the option of one or both parents participating in the interviews. For all completed interviews,

parents elected to have only one parent interviewed. This substudy was approved by the Duke University Medical Center Institutional Review Board. The WES results had been reported using clinically informed diagnostic categories, developed by us previously (Shashi et al. 2015a). These diagnostic categories of Definite, Likely, Possible, and No diagnoses were the result of incorporating the "fit" of the molecular results with the patient's phenotype, the mode of inheritance, whether additional evidence was necessary to confirm the diagnosis, and whether the results were secure enough to be used for predictive/prenatal testing. Variants that resulted in a Definite or Likely diagnosis had been CLIA confirmed prior to reporting (for Likely the confidence level was not high enough to allow for the results to be used for prenatal/predictive testing, whereas Definite diagnoses were). All results were communicated during a clinic visit arranged for that purpose, with the exception of one family wherein the results communication occurred over a conference call, due to distance and the child's disorder preventing travel to clinic. For those with a Possible diagnosis and No diagnosis, the results were communicated by telephone by the study genetic counselor. Those with a Possible diagnosis were only informed that candidate gene/s had been detected, but the specific gene/variant was not provided because the findings had not been CLIA confirmed, in accordance with our IRB protocol. ACMG guidelines (Green et al. 2013) for reporting of secondary findings were published during the course of the WES study, hence only 3 families were offered these secondary findings. However, all families had been informed about the possibility of incidental findings being detected as part of the WES analyses. All consented to learning incidentals and the three families offered the ACMG secondary findings also consented. In order to obtain a sample inclusive of the different diagnostic outcomes, we initially enrolled parents without regard to diagnostic category, and then after the first ten interviews selected nine additional parents so that each diagnostic category was represented.

Measure

A semi-structured interview was used to collect the necessary data. An interview guide was designed by the study team based on our clinical and research experiences, as well as a theoretical model of empowerment (McAllister et al. 2008a, b, 2011; McConkie-Rosell and Sullivan 1999), and explored specific factors contributing to empowerment. An open ended semi-structured interview was used as opposed to an unstructured interview because it increases reliability and enhances comparability across interviews (Maxwell 1996). The interview guide was piloted with five parents (not including the 19 who were the subjects of this study) whose children had undergone WES in the Genome sequencing clinic. Questions were modified based on their responses, and subsequently reviewed and revised by the study team. Redundancy for key questions was built-in to allow for internal reliability.

Key topics explored in the interview were parental expectations of the primary outcome of exome testing, parental understanding of WES and the test outcome, communication of results to others, utilization of the information (e.g. for medical, developmental educational management), and further informational needs that the parents had. Parents were also asked to provide advice to other parents and health professionals regarding WES that would allow us to refine this process for other families.

All interviews were conducted over the telephone by the first author (AMR), an experienced qualitative researcher and a genetic counselor who was not involved with the genetic counseling or communication of results to the participating families. Standard interviewing techniques (Maxwell 1996) were utilized, with the interviews lasting approximately 45 min. All interviews were audiotape recorded and transcribed verbatim for analyses.

Data Analysis

Using a directed content analysis (Potter and Levine-Donnerstein 1999), the data were analyzed using Atlas Ti (version 7). Interviews were coded and emerging themes identified and categorized with new codes developed as needed by Dr. McConkie-Rosell. Several steps were taken to ensure the validity and reliability of the coding and emerging themes. As the interviews were semi-structured, each question was considered the coding unit with multiple codes typically occurring within each unit. After initial coding was complete, three interviews were independently coded by Dr. Shashi and then jointly reviewed (AMR and VS) and codes clarified and discrepancies discussed until resolved. The interviews were then systematically re-coded by AMR, summarized and reviewed over multiple iterations, with Drs. Shashi and Pena assessing for accuracy considering conclusions, codes, and context using the primary transcribed interviews. This process allows for the development of a reliable reproducible coding scheme for use with semi-structured interviews by a single knowledgeable coder (Campbell et al. 2013). Once this process was completed, data were then analyzed assessing for themes within each coding unit and considering the diagnostic category of the outcome of the WES.

