University of Cincinnati

Date: 3/8/2021

I, Jazmine A Vaz-Baker, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:

To continue or discontinue: Factors that motivate parents' testing decisions on the diagnostic odyssey after a non-diagnostic exome result

Student's name: **Jazmine A Vaz-Baker**

This work and its defense approved by:

Committee chair: Cynthia Prows, R.N., M.S.N.

Committee member: Loren Pena

Committee member: Elizabeth Ulm, M.S.

38189

To continue or discontinue: Factors that motivate parents' testing decisions on the diagnostic odyssey after a non-diagnostic exome result.

A Thesis submitted to the

Graduate School

of the University of Cincinnati

in the partial fulfillment of the

requirements for the degree of

Master of Science

In the Genetic Counseling Graduate Program

of the School of Medicine

By

Jazmine A. Vaz-Baker

B.S. Florida State University

May 2017

Committee Chair: Cynthia A. Prows, MSN, APRN

Research Advisory Committee: Loren Pena, MD, PhD Elizabeth Ulm, MS, LGC

Abstract

Introduction

Exome Sequencing (ES) is a powerful diagnostic tool in genomic medicine. ES has led to the identification of disease-causing variants that gave way to diagnoses, effectively ending the diagnostic odyssey for some families. However, many families remain undiagnosed after ES. Our study sought to investigate what motivates parents, after their child has received a non-diagnostic exome result, specifically in their decisions about further testing and how their perceptions of genomic testing factor into that decision.

Methods

The study population consisted of parents with children that have non-diagnostic exomes. We interviewed 10 parents, 9 mothers and 1 father by phone after obtaining informed consent electronically through REDCap. An interview guide was developed prior to recruitment and was modified throughout the interview process. The interviews were recorded and transcribed. The transcripts were entered into Atlas.ti 8, a qualitative data management program. Several á priori categories were used to help organize the data including knowledge, parent/provider relationship, management/treatment, reasons to pause/discontinue. All transcripts were coded by first author (FA) and a second coder separately. Any discrepancies were resolved through discussion and consensus.

Results

Three main topics of conversation emerged in our study. 1) Parents motivations for testing: which included the themes of planning for future and guiding medical management. 2) Aspects that modified parents testing decisions: which included the themes of parental state of mind, parent/provider

relationship, and invasive procedures. 3) Perceptions towards genomic testing: which included the themes of genetic testing being perceived as non-invasive and genetic testing being secondary.

Conclusion

Parents in this study are motivated to continue the diagnostic odyssey because of their desire to anticipate and plan for the child's future medical needs. This motivation stems from the parents' perception that genomic testing can provide prognostic information coupled with the parents perceived association of genetic testing and non-invasiveness. Parents understand that a diagnosis may not come immediately but believe that when one is finally available it will provide them with anticipatory guidance for their child. It is important for clinicians to know that parents want to feel validated about their management decisions. Clinicians should take care to assure parents that even without a diagnosis, they are doing all they can to meet their child's needs at this time. Additional studies on why parents decide to discontinue or pause the diagnostic odyssey are needed to better assess these families concerns in clinic.

Key Words: diagnostic odyssey, exome sequencing, non-diagnostic exome result, parent perceptions, undiagnosed, pediatric probands, qualitative interviews, genetic testing

(This page was intentionally left blank.)

Acknowledgments

I would like to thank the following contributors for their guidance and support:

Loren Pena, MD, PhD, Division of Human Genetics, Cincinnati Children's Hospital, Cincinnati, OH

Elizabeth Ulm, MS, LGC, Division of Human Genetics, Cincinnati Children's Hospital, Cincinnati, OH

Cynthia A. Prows, MSN, APRN, Division of Human Genetics, Cincinnati Children's Hospital, Cincinnati, OH

This study was conducted when the first author was enrolled in the Genetic Counseling Graduate Program, College of Medicine, University of Cincinnati and Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Table of Contents

List of Tables

Introduction

Exome Sequencing (ES) has helped to revolutionize diagnostic medicine and the field of medical genetics (Baldridge et al., 2017). The utility of ES has been demonstrated in the clinic and research setting through the identification of disease-causing genes and various genetic disorders. However, despite the diagnostic utility of exome sequencing, at least 50% of people remain undiagnosed after ES (Marshall et al., 2019; McConkie-Rosell et al., 2018; Rosell et al., 2016). At this point, many families are tasked with making the choice whether to continue or discontinue the diagnostic odyssey for their child, a long and tiresome process of evaluations and extensive genetic testing to obtain a diagnosis.

Motivations for Testing

Recently we have learned some of the motivations for why families choose to pursue diagnostic testing. One of the primary reasons' parents embark on the diagnostic odyssey is to establish a genetic diagnosis for their child. For some parents, the genetic diagnosis is less about having a name or a label of a condition and more about having a diagnosis for healthcare management purposes (Blosser, 2014). For these families, changes in clinical care may result in an addition or discontinuation of therapy, more targeted testing, or preventive screening. Harris et al. noted that parents of children with developmental disorders felt motivated to seek additional testing to gain a deeper understanding of what their child was going through. Parents felt that having a diagnosis would allow them to manage their expectations and provide their child with a better life (Harris et al., 2012). Other families have stated that a desire to build community with those that share a common experience and altruistic aims also motivated them to seek out a diagnosis (Rosell et al., 2016; Sapp et al., 2014).

While the desire for the potential benefits of targeted treatment and community support pushes some parents to continue testing, the diagnostic odyssey itself can be emotionally taxing for families and probands. Parents of children who remain undiagnosed have shown clinical symptoms of anxiety,

depression, and uncertainty (McConkie-Rosell et al., 2018; Yanes et al., 2017). Parents who desire a name/label, especially when trying to acquire services for their child, noted the frustration that comes with having to validate their child's illness to providers or others. Overall, these same parents had a decreased sense of hope, perceived self-efficacy and support (Yanes et al., 2017).

The parent-provider relationship forged during the diagnostic odyssey continues to play a crucial role in how families navigate the odyssey, process exome findings, and approach next steps. The medical geneticists and genetic counselors who work with the families going through the diagnostic odyssey, play a huge role in addressing their concerns and emotional needs. Rosell et al., in qualitative interviews with parents of undiagnosed children, state that pretest counseling adequately addressed parents' concerns, while posttest genetic counseling allowed them the opportunity to learn new information and plan their next steps (Rosell et al., 2016).

Reasons for Decline

Although some undiagnosed families choose to continue their pursuit for a diagnosis through genomic testing, other families choose to decline further testing. Amendola et al., aggregated data from seven clinic sites participating in the study to explore reasons participants declined participation in genomic sequencing research. For the sites that recruited pediatric patients some of the top reasons listed for declined participation included: privacy/discrimination, time commitment or study logistics, feeling overwhelmed, and psychological impact (Amendola et al., 2018). At one site, recruiting patients with cancer diagnoses, parents were given the option to enroll their child in a clinical tumor and germline exome sequencing study. About 10% of families chose to decline enrollment. When asked about their reasons for declining, parents stated feeling overwhelmed by their child's recent diagnosis (Scollon et al., 2014). In the clinical setting, motivation to pursue additional testing may be heavily impacted by

feeling overwhelmed or losing control. For these families services to help them address their emotions may be helpful.

Exome Re-analysis

The diagnostic yield for ES can vary from 24% to 40%, depending on the clinical indication (Arts et al., 2019, Demos et al., 2019, Farwell et al., 2015, Retterer et al. 2015, Romasko et al., 2020). However, with the reputation of ES being framed as the "best technology" that genomic medicine has to offer, a sentiment has been created among some parents that a nondiagnostic exome result is the end of the line. A second chance for these families has arrived through exome re-analysis, which can include realignment, new analysis pipelines, and new disease gene identification. This has been made possible due to the ever-expanding knowledge of the human genome. Diagnoses can now be made by re-classifying previous variants of unknown significance through functional studies or identifying other patients with similar variants and deleterious effects. Beyond exome-reanalysis there are options available for families still seeking a diagnosis, including re-testing (Vears et al., 2019). As genomic testing technology continues to evolve, clinical whole genome sequencing is also becoming an option for patients who remained undiagnosed after ES.