Results

Sample

Of the 24 parents who had been offered the study, sixteen mothers and three fathers were consented and interviewed (details of demographics in Table 1). Eleven of the nineteen

Table 1 Sample N (%)

	Total interview $N = 19$ (%)
Sex	
Male	3 (15.8)
Female	16 (84.2)
Age (years)	
31–35	5(26.3)
36–40	2 (10.5)
41–45	7 (36.8)
46–50	3 (15.8)
51–55	2 (10.5)
Age of first parental concern about child (years)	
0–1	15 (78.9)
2–3	4 (21.1)
Highest level of education of interviewee	
High school	2 (10.5)
Some college	7 (36.8)
College degree	5 (26.3)
Post graduate degree	5 (26.3)
Race/Ethnicity of interviewee	
Caucasian	19 (100)
Non-Hispanic	19 (100)
WES Diagnostic Category	
Definite	2 (10.5)
Likely	6 (31.6)
Partial (definite or likely)	3 (15.8)
Possible with VUS of interest	3 (15.8)
No diagnosis	5 (26.3)

patients had received a Definite/Likely diagnosis (inclusive of three wherein the finding explained only part of the phenotype and thus designated as a partial diagnosis) and all eleven had a *de novo* causal variant; three had a Possible diagnosis, and five had No Diagnosis. No incidental findings were identified in these families. The length of time since the WES results communication to the time of the interview ranged from 1 month to 2 years (Fig. 1). Fifteen of the nineteen parents reported that the age of first concern with their child was less than one year, and the length of time they had been searching for a diagnosis at the time of WES varied from 2.8–16 years (mean 7.6 ± 4.4). The five parents who could not be reached did not differ from those who were interviewed and had children across all diagnostic categories Definite or Likely diagnosis (2), a Partial diagnosis (1), or No diagnosis (2).

Expectations of Primary Outcome from the WES

While there was a range of expectations for study results, all parents indicated that they hoped for a diagnosis.

> We wanted to know what was wrong with (my child). It had been almost a decade and we were none the wiser why (my child) was as handicapped as severely as she was. We had been through just about every type of neurological, genetic testing. Respondent 3: Father; WES Category: Likely Diagnosis

Several parents (4/19) had high expectations that the WES would lead to a diagnosis.

> I really thought we would have an answer. I thought that we would find out that we have some sort of, you know, mutation or error, just something. Respondent 9: Mother; WES Category: Partial Definite diagnosis

However, in the majority of the parents (13/19) this hope of a diagnosis was tempered by prior experiences and not wanting to get their hopes up, just to be disappointed.

> I was very skeptical since we had so much done in the past and you know everything was fine and negative. But at the same time I was hoping that something would show up somewhere with this advanced technology. Respondent 7: Mother; WES Category: Likely Diagnosis

Two parents had very low expectations.

> We had not found anything wrong with her. You know, in the previous years so we did not think we would find anything this time either. Respondent 2: Mother; WES Category: Definite diagnosis

When asked why they decided to go forward with the WES, the majority of the parents (11/19) felt that they had to proceed with testing as they had no other options for diagnostic testing. WES was perceived as a chance to learn more and a chance for a diagnosis, so they felt that they had to try.

> We felt like it was our responsibility to do whatever was within our ability to try to find out for his care. Respondent 13: Father; WES Category: Possible Diagnosis

When asked how they saw findings from the WES helping their child, the majority of parental responses suggested that the WES offered hope for providing targeted assistance to them in the care of their child. Parents emphasized that they were seeking the information that stemmed from the diagnosis, including the possibility that the unknown disorder may have a medical treatment; it could inform decisions about life planning for the child as well as reproductive decisions for themselves and other family members.