The following study aims to identify and describe the motivators that influence parents' testing decisions about whether to continue or discontinue diagnostic genetic testing after receiving a non-diagnostic exome result. Previous qualitative studies of this nature have explored parents' emotions and perceptions prior to their children undergoing ES. This study exclusively explores parents of undiagnosed patients' decision-making processes going forward after a non-diagnostic exome in the clinical setting. Results from this study will add to the knowledge of work on the impact of the diagnostic odyssey and how parent perceptions of genomic testing can influence their decision making about future testing. This knowledge can help promote patient informed decision making, inform providers on how to

educate patients about the benefits and limitation of genomic testing and help set expectations about the information further genomic testing can provide.

Methods

Sample

The data in this study was collected from participants who were recruited from Cincinnati Children's Hospital Medical Center Genetics Clinics. The study was reviewed and classified as exempt by the Cincinnati Children's Hospital Medical Center Institutional Review Board. The participants for the study were parents of children with non-diagnostic exome results, which included results with no reported variants or with variants of uncertain significance (VUS). Inclusion and exclusion criteria are outlined below:

Inclusion criteria for participants includes the following: patient/families who have had previous genomic testing with negative or inconclusive results; patients/families with access to a phone; patient/families who are English-speaking.

Exclusion criteria includes the following: parents of patients who have a definitive diagnosis.

Parents were initially contacted by phone by a genetic counselor involved in their care to gauge the parent's interest in participation. Parent's contact information (telephone number or email) was passed along to the first author (FA) who contacted the parents via email or phone to schedule a date and time for the interview. In the beginning of the study, scheduling took place through email and interviews took place through a remote conference app (Skype for Business). After several participants did not respond to the email recruitment and failed to join for their online scheduled interview, the decision was made to switch recruitment, scheduling, and interviewing via the phone only for the remainder of the study.

This method switch proved to be more convenient for parents and more successful in terms of recruitment and interview follow through.

Measures

Semi-structured telephone interviews were used to collect the data. Prior to the start of the interview, informed consent was obtained electronically through REDCap. The consent form was verbally reviewed with the parents and sent to them via email through REDCap for them to digitally sign. Following the informed consent, parents received a brief demographic survey that asked about their sex, age, race/ethnicity, educational level, and caregiver status [primary or secondary] in relation to their child. The demographic survey also included questions about their child including sex, age, race/ethnicity, and the year their child's non-diagnostic exome was obtained. The demographic survey process was expanded to include verbal collection when the interviewing process moved exclusively to the phone. Due to technological issues, one paper consent was collected from a participant via mail.

The telephone interviews lasted about 40 minutes. The semi-structured interview guide was developed and revised throughout the study by the research team. The semi-structured interview style allowed the first author to guide the interview, but also allowed the parents to speak freely to capture the most authentic thoughts regarding the diagnostic odyssey and what factors motivate their choice to continue or discontinue testing. The interview questions centered around three domains: parent's experience with the diagnostic odyssey, perceptions towards testing and its utility in their child's diagnostic odyssey, and their current decision and factors that motivate or (potentially) hinder their choice (see Appendix 1/1a for interview guide).

Data Analysis/Coding Methods

Interviews were digitally transcribed using Descript, a paid transcription service. Completed transcripts were compared to the original audio recordings to correct for errors made in the transcription process. Data analysis began with the FA creating memos of each transcript that could be used to create inductive codes and elicit themes. Each transcript underwent two coding cycles. The first coding focused on creating in vivo, descriptive, and causal codes that described or were associated with specific quotes/statements from the transcripts. Then, the first author and second coder coded all transcripts independently and any discrepancies were discussed to achieve consensus. At this point codes with indistinguishable meanings were deleted and/or merged, as necessary. If consensus could not be reached the study team was consulted. The second cycle of coding called for codes with similar meaning/messages to be grouped into categories. Results themes were discussed and defined by the first coder and the research study team.

Results

Response Rate

A total of 18 parents were contacted and offered participation in the study. Out of the 18 participants initially contacted, 4 parents declined participation at initial contact. 14 parents stated they were interested and were contacted by the first author to schedule a date and time for the informed consent and interview to take place. Out of 14 parents that stated their interest, 10 were consented and interviewed. The remaining 4 parents were either unable to be reached or declined participation at the second contact. Recruitment was discontinued due to data saturation.

Demographics

We interviewed a total of 10 parents. Most of the participants were the mother of the proband, with one participant being the father of the proband. Majority of the parents were between 40 and 50 years of age and all interviewees described themselves as their child's primary caregiver. Most of the parents described themselves as being of a Caucasian non-Hispanic racial/ethnic background. Parents' education levels ranged from high school education to a MD, PhD, or JD degree. Details of the demographics can be found in Table 1. While specific information about proband phenotypes was not formally collected as part of the study, throughout the interviews parents described features such as limb and hand anomalies (polydactyly, arthrogryposis, club foot), tracheoesophageal fistula, a clinical diagnosis of Diamond Blackfan Anemia, Cerebral Palsy, congenital anomalies (brain and heart defects), global developmental delay, blindness, hypotonia, and dysmorphic craniofacial features.

Motivations influencing parents' decision about testing.

Planning and Preparing for the Future

Most parents (9/10) expressed a desire to know or a genuine curiosity to learn the cause of the child's symptoms.

"It would definitely be reassuring. We still, I mean, think we still want to know [and] the more time it takes us to get an answer. I think that's for me, at least gonna just make me keep more and more curious of, you know, the answer's gotta be out there somewhere." Participant 2; Mother

Over half of parents (6/10) felt motivated to take active steps in their child's health. Parents described research and finding support groups as way they could actively participate in the diagnostic odyssey.

"Yeah, I think it will be helpful because I would research the hell out of it and I would find a support group and I can't do any of that. So, um, and I'm somebody who would do my homework and do everything I'm supposed to do. And I can't do any of that." Participant 9; Mother

When parents were asked why it is important to get a diagnosis for their child or to envision what the end of the diagnostic odyssey looked like for their child and/or family, many parents spoke about setting expectations. The majority of parents (7/10) described wanting an outline as to what their child's future will look like. They want to know what goals will be attainable for their child in order plan/prepare for things that may not be possible.

"What potential risks he has and then if he does have genetic condition knowing what can help treat it or better manage symptoms, what's coming down the line?" Participant 10; Mother

"When you don't even know if they're gonna be regressive or, um, you know, if he's going to get better, he's going to get worse or stay the same. You don't know anything, we just treat symptoms. So, if we had a diagnosis, we could say, okay, this is what, you know, at some point, this is what we're expecting. And you can just prepare." Participant 5; Mother

Some parents (4/10) expressed a desire for a diagnosis in order to connect with other families in similar sitautions.

"What is it gonna look like for her and maybe even reaching out to other families and seeing a similar situation that may have a similar or the same diagnosis and learning from each other. And I mean, Sometimes it's very lonely in this special needs world." Participant 4; Mother

A few parents (3/10) stated that they hope to obtain a genetic diagnosis for family planning purposes.

"Well, so, I mean, he's our first child, we don't plan for him to be our only child. Um, so there's that piece of it." Participant 10; Mother

A few of parents (3/10) expressed altruistic views about their child's diagnostic odyssey.

"It's not going to help her, it's going to help every other person that he has to kid like [child's name]. There's nothing we can do if they come out with oh, she got this, but it's not going to help her. You Know, but it might help another person." Participant 3

Establishing and Guiding Medical Management

Some parents (4/10) felt that a genetic diagnosis or a "name" is the key part to establishing a management plan for their child. What constituted as management varied amongst the parents, but could include surgical interventions, therapies, and medications.

"We felt like there probably should be a piece that would tie it all together and then also help us to be better prepared and equipped in treatment options for her and prognosis." Participant 8

"Like ideally I think what would happen is that we could find something that there is a change and there's knowledge of that change and information on how to better treat his symptoms or manage his care." Participant 10

"So, I mean, there might be a lot of stuff out there for him just as a special needs child, you know, that he could do, but we don't know because you know, you only find that out if you have a diagnosis." Participant 5

Most parents (6/10) expressed some sort of concern with their child's current management plan and alluding to that being a reason why they were still motivated to continue their child's diagnostic odyssey.

Some parents have already embarked on a management plan based on their child's symptoms and hope that a genetic diagnosis can help adjust that plan. While the management plan may be working, 4 out of 10, parents state a need to see additional improvement.