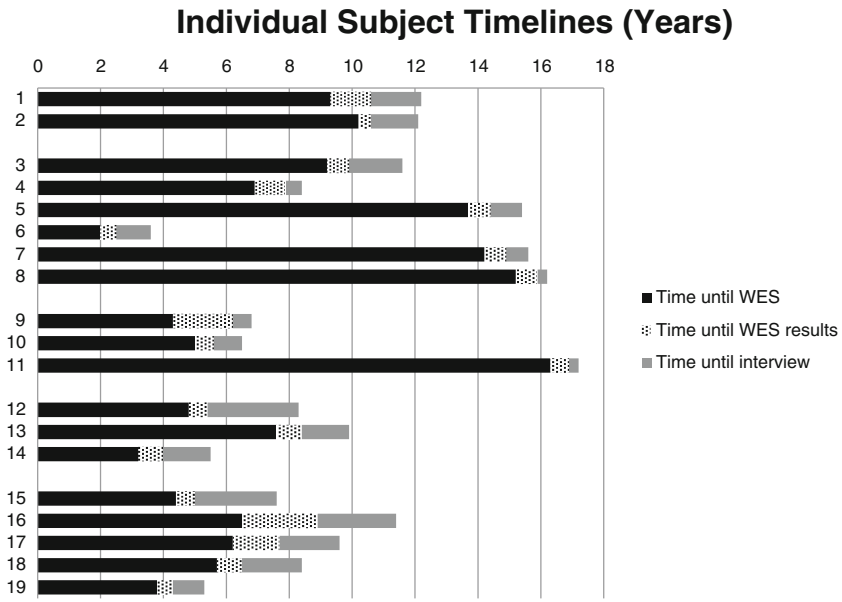

Fig. 1 The length of time, from birth to study interview for all 19 parents interviewed. The data are grouped by WES results. *Eleven of 19 parents received some type of diagnostic information from WES for their child.* Parents 1 &2 received a definite diagnosis; Parents 3–8 received a Likely diagnosis; Parents 9–11 received a Partial diagnosis. *Eight of 19 parents* (*12–19*) *did not receive any diagnostic information from WES for their child.* Parents 12–14 were informed that team was monitoring a VUS; Parents 15–19 were told there was no diagnosis or data from WES

> We had so much genetic testing on (my child). Years and years of testing and everything was inconclusive. So we were kind of hoping to find some sort of disorder or something, not necessarily for a name, but just for a treatment process. Respondent 7: Mother; WES Category: Likely Diagnosis
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> We were seeking answers as to why she was you know the way she was, but my biggest motivation for (my child) is life expectancy and that has always kind of been my thing because she is so fragile. Respondent 10: Mother; WES Category: Partial Diagnosis
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> I was hoping that if any information could be given to me it would also answer future questions as far as if I have more children. Will they have the same issues? If my child is able to marry and have children, will he pass it on to his children as well? Respondent 19: Mother; WES Category: No Diagnosis

Others (9/19) expressed concern that the WES would identify a primary diagnosis in their child which had significant life threatening complications and that was currently unknown to the family.

> We needed answers. But, there was also a part of you in the back of your mind, how does the saying go? What you do not know cannot help you or cannot hurt you. You know, what are they going to discover? What happens if we find out that (my child) is going to die in 12 months? How do we deal with this? You know? So there was a little bit of doubt, but really when you sit down and weigh up all the options, it was a no-brainer at the end of the day. Respondent 3: Father; WES Category: Likely Diagnosis
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> I guess that is my nervous part of it. Was them actually coming back and telling me she is 3 now and her life expectancy for what she has is 5 years old. Respondent 6: Mother; WES Category: Likely Diagnosis

Two parents expressed concerns about how the genetic information might be used by others.

> For instance, would the research that we were participating in lead to families choosing not to carry their babies to term or abort their babies because of particular genetic variants and would the research that we were involved in contribute to that? That would have been something that we would have really struggled with because of our ethical view on abortion and not wanting to be a part of that. Respondent 13: Father; WES Category: Possible Diagnosis

Almost half (9/19) of the parents commented that their child was unique and there was not another one like their child, and they hoped to be able to identify other families with the same disorder.

> You have an idea of what to expect. Yes, and go from there or (ask) other parents, if they had any strategies that worked with some of the behaviors. Respondent 17: Mother; WES Category: No Diagnosis

Understanding of WES

When asked to describe how WES is different from other genetic testing, all of the parents described key characteristics

of WES, and some noted that WES might find something because it is not a targeted test.

> Well, the other ones (other genetic testing done) were diagnostic specific. With the whole sequencing they totally take everything apart and they look at every little DNA and that opens up the door to see things that they cannot see with a specific test. Respondent 11: Mother; WES Category: Partial Diagnosis

> Many parents saw WES as just another blood test.

> I asked, okay what do you have to do? I mean I wanted to know what was involved. If there was any type of risk or pain obviously for her? We did not hesitate because we have been dealing with questions for many, many years. Respondent 5: Mother; WES Category: Likely Diagnosis

Although not always able to provide the name of a specific gene or variant, all parents were able to describe their results correctly, and could accurately report their genetic risk and the risk to their other children and/or family member(s).

> It was good to know that it was de novo, because otherwise we would have tested our boys to see if they would have been carriers. Respondent 1: Mother; WES Category: Definite diagnosis

Parents' responses also accurately reflected the clinical diagnostic category of their child's finding.