"I was concerned because I think these undiagnosed conditions are impacting her medical treatment. And she's had like 40, some odd surgeries in two years. And so my hope was if we can just figure out something, we can actually modify the treatment that she needs and we can potentially keep her in school and keep her a little healthier and maybe not have to have surgeries." Participant 1; Mother

Parents state (4/10) that they have doubts/reservations about the management decisions they have made thus far in the diagnostic odyssey. Parents alluded to adverse side effects, not starting a treatment or therapy sooner, or wishing they had made a different management decision altogether.

"We've always had that concern. You know, if it came out genetically that she had, you know, something like X, Y, and Z, and then, Oh, if we would have just given her this, it would've went away, then that's a shame." Participant 7; Father

Aspects that Modify parents' motivation to continue the diagnostic odyssey.

State of Mind

All parents in our study state that they are pushing forward and are willing to keep trying and pursue additional testing options if they are offered to them.

"And so I don't want to just sit by and watch her feel terrible and miss life and not have fun. And so I'll keep trucking along. So we can maybe find something that, you know, kind of at least manages those things a little better or makes it more tolerable. I don't think it will ever go away. I don't have any visions that all of these problems will just vanish, but if we can have a treatment plan and effective treatment plan, we'll keep trucking along, I guess."

Half of the parents (5/10) state they do not expect different results.

Like, whether or not I think that they're going to find something this next time around I don't necessarily know that I'm confident that they're gonna find anything different, but I guess I don't want to close the door on the possibility that they could." Participant 10; Mother

Some parents (3/10) remain hopeful that an answer will come in time.

"It would definitely be reassuring. We still, I mean I think we still want to know what's [happening] the more times it takes us to get an answer. I think that for me, [it's] gonna just make me more and more curious [that] the answer's gotta be out there somewhere." Participant 2; Mother

Most parents (7/10) acknowledge that a diagnosis may not be possible and accept that possibility.

"If the end of her diagnosis were today, I don't know at the end of the journey looks like, or what's in store for us. But if the end of the journey were today, I'm fine with it. You know, we're going to keep on living our life and trying to help [child's name] any way we can. And it's to us it's yes, we would love answers, but also if we don't have them, it's not the end of the world… I think most people realize this, but a diagnosis doesn't define my child. A diagnosis just helps me equip my child. It's not about the diagnosis. It's about how we as parents can help our children and how the diagnosis benefits the life of my child. It's not about the diagnosis." Participant 4; Mother

When asked to consider circumstances that may cause them to change their decisions about pursuing further testing a few parents (2/10) state that mental exhaustion would contribute to them choosing to discontinue or pausing the diagnosis odyssey.

"I guess I think the big thing would be a kind of mental exhaustion. Cause I know I [00:41:00] said that we're going to test again now. And if this time doesn't get the answer, I would be willing to do it again. But then there's the question, you know, at some point it would probably get exhausting mentally and

emotionally to keep over and over getting our hopes up that we're going to have an answer and then having, well, we didn't find anything new or, you know, once again we found a mutation, but it doesn't explain anything." Participant 2; Mother

Invasive Procedures

Most parents (7/10) state that they would have to have further discussion about or reconsider the diagnostic odyssey if they had to put their children through invasive or extensive procedures for diagnostic purposes. Parents generally view blood draws as non-invasive procedures.

"I guess if it's a more invasive procedure than a blood draw we would strongly consider drawing the line. His symptoms could match prematurity, that they always see with micro premies of his size but that doesn't mean that he was born so early... [inaudiable]... so I think without good understanding, or promising lead or promising area to look into, I think we probably would draw the line at testing beyond a blood draw right now." Participant 10; Mother

Parent/Provider Relationship

Majority of the parents (7/10) discuss that healthcare providers are uncertain about how to approach their medical needs. Parents state that providers are often "guessing" on what tests/treatments will and will not work.

"I mean, so we just don't have an understanding why it leaves us open to, is this the right treatment? Is there a different treatment because it wasn't genetically tied, right? So we continue with the type of treatment based on clinical diagnosis, but we feel that if it was genetically diagnosed than it would be, confirmed instead of a doctor's theory." Participant 7; Father

One parent expressed her frustration and confusion at the uncertainty.

"But, I mean, it just gets more confusing and more frustrating when you actually find out that uncertainty. That they're not a hundred percent as to what's going on it gets frustrating to say, hey, they don't know what it is or they don't know they haven't found nothing." Participant 6; Mother

Despite the uncertainty one parent stated she still has trust in child's medical providers.

"We're just guessing. And it's kind of hard to feel confident. I mean, I trust her team. I trust the [specialist], but they're guessing, and I know they're guessing, and they acknowledge that they are hopeful that it will work." Participant 1; Mother

For one parent, the "guessing" and lack of guidance and a diagnosis makes them feel like they must take on stress of communicating their child's needs to healthcare providers.

"I feel like sometimes when you have a name, it shifts the responsibility of education to the medical professional and off of you, because it's always on me." Participant 1; Mother

Considering the quote above, most parents (6/10) look to their child's healthcare provider to guide the diagnostic odyssey. Parents express that without the guidance of the provider they would not know what/if additional testing options are available or what steps to take regarding treatment or therapies.

"I'm not actively pursuing it. I kind of have just left it in the hands of the geneticist because I don't even know what that would look like if I wanted to. So, you know, I have faith in them that they are pursuing it or, you know, they're at a place where they say, this is the end of the road, you know, until further notice. Which they have said, they've told us, like, this is kind of the end of it, but then they've come back and said, well, you know, we want to try this. So I just leave it in the hands of the geneticist. I trust her she's I mean, she seemed like she has [child's name] best interest in mind." Participant 5; Mother

A few parents (3/10) shared they appreciated that their child's health care provider was still interested in treating their child.

"This sounds kind of weird, but they're still intrigued by [child's name]. They're still interested in her and still trying to figure her out. I'm glad that certain traits is hard because I feel like if they find her, I don't know, interesting or a challenge they're going to, they're going to keep researching versus, and like, there are some times when she's healthier than a lot of kiddos, but then she doesn't make it to the top of the pile. I don't think anybody's lost interest in her, I guess it's the whole thing. And I think that people are still trying to figure it out. Um, so I would, I feel like that's encouraging." Participant 9

Parents shared the positive experiences they have had with various providers throughout their child's diagnostic odyssey. The positive experiences could stem from providers offering guidance, support, or explaining complex genetics information in a way that was understandable. These positive provider experiences foster hope and trust in parents.

"So she's, you know, been there from the beginning and, and guided us in ways that, you know, we consider she would guide her own daughter… We have become very close to Dr. XXX and we're very lucky to have this situation. This is, I would say a rare situation where we have really leaned on this individual for support and we trust, we trust her over anybody else over her pediatrician over, you know, if we need help, we call her." Participant 7; Father

Negative provider experiences have discouraged and taken away hope from parents. Parents have described experiences with past providers who were perceived as pessimistic or discouraging when it came to the diagnostic odyssey. Parents would feel discouraged from pursuing additional answers and would usually seek out a new provider.

"Some of the other specialists that we have seen, we had one specialist, the pediatric specialist tell us that because of our child or our daughter's conditions, it wasn't worth pursuing options as far as figuring out what was going on. So, it was just really nice to talk to somebody that helped us have hope again." Participant 4; Mother

Fear

When asked about what fears, if any, they have about pursuing the diagnostic odyssey parents shared fears of a diagnosis with a limited life span or developmental regression. However, half of the parents stated that they would not let their fears deter them from continuing the diagnostic odyssey.

"I think at this point now I'm in the if there's more options, let's find out. Let's keep looking because I think, I mean, trying to keep faith with every time she makes more progress that it's going to stick. You know, there is no reason in particular to believe that she's not going to go on to live for relatively long, you know, that she's not gonna live to be 30 or 40 or 50 or 60. So not getting the answer the first time now. It makes me really want to know." Participant 2; Mother

"Yeah. I felt from the beginning, like I'm the adult, like, I'm the one, I'm the one that needs to put my big girl pants on and do the hard thing. Like, so I will get over it, whatever she needs, I can handle it because I'm the adult and she's not." Participant 8; Mother

Parents acknowledge the fear, but they do not dwell on it.

"A result of shortened life expectancy would help us prepare and help our other children, prepare for that type of situation. But, I'm not going to live in fear of that. It is what it is and it's out of my control. So I don't have to worry about it. That's my perspective anyway." Participant 4; Mother

"I don't have no fear, I guess. I mean, I worry, you know about them, but I'm not going to fear over anything bad. [The] outcome of an answer or whatever the diagnosis, I'm not gonna fear that. [Start] freaking out and making a mountain out of a molehill type situation, I guess. I don't want to fear it. That's my thing. I don't want to fear." Participant 6; Mother

Some parents have stated that while receiving a diagnosis of life limiting diseases would be difficult, they would rather be aware (than unaware) so they can make the most of the time they have with their child.

"One of the fears is that maybe she does have a condition that drastically shortened for life expectancy. Um, that's um, living in fear of that result. I mean, I have friends that have adopted terminally ill children and I guess, like, I want to live each day as if it's my last and if we get that type of result, then that would give us more incentive to soak up and cherish every moment." Participant 4; Mother

"So if something were to indicate that we'd be moving in the opposite direction, that would be really hard. But at the same time, I would want to know that because you want to take advantage of, of the days and the time that you have." Participant 8; Mother

Perceptions of Genetic testing

Throughout the interviews, parents expressed their perceptions about genetic testing that contributed to their decision to continue the diagnostic odyssey.

Half of parents (5/10) referred to genetic testing as a "blood-draw". Parents alluded to genetic testing as a non-invasive route to diagnosis and not as concerning as more invasive or extensive procedures. They were willing to pursue additional blood draws if necessary, for additional genetic testing.

"We're pulling blood already. We have to test her blood, that doesn't concern us." Participant 7; Father

"So far there's not been any testing that has had a detrimental impact on her. The blood draws we've always waited for blood draw until she has to do another one for something else, but we can do them together. Honestly it really hasn't been a big deal. It's been pretty easy." Participant 8; Mother

Parents shared their desire to avoid more invasive routes like bone marrow biopsy, surgery, or scoping procedures. Some detailed stories about negative experiences with past invasive procedures and difficult decisions they had to make.

"And we've, we've made decisions before where we put things on the back burner that we knew we weren't getting anything out of, or it was just too much for our daughter with too many different things going on at the same time. I mean, there were occasions when she was seeing so many different specialists, a couple of [00:28:00] years ago that we backed down out some, because it just, it was just too much. There have been occasions where we've pushed back tests, where she had to be put under anesthesia. Cause we felt like, you know, we didn't, we didn't want her to be put under, you know, frequently as she was." Participant 9; Mother

Parents were asked their feelings upon receiving the news their child's nondiagnostic exome results. There is a belief amongst parents that genetic testing will be able to "predict the future" or give a "definitive answer" as to what to expect for their child. Due to this perception, when parents received a nondiagnostic test result they expressed a range of emotions from indifference to disappointment.

"I mean I was kind of confused as to like, you know, my thought was genetics - like they know everything - because that was my thought. Like because they've tore apart everything, the blood, that they receive. And like, Everything in this world has an answer you know and it's all related to genes, but I just assumed that it was going to be an easy peasy, you know, just have an answer and be done." Participant 6; Mother

For parents of children more complex medical concerns, pursuing a genetics route to diagnosis was a secondary concern compared to dealing with their child's other health concerns.

Although parents are interested in the role that genetics play in their child's symptoms, they state that dealing with their child's other health concerns are more of a priority.

" I didn't really think about [genetic test results] at all because we had, you know, that was like, a backburner question. And we had so many other things going on health wise, but you know, we just had to keep moving forward with the other stuff." Participant 5; Mother

Parents describe the difficulties they face with other specialties especially around coordinating care if the family is not local. Genetic testing can often be analyzed, discussed, and coordinated in way that does not require the family to rearrange their daily routine.

"Yeah, I would say genetics hasn't been a problem at all for us. Our insurance is taking care of it, so to date genetics, hasn't caused us in the real challenges. Now [child's name] eyes, that's a different matter entirely… we live about five hours outside of Cincinnati and we were going, I think last year… we were going back and forth to Cincinnati every other day… We value spending time with all of our children...[To go to] a doctor's appointment several times a week that, that eats up a lot of family time. Um, it affects the finances that causes stress. That's not fun. Genetics hasn't done that to us. It's been trying to keep up with [child's name] eyes. That's what made us worn out." Participant 4; Mother

Discussion

In more recent years ES has proven itself to be powerful diagnostic tool in genomic medicine. For many families it has led to the identification of disease-causing variants that gave way to diagnosis, effectively ending those families' diagnostic odysseys. However, for other families the odyssey goes on, as about half of people remained undiagnosed after ES. Our study sought to investigate what motivates parents, after their child has received a nondiagnostic exome result, specifically in their decisions about further testing and how their perceptions of genomic testing factor into that decision. In this study non-diagnostic results were defined as negative or uncertain/inconclusive results. All the parents in our study classified themselves as continuing the diagnostic odyssey.

In this study, parents were motivated to pursue additional testing because they expected that a genetic diagnosis would help establish or guide their child's medical management. Aspects that impacted parents' motivation, referred to in this study as "modifiers" included the non-invasive nature of genetic testing, which encouraged parents to continue, considering most parents stated that an invasive test/procedure for diagnostic purposes would discourage them or cause them to reconsider continuing testing. The parents' state of mind modified their outlook on the diagnostic odyssey where parents expressed feelings ranging from optimism to indifference. The parent provider relationship played a crucial role. Parents expressed feeling more comfortable continuing the diagnostic odyssey with providers who fostered hope. Fears of life-limiting diagnoses were acknowledged by many of the parents but was not deemed to be a modifier of their motivation to continue the odyssey. The general perceptions of genomic testing shared by parents in the study included the non-invasive nature of genetic testing, accessibility of testing, and the ability for genetic diagnosis to be pursued while addressing more acute or long-term symptoms. The perception that a genetic diagnosis will be able to provide prognostic information parents can use to anticipate long term outcomes for their child relates back to their main motivations to continue the odyssey.

Parents in our study are motivated by a deep desire for knowledge so that they can take active steps to provide the best care for the child. Nearly all the parents expressed a desire for this knowledge. For many parents, the lack of diagnosis is a direct hindrance in their ability to set expectations for their child's future. Parents stated that they wanted to be able to set expectations for their child developmentally, academically, and therapeutically. For these parents, the struggle presents in the difficulty of planning for something when you do not know what to expect down the road. There is a belief among many families in this situation that if genetic testing leads to a diagnosis, prognostic information will be available to serve as a guide to help them navigate their child future health care needs (Harris et al., 2012). This speaks to the larger concept of diagnostic versus prognostic ability.

While parents respect that the information and process needed to create complex diagnostic tools such as exome takes time and some allude to accepting that a diagnosis for their child may take time, the belief that once a diagnosis is found providers will be able to give them an outline of expectations remains (Mollison et al., 2019). This reinforces the need for thorough pretest counseling to help parents set realistic expectations for the diagnostic odyssey and the medical utility of genomic sequencing, which continues to be a challenge, which was also noted by Wynn et al., 2018. As the field of genomics rapidly expands, the discovery of new genetic conditions continues to grow, many of them rare and only seen in a few reported cases in literature. It is imperative that parents understand that even with a diagnosis the outline of expectations they seek may not yet be possible.

There was a strong emphasis on establishing/guiding medical management throughout our study, which was similar to findings in previous qualitative studies on the parental perspectives of the diagnostic odyssey (Rosell et al., 2016; Blosser, 2014). The term was used in different contexts depending on the participant, but encompassed surgical interventions, therapies, medications, and evaluations. For children without an established management plan, their parents look to genetics to provide a diagnosis that will outline any therapies, surgeries, medical devices their child may require in the future. For the other families that have already embarked on a medical management plan, parents report making decisions based on clinical information. These parents often express doubt in their decisions especially when the interventions are not alleviating or improving their child's symptoms. That is to say that parents do not express doubt in the services/interventions their child is being offered, but the effectiveness of those services without the context of a diagnosis. This gives parents the feeling that they are taking "stabs in the dark" as to what is beneficial for their child's health.