- **Definite Diagnosis.** *When I met with Dr. ***, she felt this was very likely this is what (my child) had. She felt that this was a very good fit. (My child) met a lot of the characteristics. And, you know when you look and read some of the research papers on it, it was like oh yes, they are talking about (my child). Respondent 1: Mother*

- **Likely Diagnosis.** (*My child's*) *situation is that she is the only one with this they have found. She is their only known case, so I guess it is not a cut and dry this is what she has, this is what we have seen with other children so this is what you can expect. Respondent 4: Mother*

- **Possible diagnosis (variant identified in a gene, name not provided to parent).** *They did find two; I guess it was two genomes that were, I do not even know how to phrase it exactly. They found two things that (my child) had, that my husband and I do not have. And so they did find something, but they do not have any names for them. Respondent 12: Mother*

When asked how they felt about the outcome of their child's WES 17/19 of the parents felt that the WES was beneficial (11/11 Definite diagnosis/Likely diagnosis/ Partial diagnosis; 2/3 Possible diagnosis; and 4/5 with No diagnosis).

> I am 100 % sure that us finding out about (our child's) diagnosis has been a positive thing. The information they have given us through the sequencing has changed our lives. We feel more confident in ourselves looking after (our child) knowing now that there is nothing untoward coming around the corner. Respondent 3: Father; WES Category: Likely Diagnosis

Several of the parents expressed positive feelings about the clinic process itself and how the clinical experience shaped their feelings about the WES, even if they did not get a diagnosis.

> The most positive was that they (genetics team) got to see (my child) as a real person and as a whole person and got to see her personality. Respondent 7: Mother; WES Category: Likely Diagnosis
> The knowledge that people are working on it and caring for kids like ours. There are communities of people that are committed to investing in caring for kids whose diagnoses are not as easy and then on our end, the major benefit was just knowing, that we, as parents, are continuing to do all that we can to care for (our child). Respondent 13: Father; WES Category: Possible Diagnosis

A few (3/19) parents, one with a Likely diagnosis and two with No diagnosis, commented on how the process had changed their own feelings about searching for a diagnosis and how they no longer felt they "had to have a diagnosis" to care for their children.

> It has proved to me that we are doing the right thing with (my child) because we are going to be on this path for a while. And so our best thing is to understand symptoms, behaviors, what she is doing, read them, and that is going to give us more information for her educational program or her medical program than her genetics right now. Like, that we were doing the right thing. So it is like confirmation that, even though we wanted an answer, the real answer was you have it all already. Respondent 16: Mother; WES Category: No Diagnosis

Five of the parents, whose children did not get a definitive finding from the WES felt testing was positive because it might help someone else's child in the future.

> Hopefully other children, you know, families would be able to care for their children in ways that we are not able to right now. Respondent 13: Father; WES Category: Possible Diagnosis

A few of those who were given a Possible diagnosis wanted to be given more specific information on the variants of uncertain significance that were being investigated further by functional studies/monitored in the literature, since they wanted to be able to explore these on their own.

> We would love to be more of a participant. We would like to be given more information so that we could (investigate it). Respondent 15: Mother; WES Category: No Diagnosis

And some parents voiced frustration and disappointment with waiting and not getting complete answers.

> The waiting. The waiting. And then for us, you know, obviously not really getting any answer. It is frustrating because it is like it has to be genetic. But, you know, when are they going to find it? Where are they going to find it? Respondent 9: Mother; WES Category: Partial diagnosis

Utilization of Findings

Parents were asked about the usefulness of the WES finding for their children and their families. For five with a Definite diagnosis or a Likely diagnosis, even if there was little known about the disorder, the parents felt it led to more focused medical management for their child:

> It is helpful because the spells that my child was having, breathing spells, shaking spells, now they have a name and we know what they are and it has kind of changed the course of medication she is taking for different things. (My child) is on a lot less now that we know some of the names of these things because we were trying to treat things that we did not know why they were happening. Respondent 10: Mother; WES Category: Partial diagnosis

If there was a diagnosis, some found answers, and the end of the search for a diagnosis.

> We did find answers in the end and it was beneficial. I mean we got answers for our sons and we got answers for my child. Respondent 1: Mother; WES Category: Definite diagnosis

The diagnosis also led to greater understanding of their child.