The non-invasive nature of genetic testing proved to be a strong modifier of parental motivation when deciding to continue testing or not and has not been noted explicitly in other studies. For parents of children with more complex medical needs, the diagnostic odyssey can be stressful due to the

evaluations and/or invasive procedures needed to ensure their child's health. While some of these procedures are minor, other procedures may require anesthesia, scoping, and extensive imaging on a routine basis (and often done at medical centers that require families to travel) that can be quite distressing for the children and their parents (Carmichael et al., 2014). Parents stated a desire to avoid invasive procedures if possible, but if that outcome were unavoidable, at least knowing ahead of time would allow them time to prepare. However, other parents mentioned stepping away from these avenues to minimize these experiences for their child, which some parents reflected on negatively. One parent in our study discussed starting their child on medication based on her clinical diagnosis that later was revealed to have a toxic effect on her health. The parent expressed regret about the decision and wondered if they would have made a different decision if they had a genetic diagnosis. Despite this, parents do not hold these sentiments against the providers, but internalize them. Parents in this position are hoping that a genetic diagnosis will validate their decision to pursue these management options, especially after struggling with other specialties.

For parents who have received nondiagnostic results, the lack of clarity on what the results mean for their child's future can bring about feelings of confusion, disappointment, and frustration especially for parents who are information seekers. These wide range of emotions are consistent with findings in other studies (Rosell et al., 2016; Werner-Lin et al., 2018). For these parents, information about a diagnosis would spawn self-guided research that parents state helps them set their own expectations (outside of provider's opinion) and locate support groups where they hope to connect with parents who share similar experiences. Some parents express indifference at the nondiagnostic results due to past experiences with nondiagnostic genetic testing. These parents stated that lack of results was not surprising, and some admitted to having tempered expectations for the results of any future testing. To receive ES, the parents in our study received pre-test counseling where the logistics of the test and possible outcomes are discussed. Parents expressed an understanding for the potential of nondiagnostic

results but mentioned they would readily agree to any additional testing or reanalysis offered by providers despite past nondiagnostic results. This is referred to in our study as “pushing forward” (additional definition of other codes provided in Appendix 2). The idea of “pushing forward” was shared among all parents, but the acceptance of not finding a diagnosis and tempered expectations were also shared amongst some of those same parents, while explicit expressions of hope/optimism were noted to be low. These findings are at odds with each other but could allude to an inner conflict within the parent between what they hope for and what they believe is possible. Sisk et al., describes hope as a parent’s wants/desires, emotions, and sense of parental duty versus optimism as parent’s expectation of realizing a particular goal (Sisk et al.,2018). In this case, the discrepancy could be explained by the parents pushing forward out of hope and the sense responsibility they feel to try whatever options given if it could lead to the possibility of helping their child. However, their confidence in that outcome where they gain meaningful prognostic information being a reality is low and they may seek out other reasons to justify their decision to continue. Werner-Lin et al., 2018, describes this discrepancy as “cognitive dissonance”, which may display as altruistic attitudes towards inconclusive results and was noted as a motivation among only a few parents in our study. A few parents acknowledge that perhaps after years of remaining undiagnosed they may become mentally fatigued and consider pausing or walking away from the odyssey in the future.

The influence that the provider’s outlook had on parents’ decision to continue or discontinue the odyssey varied among the participants. Some stated that the provider’s attitude towards their child’s diagnostic odyssey had little to no impact on their motivation to continue the diagnostic odyssey. For others, past negative experiences slowed or discouraged the parents in their pursuit for a diagnosis and if possible, parents would seek out more personable providers. The importance of the clinical relationship between provider and parents has been noted in previous studies (Rosell et al., 2016). For parents who are already highly motivated, positive provider experiences only bolstered their hope to

continue the odyssey. Parents noted providers who explained complex genetics information in an understandable way and addressed their child in a respectful and personable way made the whole family feel included in the testing process. While parents took ownership of their motivation, they expressed appreciation for provider's ability to explain information and seek out new avenues for a possible diagnosis. Parents recognized the provider's vital role in guiding the odyssey and stated that they would not be privy to additional testing options without the provider's input. While the motivation to push forward despite the setbacks of having nondiagnostic results belonged to the parents, parents perceived that the responsibility of when and what the next steps would be rested with the provider (Mollison et al., 2019). For the parents who highlighted support of their child's provider, trust and communication play a major factor in allowing the provider to lead the charge. A novel finding was that select few of the parents stated the provider offering additional testing meant that the provider still found their child to be a mystery which demonstrated the provider's interest in their child. Perhaps for these parents the provider guided odyssey in rooted in some subjective interest in their patients. While this sentiment was only expressed by a few, it has not been noted in previous literature and warrants further exploration perhaps in future studies.

Throughout our study, the families equated "blood draw" with genetic testing. This method of testing/evaluation was not seen as invasive to parents and usually not a cause for concern. Parents stated their willingness to have their child's blood drawn again for additional testing without incident. For several of the parents genetic testing beyond a blood draw would be deemed to invasive and cause some of the families to stop or reconsider the diagnostic odyssey. Some parents alluded to the fact that genetic testing can be done on previously collected samples, so their child did not have to come in to get their blood drawn again. For some of these parents this was highly desirable because they did not live locally and traveling to the hospital required time and coordination. For non-local families travel and coordinating care is one of the most challenging parts of the odyssey. For these families, multiple

appointments in a day are not uncommon, but can be burdensome. One mom detailed the weekly trips her family had to take to address her daughter's ophthalmologic issues and the stress it placed on their family routine. She explicitly stated that genetics had not placed those strains on her family because the samples could be evaluated without the family needing to travel. Time commitment, travel and logistics were noted among some of the reasons why parents declined exome in the research setting (Amendola et al., 2018). Our study displays similar sentiment, however, shows that in the clinical setting complications in these aspects can lead to some families deciding to discontinue/pause the odyssey or other medical care. Perhaps for some family's genetics and genetic testing is a path of least resistance on an already tumultuous journey.

Overall, through genetic testing, nondiagnostic results, and invasive procedures, parents remain highly motivated to continue the diagnostic odyssey and pursue whatever options are presented. The concept of fear was also assessed for its impact on parents' motivation and decision making in the odyssey. Multiple parents acknowledge fear and even shared their fears of a life-limiting or regressive diagnosis, however, actively chose not to let fear dictate their decision making. Parents stated that while receiving a life-limiting diagnosis would be immensely difficult, it would allow them to make the most of the time they have with their child. Parents perceive that genetic testing will one day be able to provide them with the tools needed to set expectations and provide treatment for their child, so with that hope in mind and supportive providers to guide them, they are continuing to push forward.

Limitations

This study has several limitations that should be taken into consideration. This study assessed parents' motivations at a single time point, after their child's exome returned non-diagnostic results. The interval of time that passed between the original exome and our interview varied by participant, so their perceptions may have evolved over time. To assess how parents' motivations and perception towards

genomic testing change throughout the diagnostic odyssey, future studies could look at taking a longitudinal approach. A second limitation of this study is sample size. Since this is a small study it is possible that we may not have identified every possible theme. However, the study did reach data saturation with 10 participants. Another limitation is that all participants at the time of the interview expressed that they were motivated to continue the diagnostic odyssey. Therefore, we were unable to assess the motivations and perceptions in families that chose to discontinue the diagnostic odyssey. Due to the nature of the questions, parents were able to explore some hypothetical situations that would influence their decision to discontinue the odyssey that could be used to create the framework of a future study. Our study also included mainly female participants (90%); however, those demographics are not uncommon in qualitative studies surrounding this subject.

Conclusions

This descriptive study explored the motivations and perceptions of genomic testing that influence parents to continue or discontinue the odyssey. Our study provides insight into how parents' perceptions of genomic testing, from the belief in its prognostic abilities to its association with non-invasiveness, influences their motivations to continue or discontinue the diagnostic odyssey. For providers who are offering additional testing after non-diagnostic exome it is important to understand that parents may be seeking validation for their medical management decisions through pursuing a genetic diagnosis. It can be helpful to reassure parents that even without a diagnosis they are doing all that they can to address their child's health concerns at this time and that a genetic diagnosis will not invalidate the difficult choices they may have made in the past. Continuing to set realistic expectations during pre-test counseling is critical since our findings suggest that parents continue to display the mindset that genetic diagnosis can provide prognostic information. For families with a clinical diagnosis and/or for patients who are being managed effectively perhaps careful consideration as to how informative additional testing might be considering that most parents will agree to any testing offered.