> Knowing that you know exactly this is a *** gene mutation issue. And even talking with them when they were able to tell us about certain signs or symptoms or things that we had seen in (my child). It has been you know it has been right on the money. I mean, "Have you seen type of behavior? Does (your child) have problems with this"? And we would say "yes, yes, yes, yes". Respondent 5: Mother; WES Category: Likely diagnosis

Three of those with either a Definite or a Likely diagnosis reported feeling frustrated, alone, or disappointed because the finding was rare and little information was known.

> Well, (my child) had a gene that has mutated and they have seen that gene mutated before but they have not seen it on this variant. And for the ones that have mutated they have never seen it in a child as old as (my child). So that is what makes (my child) a one of a kind right now. Respondent 11: Mother; WES Category: Partial diagnosis
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> I guess in a weird way that they could not call it something recognizable to the layperson. We were hoping to get something definitive. You know, something known, something maybe that someone else has that we could figure out if somebody else who has the same thing that is being treated effectively for it. We did find out that (my child) was sort of like someone else but nothing that we can definitely call X or treat with a medication. Respondent 8: Mother; WES Category: Likely diagnosis

The majority of the parents (11/19) across all diagnostic categories, expressed hope for more information either related to their child's finding or that more would be learned in the future and a finding would be reported.

> It gave us closure. Did it help us a lot right now? No. But when more information comes out over the next few years when more people are tested in the genetic areas then I feel when we have a larger pool of people at different age ranges, and then you are going to start to be able to find out okay, this is kind of the pattern we see with these children that carry this syndrome. Respondent 1: Mother; WES Category: Definite diagnosis
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> I guess you could classify us as optimistic realists. Realistic in the sense that we do not want to be disappointed but we are still hopeful enough to keep the faith that something is coming. But in the meantime we are

realistic enough to know that you cannot live your life waiting and you cannot just put everything on hold waiting on an answer. Respondent 19: Mother; WES Category: No diagnosis

For those with a diagnosis and a *de novo* finding, parents felt reassured for their other children and were able to reassure their siblings who were concerned.

Now, we already know that (my child) is the only one that can pass it down because (my child) is the only one that has it and that her brother unless he ends up with a child that ends up with a 1 in gazillion mutation there is no way that he is going to have a child like this. Respondent 2: Mother; WES Category: Definite diagnosis

Two parents reported that they had previously made the decision not to have any additional children because of risk concerns: one of those who now had a *de novo* diagnosis expressed regret that they did not have another child.

And if we would have known when we were younger we would have been able to have a third child and not be concerned. Respondent 5: Mother; WES Category: Likely diagnosis

Communication of WES Findings

Information about WES was openly discussed with the majority of families (their children and extended family, parents' sibling and grandparents) as well as with their child's physicians and therapists.

Oh yes, absolutely. We have great relationships with all of my family members and we have kept everyone from my grandparents down to our daughter, obviously at a 9-year-old level but she knows and my parents know. My brothers know. Really anybody that is in our circle of friends. Respondent 13: Father; WES Category: Possible diagnosis

A few (3) parents reported that the information was complex and that it was challenging when discussing with family and professionals.

We were very good at explaining, but some people trying to understand the DNA process just like my mom was like well it is just too bad that they cannot take that one DNA gene out. Well it is all throughout (my child's) system you know. Respondent 11: Mother; WES Category: Partial diagnosis

One parent talked about the difficulty in explaining why their child did not have a diagnosis.

The question we get quite often is "what is wrong with him?" and we say "gosh we do not know" and then we get the look of "well you should probably find out." That is what we get quite commonly. You know I say "we have been trying for the better part of six years now." Respondent 18: Father; WES Category: No diagnosis

Parents (9/19) reported that they wanted to connect to other families with the same diagnosis to learn from their experiences. For a few, the diagnosis allowed them to do this.

Through Facebook. There are 30 or 40 families now. The support group is there you know. We even had a **** awareness day earlier this month. The information we have been able to get has been through other families. Respondent 3: Father; WES Category: Likely diagnosis

For one mother the need to connect to other families led her to join a support group whose children had similar clinical features to her child, although her child did not have this diagnosis.

Adopt a syndrome if you are an orphan, and we love the fact that we can ask the parents like "Hey, what did you do about this" and "Hey, what did you do about that?" We are able to meet people that you know were 50 years old and that are diagnosed with *** syndrome. You know, it is such a wonderful thing to be able to see sort of the future or the possibilities of the future. Respondent 16: Mother; WES Catagory: No Diagnosis

Informational Needs

The majority of the parents felt that the information given to them as part of the consenting process and pretest genetic counseling adequately addressed their questions, and that the medical geneticists and genetic counselors provided information in a way that was understandable.