Reanalysis and genomic testing do require insurance authorization and denial of testing can be source of stress for these families. Our findings emphasize the need to study parents who have made the decision to discontinue or pause diagnostic odyssey to understand their perceptions and motivations, which can help providers better address these family's needs in clinic.

References

Amendola, L. M., Robinson, J. O., Hart, R., Biswas, S., Lee, K., Bernhardt, B. A., . . . Blout, C. (2018). Why Patients Decline Genomic Sequencing Studies: Experiences from the CSER Consortium. Journal of Genetic Counselling, 27(5), 1220-1227. doi:10.1007/s10897-018-0243-7

Arts, P., Simons, A., AlZahrani, M. S., Yilmaz, E., AlIdrissi, E., Aerde, K. J. v., . . . Hoischen, A. (2019). Exome sequencing in routine diagnostics: a generic test for 254 patients with primary immunodeficiencies. Genome Medicine, 11(1), 1-15. doi:10.1186/s13073-019-0649-3

Baldridge, D., Heeley, J., Vineyard, M., Manwaring, L., Toler, T. L., Fassi, E., . . . Shinawi, M. (2017). The Exome Clinic and the Role of Medical Genetics Expertise in Interpretation of Exome Sequencing Results. Genet Med, 19(9), 1040-1048. doi:10.1038/gim.2016.224

Blosser, B. (2014). Meanings Parents Attribute to an Answer from Whole Exome Sequencing Research. (2019). Retrieved from https://etd.ohiolink.edu/!etd.send_file?accession=ucin1406809942&disposition=inline (11/16/19)

Carmichael, N., Tsipis, J., Windmueller, G., Mandel, L. and Estrella, E. (2015), "Is it Going to Hurt?": The Impact of the Diagnostic Odyssey on Children and Their Families. Journal of Genetic Counseling, 24, 325-335. doi.10.1007/s10897-014-9773-9

Demos, M., Guella, I., & DeGuzman, C. (2019). Frontiers | Diagnostic Yield and Treatment Impact of Targeted Exome Sequencing in Early-Onset Epilepsy | Neurology. doi:doi:10.3389/fneur.2019.00434

Farwell, K. D., Shahmirzadi, L., El-Khechen, D., Powis, Z., Chao, E. C., Tippin Davis, B., . . . Tang, S. (2015). Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genetics in Medicine, 17(7), 578-586. doi:10.1038/gim.2014.154

Harris, E. D., Ziniel, S. I., Amatruda, J. G., Clinton, C. M., Savage, S. K., Taylor, P. L., . . . Holm, I. A. (2012). The beliefs, motivations, and expectations of parents who have enrolled their children in a genetic biorepository. Genetics in Medicine, 14(3), 330-337. doi:doi:10.1038/gim.2011.25

Marshall, D. A., MacDonald, K. V., Heidenreich, S., Hartley, T., Bernier, F. P., Gillespie, M. K., . . . Boycott, K. M. (2019). The value of diagnostic testing for parents of children with rare genetic diseases. Genetics in Medicine, 21(12), 2798-2806. doi:doi:10.1038/s41436-019-0583-1

McConkie-Rosell, A., Hooper, S. R., Pena, L. D. M., Schoch, K., Spillmann, R. C., Jiang, Y. H., . . . Shashi, V. (2018). Psychosocial Profiles of Parents of Children with Undiagnosed Diseases: Managing Well or Just Managing? J Genet Couns, 27(4), 935-946. doi:10.1007/s10897-017-0193-5

Mollison, L., O'Daniel, J.M., Henderson, G.E… Skinner, D. (2020) Parents' perceptions of personal utility of exome sequencing results. Genetics in Medicine, 22**,** 752–757. doi:10.1038/s41436-019-0730-8

Retterer, K., Juusola, J., Cho, M. T., Vitazka, P., Millan, F., Gibellini, F., . . . Bale, S. (2015). Clinical application of whole-exome sequencing across clinical indications. Genetics in Medicine, 18(7), 696-704. doi:10.1038/gim.2015.148

Romasko, E. J., Devkota, B., Biswas, S., & Jayaraman, V. (2020). Utility and limitations of exome sequencing in the molecular diagnosis of pediatric inherited platelet disorders - Romasko - 2018 - American Journal of Hematology - Wiley Online Library. American Journal of Hematology. doi:10.1002/ajh.24917

Rosell, A. M., Pena, L. D., Schoch, K., Spillmann, R., Sullivan, J., Hooper, S. R., . . . Shashi, V. (2016). Not the End of the Odyssey: Parental Perceptions of Whole Exome Sequencing (WES) in Pediatric Undiagnosed Disorders. J Genet Couns, 25(5), 1019-1031. doi:10.1007/s10897-016-9933-1

Scollon, S., Bergstrom, K., Kerstein, R. A., Wang, T., Hilsenbeck, S. G., Ramamurthy, U., . . . Parsons, D. W. (2014). Obtaining informed consent for clinical tumor and germline exome sequencing of newly diagnosed childhood cancer patients. Genome Med, 6(9), 69. doi:10.1186/s13073-014-0069-3

Sisk BA, Malone JR. (2018). Hope, Optimism, and Compassionate Communication. JAMA Pediatrics, 172(4), 311–312. doi:10.1001/jamapediatrics.2017.4536

Vears, D. F., Senecal, K., & Borry, P. (2019). Genetic health professionals' experiences returning results from diagnostic genomic sequencing to patients. *Journal of Genet Counselling, 4*, 1200-1209. https://doi.org/10.1002/jgc4.1209

Werner-Lin, A., Zaspel, L., Carlson, M., Mueller, R., Walser, S. A., Desai, R., & Bernhardt, B. A. (2018). Gratitude, protective buffering, and cognitive dissonance: How families respond to pediatric whole exome sequencing in the absence of actionable results. *American journal of medical genetics. Part A*, *176*(3), 578–588. https://doi.org/10.1002/ajmg.a.38613

Wilfond, B. S., Fernandez, C. V., & Green, R. C. (2015). Disclosing Secondary Findings from Pediatric Sequencing to Families: Considering the "Benefit to Families". J Law Med Ethics, 43(3), 552-558. doi:10.1111/jlme.12298

Wynn, J., Ottman, R., Duong, J., Wilson, A. L., Ahimaz, P., Martinez, J., Rabin, R., Rosen, E., Webster, R., Au, C., Cho, M. T., Egan, C., Guzman, E., Primiano, M., Shaw, J. E., Sisson, R., Klitzman, R. L., Appelbaum, P. S., Lichter-Konecki, U., Anyane-Yeboa, K., … Chung, W. K. (2018). Diagnostic exome sequencing in

children: A survey of parental understanding, experience, and psychological impact. *Clinical genetics*, *93*(5), 1039–1048. https://doi.org/10.1111/cge.13200

Yanes, T., Humphreys, L., McInerney-Leo, A., & Biesecker, B. (2017). Factors Associated with Parental Adaptation to Children with an Undiagnosed Medical Condition. J Genet Couns, 26(4), 829-840. doi:10.1007/s10897-016-0060-9

Table 1 – Demographics

Total Interviews – 10 (%)

Biological Sex	
Male	1 (10%)
Female	9 (90%)
Age (in years)	
30 – 40	5 (50%)
40 – 50	5 (50%)
Race/Ethnicity of the Interviewee	
Asian	0
Black/African American	0
Caucasian	9 (90%)
Hispanic/LatinX	0
Native American	0
Mixed Race	1 (10%)
Pacific Islander	0
Caregiver Status	
Primary	10 (100%)
Secondary	0
Education Level	
High School	3 (30%)
Some College	1 (10%%)
Associates Degree	0
Bachelor's Degree	4 (40%)
Master's Degree	0
MD. PhD Degree	2 (20%)