I think it was good. I think that there was a pretty thorough thing that I signed off on that gave a lot of information. It was a while ago now so I am not exactly sure but I feel like, yes, like I knew that we might not find out anything new. Respondent 17: Mother; WES Category: No diagnosis

Parents felt they needed to know: 1) potential outcomes; 2) what did the testing entail (i.e. What types of samples were needed and what would be expected from them and their children; 3) how long would testing take; and 4) what was required to prepare them for the potential outcomes (e.g., their expectations of the WES).

> Again, first of all, what kind of test it is, if it was invasive or not, if there could be any type of risk or danger. It was not a problem but that was one of the first questions that we asked when it was brought up and so I would say that is definitely important. And then probably second, do you want to know because there are some people out there that would rather go through life without knowing. So I think being able to realize, okay, as a family we are going to learn something here, we are going to get answers which is wonderful, but it might not be the answers we want so you have to also emotionally get yourself ready to hear that too. Respondent 5: Mother; WES Category: Likely diagnosis

One parent, who struggled with ethical concerns, felt that this was an important discussion.

> Well, I do not know for all families what would be important but for us, the incidentals were a discussion that was a significant discussion for us together and I felt they honored the difficulty of that decision in the conversation that they had with us. The ethical, you know, issues everybody has a bit of a different take on what they do, but just being able to have that discussion with family. Respondent 13: Father; WES Category: Possible diagnosis

Some expressed the need for closer follow-up.

> We went in and we had the first work-up appointment and then it is kind of like, we will let you know. Well then, I want to say we went maybe a year. I mean it was a really long time without knowing anything at all; so yes, having a follow-up appointment just to touch base. Respondent 9: Mother; WES Category: Partial diagnosis

> When families do get the diagnosis of these conditions they need some help. You got to counsel [them], you have to call them and say right you found out the other day that your daughter/son has got ***, how do you feel? You know and how can we support you? Respondent 3: Father; WES Category: Likely diagnosis

Parents' Advice

Advice to Other Families Parents were asked to provide advice to other families who are considering WES. The majority of parents felt very positive about the WES and all would recommend it to other families, and none regretted their own decision to pursue the WES. At the same time, parents also cautioned that it was important to ask questions and be aware that it may take longer to get information back than expected, that there may not be an answer, and even if a diagnosis is made, it may not be a complete answer.

> Ask all your questions up front. They are there, that is what they are there for if you have concerns, but understand the bottom line is you may not get your answers today or tomorrow, but your chances are so much higher to finding that answer. Respondent 1: Mother; WES Category: Definite diagnosis

Many of the parents advised families to be emotionally prepared to hear both the positive and negative findings.

> So that is what I am saying so first of all you need to know if you really want that information. And you need to have a plan on how you are going to process it and handle the information because they could be absolutely nothing or you could get one diagnosis; you could get many diagnosis from this, who knows? Respondent 11: Mother; WES Category: Partial Diagnosis

Advice to Medical Geneticists and Genetic Counselors Advice to medical geneticists and genetic counselors focused on establishing a relationship with the family built on respect, understanding, and communication.

> To keep being positive and to just keep in mind that, even though they are a doctor and even though they look at this tiny little human being from a scientific point of view, they are still people and it is still a very scary process. To just always keep in mind that if we, as the parent and child did not need their help, we would not be there. Respondent 19: Mother; WES Category: No diagnosis

> He (the medical geneticist) spent as much time as we needed to understand, to explain. He gave us time to process the information so we could come up with questions and of course we knew after as more questions would come you know all we had to do is contact (the genetic counselor) and she would pass it on to Dr. *** or if she could, answer it herself. So, I mean we always have that lifeline. Respondent 11: Mother; WES Category: Partial diagnosis

Parents also expressed the need for the professional to explore with the family their sense of how WES might help them to manage expectations for their child and to be emotionally prepared for the outcome.

> It may be good to tell families that this may not get you your answer, and may raise more questions than it answered. Respondent 9: Mother; WES Category: Partial diagnosis
> I would say just more simple terms as far as this may or may not help you with your course of treatment. I think parents are probably really dying to know what will it change after we get this result? What in my life or in my kid's life is going to change"? You know like do you think this will change your course of treatment? What did you expect? What do you think? You know that kind of thing. Respondent 8: Mother; WES Category: Likely diagnosis

A few recommended offering resources if some questions are outside the knowledge/specialty area of the genetics team.