Table 2 – Themes

Categories	Themes	Examples
Motivations for Testing	**Planning and Preparing for the future:** Parents describe wanting a diagnosis to set expectations about their child's future or anticipate future needs.	*"When you don't even know if they're gonna be regressive or, um, you know, if he's going to get better, he's going to get worse or stay the same. You don't know anything; we just treat symptoms. So, if we had a diagnosis, we could say, okay, this is what, you know, at some point, this is what we're expecting. And you can just prepare." Participant 5; Mother*
	Establishing/Guiding Medical Management: Parents describe how a diagnosis can help establish a medical management plan or adjust the current medical management plan	*"We felt like there probably should be a piece that would tie it all together and then also help us to be better prepared and equipped in treatment options for her and prognosis." Participant 8*
Aspects that Modify Testing Decisions	**State of Mind:** Parents describe how their emotions/ mentality impact their outlook on the odyssey and whether to continue testing	*"We would love answers, but also if we don't have them, it's not the end of the world… I think most people realize this, but a diagnosis doesn't define my child. A diagnosis just helps me equip my child. It's not about the diagnosis. It's about how we as parents can help our children and how's diagnosis benefits the life of my child. It's not about the diagnosis." Participant 4; Mother*
	Parent/Provider Relationship: Parents detail how their relationship with the child's provider or the provider's outlook on the odyssey impacts their perception of the odyssey	*"I feel like sometimes when you have a name, it shifts the responsibility of education to the medical professional and off of you, because it's always on me." Participant 1; Mother*
	Invasive Procedures: Parents describe how invasive	*"I guess if it's a more invasive procedure than a blood draw,*

	procedures would prompt further discussion or a reconsideration of diagnostic odyssey	*we would strongly consider drawing the line. His symptoms could match prematurity, that they always see with micro premies of his size but that doesn't mean that he was born so early... [inaudiable]... so I think without good understanding, or promising lead or promising area to look into, I think we probably would draw the line at testing beyond a blood draw right now." Participant 10; Mother*
Perceptions towards Genomic Testing	**Genetic testing is non-invasive**: Parents refer to genetic testing as "blood draw" and state it is not a cause for concern	*"So far there's not been any testing that has had a detrimental impact on her. The blood draws we've always waited for blood draw until she has to do another one for something else, but we can do them together. Honestly it really hasn't been a big deal. It's been pretty easy." Participant 8; Mother*
	Genetic testing is secondary: Parents state a desire for genetic knowledge but imply that diagnosis is secondary to addressing their child's other health care needs.	*" I didn't really think about [genetic test results] at all because we had, you know, that was like, a backburner question. And we had so many other things going on health wise, but you know, we just had to keep moving forward with the other stuff." Participant 5; Mother*

Appendix 1a – Interview Guide

Hello, thank you for agreeing to participate in this research study. The time you have set aside and your responses to the following questions are incredibly valuable and greatly appreciated. The purpose of this interview is to ask parents of children who remain undiagnosed, what motivates them to continue or discontinue genetic testing after their child's exome sequencing did not obtain diagnosis? The process of trying to obtain a diagnosis is sometimes called the diagnostic odyssey, and I would like you to take this time to share your experiences and journey with me. This interview is completely voluntary, and you are free to stop the interview at any time or skip questions you do not feel comfortable answering. Should you choose to stop the interview or skip a question, you, and/or your child's care at CCHMC will not be impacted in anyway. This interview will be recorded and should take approximately 30 minutes.

If you have any questions or concerns about your child's health or questions relating to testing and results, I will be more than happy to connect you with a genetic counselor at the end of the interview.

1. Will you please start by describing your experience has been pursuing a diagnosis for your child?
    a. How long have you been pursuing a diagnosis?
    b. How has pursuing a genetic diagnosis impacted your relationship with your extended family, friends, your finances, etc.?
    c. How would changes in these aspects influence your current decision to continue or discontinue testing?

2. I am going to ask you to think back a bit. What do you recall learning about the results?
    a. How did you feel about the results you were given?
    b. Did you decide to have additional testing after receiving those results? Why or why not?
    c. As you reflect on testing done for your child in the past, would you have still opted to do those tests? Why or why not?

3. Are you still actively looking for a genetic diagnosis?
    a. If so, what steps are you taking to look for a diagnosis?
    b. If not, please describe the point at which you decided to discontinue?

4. Why it is important to you to get a diagnosis for your child?
    a. How will a diagnosis help your child?
    b. Would a genetic diagnosis for your child change your child's current health care management? Why or why not?
    c. Do you think obtaining a diagnosis would allow your child access to certain services that are unavailable to them now because they do not have a diagnosis?

5. How does stopping the pursuit of a diagnosis impact your child? Your family?

6. What role has genetic counseling played in your decision to continue or discontinue testing?

    a. How did genetic counseling help you understand your next steps?
    b. Did you feel validated in your decision to continue or discontinue testing?
    c. Did you feel that the genetic counselor supported your decision?

7. At the most recent visit with genetics do you recall what testing options may have been discussed?

   a. If yes, what were the options?
   b. Who initiated the conversation? You or the counselor?
   c. If so, how did you feel when you learned this information?
   d. If not, was that information you would have liked to learn?

8. Has there ever been a point in the diagnostic odyssey were you and your partner/spouse/significant other were not in agreement about whether to continue or discontinue testing?
   a. If so, why?
   b. How were you able to resolve the disagreement?
   c. Do you feel like your current decision on testing is one of agreement? Why or why not?

9. What role has your child had in the decision to continue or discontinue the diagnosis odyssey?
   a. How have you incorporated his/her role into your decision making?
   b. Why is incorporating your child's preference in their decision on diagnostic odyssey important to you?

10. At this time, you have stated that *you are not* pursuing genetic testing for your child. Do you see yourself changing your mind in the future?
   a. If so, what factors are influencing you to pause for now?
   b. What factors would encourage you to continue again?
   c. If not, why?

11. At this time, you have stated that *you are* pursuing genetic testing for your child. Do you see yourself changing your mind in the future?
   a. If so, what factors influence you to continue?
   b. What factors would discourage you from continuing in the future?
   c. If not, why?

12. If you were told and felt that your child symptoms were milder in severity, would you still be interested in finding a genetic cause for their symptoms?
   a. Why or why not?

13. Do you feel responsible for finding a diagnosis for your child?
   a. Why or why not?

14. Can you describe to me how you envision your child's diagnostic journey as complete?
   a. How long do you think this journey will take?
   b. To what lengths are you willing to pursue this journey?

Appendix 1b – Interview Guide (Additional Questions)

Does the attitude of your child's genetics team towards your child diagnostic odyssey impact your motivation to continue or discontinue the diagnostic odyssey? Why or why not?

How would an overly optimistic (pessimistic) HCP impact/hinder your motivation to pursue the diagnostic odyssey?

What is your biggest fear (concern) about pursuing the diagnostic odyssey?

- Does this concern motivate you? Why or why not?
- Does this concern discourage you?

What is your biggest fear since discontinuing the diagnostic odyssey?

How does testing for genetic diagnosis compare to testing/seeking treating in other specialties?

- If seeking a genetic diagnosis was like seeking care/treatment in other specialties would be interested or disinterested in pursuing a genetic diagnosis?

At what point would you draw (Or at what point did you draw) the line on genetic testing? Why?

How does trust in your child's genetic team factor into your decision to continue or discontinue testing? Why or why not?

Who is responsible for deciding how and when the diagnostic odyssey continues or stops?

What genetic testing does your child have coming up? How are you feeling about those potential results? Do you expect different results?