> (Identify) People that you may want to talk to that are familiar with the medical ethics of this type of testing. That may be helpful so that, you know, the doctor does not have to have that conversation, but maybe they could refer to one or two people that have, you know, a fairly balanced and understanding of this research because I think families like us, they are just not sure exactly what they are getting into. Respondent 13: Father; WES Category: Possible Diagnosis
> I think if you found something really life-threatening about your child. If we had found out something, you know, that was so devastating. That we found out, like he might not live past the age of 10 kind of thing. Like maybe there would be counseling if you found out something like that. Respondent 12: Mother; WES Category: Possible Diagnosis

And to reassure the family that even without a diagnosis, they are likely already doing what they can.

> Somebody should say to the family like 97 % chance that you are already doing the right things. Respondent 16: Mother; WES Category: No diagnosis

Discussion

While WES has significant diagnostic potential in children with rare disorders it also poses new challenges for medical geneticists and genetic counselors, including the difficulty in determining the clinical relevance of the WES results, the frequent need for follow up of VUS, the possibility of secondary and incidental findings, and the effective communication of complex findings to families (Shashi et al., 2015a). Parents of children with rare disorders also face particular challenges with WES results, including being able to understand the process, the outcome, the certainty of the diagnosis, communicate the complex genetic and medical information to family members/providers, and use the information gained from the WES to the benefit of their families. These interrelated challenges that clinicians and parents encounter with WES may influence parental perceptions and ultimately the process of empowerment. Our study is the first to explore factors that would be expected to contribute to empowerment related to primary WES results in parents of children with undiagnosed disorders, such as their expectations, understanding of the results and utilization of the information. We additionally asked about further informational needs that they perceived as being important. The parents in this study were able to manage many of these challenges and overall, the perceptions of WES were positive, altruistic, and hopeful. They were able to manage expectations regarding the diagnostic potential of the WES, demonstrate understanding of the process of WES as well as the diagnostic outcome, communicate information regarding the outcome of the WES, utilize the information in the care of their children, and maintain hope and positive feelings about the future, all of which are important components that contribute to empowerment.

Key to the utilization of information is the ability to understand and personalize new information and to communicate that information to others (Dunst and Paget 1991). We believe that parental understanding of WES would be facilitated by the usage of well-defined clinical diagnostic categories (Shashi et al. 2015a), as findings are frequently unique (both gene and variant) and the clinical presentation is often not suggestive of a known, common genetic disorder. Parents in our study were able to accurately describe the diagnostic certainty of their child's WES findings and what was known about the specific disorder if a diagnosis had been made. For most, a diagnosis led to feelings of greater understanding of symptoms, a reduction in worry and that their child's medical care was more focused. Parents were also able to describe the mode of inheritance and reproductive risks associated with the diagnosed disorder for themselves, their children and other relatives. Although many of those who did not get a diagnosis expressed disappointment over the outcome, some felt that a negative WES had excluded a number of possibilities in their pursuit of a diagnosis or related genetic explanation. These findings highlight the important role of the clinical discussions and genetic counseling which occurred with families as part of this study, since these are critical to ensuring that communication between the clinicians and the parents is effective.

Parents had several informational needs. A few parents whose children did not get a diagnosis reported no longer

feeling the impetus to keep searching for one, suggesting that perhaps the process of WES is perceived as the ultimate test for their children, with few options beyond it. In contrast, some of the families with non-diagnostic WES expressed a desire to have all potential variants reported to them, even those that were of uncertain pathogenicity and were not in previously identified disease causing genes. This interest may attest to patients' desire for more information from genome sequencing as described in other reports (Angrist 2011; Fernandez et al. 2014). Parental involvement in pursuing their child's VUS has the potential to lead to a definitive diagnosis. A recent report of a family's efforts through social media to find additional children with abnormal variants in a candidate gene, thus confirming a new genetic disorder, attests to the power of parental advocacy (Enns et al. 2014; Lambertson et al. 2015; Might and Wilsey 2014). This desire for all genetic information led us to re-evaluate our initial protocol of not communicating variants/genes that are less than Definitive or Likely. These differing perspectives of WES should be explored further.

While the overall experience of WES was positive for the majority of parents, regardless of diagnostic outcome, we recognized some previously unidentified needs, which may have practice implications for WES. Importantly, we found that almost half of the parents articulated a worry that their child' primary diagnosis would be a disorder known to cause early death. Nonetheless, the hope that a diagnosis would be found and that they would be able to help their child outweighed this worry, and all went forward with the WES. While there has been much discussion about the potential identification of a life changing incidental or secondary findings, the fear that a primary diagnosis would be uncovered that is known to have a risk for shortened lifespan has not been previously identified. Parents also felt it was important for the genetics team to explore with families whether they were ready or if they really wanted the information that may be obtained from the WES and to discuss with them the possibility that a positive result may still result in unanswered questions. Consenting for WES typically focuses on the technical facts (i.e., different types of variants) and likelihood of a diagnosis; findings from these parents suggest that the emotional aspect of the potential outcomes of a diagnosis should be explored as part of the WES consenting process.

The diagnostic odyssey is the search for the knowledge and information that stems from that diagnosis and the search for this information is the driving force for many families with children with rare disorders. Additionally, the majority of parents in our study commented on the unique nature of their child and many sought to connect and learn from other families whose children had the same disorder. For a few of the families without a diagnosis, the WES became yet another disappointment and a barrier to the information they were seeking. However, interestingly, we also found that for some with Definite and Likely diagnoses, due to the unique variants that were found in genes causing very rare disorders, the finding from the WES was disappointing, with the realization that much still remained unknown and that there was little opportunity to connect to similar families. The diagnosis for these parents was "only a gene," leading to more questions and, for a few families, a sense of isolation. Because acquiring new knowledge and connecting to similar others are critical components to the process of empowerment (McConkie-Rosell and Sullivan 1999), for some, the process of WES has the potential to lessen feelings of empowerment, even when a diagnosis is made. Thus, it would be important in the pretest counseling to discuss that even if a diagnosis is secured, that the information parents are seeking may not exist.

We also found that post-test genetic counseling and clinical follow-up are critically important. The clinical relationship, based on trust, respect, and open communication was key to how many parents perceived the process of WES and parents both with and without reportable findings wanted closer contact with the clinicians. Parents wanted to know the next steps, and recommended that planned clinical follow-up should occur, so that as new information is learned it is discussed with them. Additionally, with respect to this parent request, it is possible that the status of variants previously reported as pathogenic or a VUS may change with new information learned about the gene and associated disorder/s. It is through follow up that the hope of securing new information can be met. Thus, for families with ultra-rare genetic disorders, our findings suggest that the "diagnostic odyssey" does not end with a diagnosis.

Limitations

This study has several limitations which should be considered when generalizing findings. The study was retrospective; therefore, it was not possible to assess expectations of the WES prior to outcome being reported. The length of time from when results were provided was also variable, extending up to two years, and time may have had an influence on how the process was perceived. Because the WES was done in a research setting, there was over an hour of pre-test genetic counseling, allowing for a detailed conversation about the process. However, in the clinical genetics clinic, such time is seldom available and it would be interesting in the future to compare the understanding of parents who are counseled under more stringent time constraints. Additionally, the cost of the WES was not considered as it was provided as part of the research study, and parents who seek to have WES through a research study may be different from those seen in a clinic setting. Since all the Definite/Likely diagnoses were due to *de novo* variants, whose inheritance patterns are straight-forward, we were unable to assess parental understanding of

autosomal dominant/recessive or X-linked inheritance and the associated recurrence risks nor their ability to communicate these risks to family members. We are aware that communicating genetic risk information in a family poses different challenges than offering reassurance, as would be the case with *de novo* findings (McConkie-Rosell et al. 2011; McConkie-Rosell et al. 1995) and this should be explored in a future study. Further, the majority of parents who participated in this study were well-educated, with at least some college education, and thus we could not assess parental perspectives across diverse educational backgrounds. We did not directly measure empowerment, as the purpose of this study was to first explore the factors, which influence empowerment.

Conclusion

This retrospective study, exploring key factors in the process of empowerment, in parents whose children have undiagnosed rare disorders, provides insight into how parents perceive the process of WES from the initial clinical evaluation through the provision and utilization of results. Our findings highlight the need for further study of the process of family empowerment in a clinical genetic setting so that WES can be optimized for families of children with undiagnosed rare disorders.

Compliance with Ethical Standards

Conflict of Interest Authors have no conflict of interests to disclose.

Human Studies and Informed Consent This study was reviewed and approved by the Duke Institutional Review Board and was carried out following the approved protocol. Protocol number: Pro00032301.

Animal Studies No animal studies were carried out by the authors for this article.

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