Appendix 2 – Codebook

	Code	Description	Definition/Example
Knowledge			
	DTK	Desire to Know	Parents state a *need /curiosity* to know information about their child's condition
	ACT	Wanting to act	Parents wants information to they can take active steps in their child's care
	CHILD_ILL	Parents wants child to understand their illness	Parents state a need for knowledge to let explain to their child what going on
	PLAN/PREPARE	Planning for the future	Parents talk about gaining knowledge to learn how to manage their child's needs in the future
	PLAN_FAMILY	Planning for future family	Parents discuss a desire for genetic dx to inform decisions about having other children. OR Can apply to future generation (i.e., grandchildren)
	EXPECTATIONS	Setting expectations	Parents talk about how a genetic dx will allow them to set expectations for their child's future
	EXPECTATIONS > PLAN/PREPARE	Setting expectations leads to preparation	Merge Code – Parents describe or state that a genetic dx will allow them to set expectations about what they should plan for in terms of managing

			their child's needs in the future
	AGREEMENT		Parent state that they agreed with their partner on testing decisions
	DISAGREEMENT		Parents state that they disagreed with their partner on testing decisions
	RECALL	Parents recall info about testing	Parents share/recall information about genetic testing and/or results demonstrating understanding of the genomic testing process
	ALTRUISM		Parents explain that they hope information learned from their child's test results can help other people
Support/Resources			
	NOSUP	Lack of Support	Parents state that there are not enough resources/education . available or they do not know where to go for help
	CONNECT	Connection with others	Parents discuss a desire to meet other families with shared experience. OR
	COPE	How to cope	Parents request resources for coping

			with their child's illness. OR Parents inquire how others manage their child's illness
	RESOURCE/EDUCATION		Parents discuss a need for resources or patient liaison to help them navigate the dx odyssey process
Management/Treatment			
Treatment can include surgical interventions, therapies, medications, evaluations	NFI	Need for improvement	Parents talk about needing to see an improvement in their child's symptoms
	GOAL	Goal is treatment	Parents discuss that their **main goal** for genetic dx is to find an ideal treatment plan for their child
	DOUBT_TREAT	Doubting the treatment plan	Parents state that they have doubts/reservations about their child's current treatment plan is working
	REGRET_TREAT	Treatment Regret	Parents express that they would have/ should have made different treatment/medical decisions (in the past or currently)
	ADJUST_TREAT	Adjusting/guiding the treatment plan	Parents talk about having a treatment plan, but hope a genetic diagnosis would adjust their

			child's treatment plan
	NAME > TREAT	Names leads/guides a treatment plan	Parents believes that a name/diagnosis will help est. a treatment plan
	SECURE_TREAT SECURE_DX	Feeling confident or secure in the treatment plan or diagnosis given	Parents want to feel confident in the medical decisions they are making for their child. OR feel confident in the dx they have been given
Closure			
	LIFE	Getting on with life	Parents express that they want to move on, for things to return to normal
	PEACE	Peace of mind	Parents want to feel a sense of comfort or relief
Financial Concerns			
	ASSIST	Assistance	Parents state that assistance (can include insurance) plays a role in their ability to continue the dx odyssey. OR Parents want assistance to cover the cost of testing
	HINDERS	Hinders the odyssey	Parents feel limited in how their ability to pursue the diagnostic odyssey because of cost.
	NO CONCERN		Parents state that finances or

			insurances issues have not impacted their dx odyssey
Disease Name			
	NAME	Name	Parents discuss wanting/needing a name for the symptoms their child has.
	NO NAME		Parents state that they do not need a name or label for their child's symptoms
	NAME > PROVIDER	Name puts responsibility on the provider	Parents discuss that having a diagnosis or disease name would transfers the burden of the odyssey to the provider
	NO NAME > PARENT	No Name puts responsibility on the parent	Parents discuss that not having a diagnosis or disease name puts them in a position, educate the provider, guide the diagnosis odyssey, track symptoms, etc.
Parent/Provider Relationship			
	GUIDE	Guidance	Parents discuss looking to provider for answers or advice. OR hoping they have assistance with making medical decisions.

	CONTROL	Wants to be/Feel in Control	Parent states they are making the primary decision. Parent wants to seek out their own answers, looks for second opinions, does their own research
	COLLAB	Collaboration	Parents state that they come to a decision with their provider. OR that various providers have worked together to est. a plan or take a course of action
	GUESSING	Guessing leads to lack of confidence	Parents state that treatment investigation shows that the providers are unsure of how to deal with the problem – these crates doubt in the parent
	STRUGGLE	Struggling w/ outside specialties	Parents explain the difficulties they have experienced with other specialties (evals, tests, coordinating appt, etc.)
	TRUST	Trust	Parents state that trust in their child's provider plays a role in their decision making about the dx odyssey

	SUPPORT		Parents describe that the support from their child's provider enables them to continue the dx odyssey
	POS PROVIDER > INCREASED HOPE	Positive provider experiences	Parent describe positive provider experiences increased their hope to continue the diagnostic odyssey
	POS_PROVIDER	Positive provider	
	NEG PROVIDER> DECREASED HOPE	Negative provider experiences	Parents describe negative provider experiences that discouraged them and made the diagnostic odyssey more difficult
	NEG_PROVIDER	Negative provider	
	NEU PROVIDER	Neutral provider experiences	Parents state that provider's attitude/perception did not have a positive or negative impact on their experience with the diagnostic or influence their testing decision
	PT INTEREST > TESTING		Parents express that their child's provider still finds the child "interesting" and is willing to continue to their odyssey to discover a dx
	RESPONSBILITY		Parents state that they are leaving the responsibility of the dx odyssey to the

			provider/ they let the provider guide the odyssey
	EXPLAIN/INFO SHARING		Parents state they appreciated how genetic info was shared or explained to them
Emotions/Perceptions about genetic testing/results	FEAR	FEAR	Parents express that they have fears
	FEAR_LIFE	Fears about life expectancy	Parents have fears that testing will reveal a dx with shortened life expectancy
	FEAR_PERCEPTION	Fear is not a deterrent	Parents state that they have no fear or whatever fears they do have will not deter them from continuing the odyssey
	STRESS		Parent discuss stress caused by the diagnostic odyssey
	INDIFEERENCE		Parents feel indifferent about the diagnostic test results OR indifference to the diagnostic testing process
	DISAPPOINTMENT		Parents state that they felt disappointed
	FRUSTRATION		Parents state that they felt frustrated or upset at the lack of answers from genetic testing

	CONFUSED		Parents state that felt confused by inconclusive test results
	NEG_INVASIVE		Parents allude to negative/stressful/ unpleasant experiences with invasive procedures
	TRANSITION		Parents describe a period of transition – from wanting test results to be negative to positive. OR Describe a transition period in their thoughts towards genetic testing in general
	HOPE/OPTIMISM		Parents state that they are hopeful that genetic diagnosis will come
	GEN_ANSWER	Genetics has the answers/ Genetics has the key	Parents feel that a genetic dx is the answer to their child's symptoms and will provide the information necessary to guide the odyssey. OR Will be able to provide prognostic information
	GEN_BLOOD DRAW	Genetics is a blood draw	Parents describe genetics as a blood draw and alluding to non-invasiveness
	GEN_SECONDARY	Genetics is secondary	Parents state that genetics is happening in the

			background, usually treatment is the most pressing concerns. OR Genetics was opening
	TEMPER/TRANSPARENCY	Tempered expectations/ Transparency about potential results	Parents explain that pre-test counseling allowed them to be prepared for possible results, so they were able to temper their expectations
	PUSHING FORWARD		Parents state they are willing are continuing to test despite negative/inconclusive results or other deterrents (finances, lack of support, etc.) OR Parents agree easily to offers of additional testing
	ACCEPTANCE	Accepting the unknown	Parents allude to accepting that an answer may not be possible. OR Accepting their child's differences and not letting those indifferences impact their relationship/outlook with their child
Reasons to Discontinue/Stop/Pause			

	Exhaustion > Stopping	Mental exhaustion leads to stopping	Parents discuss that mental exhaustion would lead them to discontinue
	Invasive > Stopping	Invasive procedures lead to stopping	Parents discuss that invasive procedures would be a pause for consideration. Parents explain they would have to examine the pros and cons of putting their child through invasive procedure
	Improvement > stopping	Symptom improvement leads to stopping	Parents state that an improvement in their child's symptoms would encourage them to discontinue the odyssey
	Financial > stopping	Financial struggles lead to stopping	Parents explain that cost of testing or lack of insurance coverage would influence them to stop or pause the odyssey
	Provider > stopping	Provider input leads to stopping	Parents state that they will defer to the provider's input as to when the dx odyssey should be discontinued
	Lifestyle > stopping	Changes in lifestyle leads in stopping	Parents discuss that if the diagnostic odyssey led to significant changes in their day to day (travel, time, commitment, etc.) they would consider

			stopping or pausing the odyssey
	Not Considered		Parents have not considered a situation that would lead them to stop/pause their child's diagnosis odyssey
	NO REASON		Parents state that there is no reason / or was unable to give a reason that would stop/deter them from continuing the diagnostic odyssey