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ADULT PATIENTS WITH UNDIAGNOSED CONDITIONS AND THEIR RESPONSES TO UNRESOLVED UNCERTAINTY FROM EXOME SEQUENCING

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Abstract

Patients pursuing exome sequencing (ES) in their quest for diagnosis will most often experience unresolved uncertainty from their ES results because the majority of ES results are non-diagnostic. This study explored and compared the experiences of receiving two types of ES results that may result in diagnostic uncertainty. Semi-structured phone interviews were conducted with 23 adult patients with undiagnosed conditions who received either a negative result or a result with one or more variants of uncertain significance (VUSs) from ES. Interviews were transcribed and subjected to thematic and comparative analyses. Participants accurately understood their results and described various sources of genomic uncertainty including probability, complexity, and ambiguity. Their acclimation to illness uncertainty resulted in realistic expectations about and acceptance of their results. Participants still hoped that ES would end their diagnostic odyssey. Hope and optimism were used to cope with continued uncertainty. No thematic differences were

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AUTHOR CONTRIBUTIONS

Ahna Neustadt contributed to the conception and the design of the study, acquisition, analysis, and interpretation of the data, and drafting and revision of the manuscript. Jill Owczarzak contributed to the conception and the design of the study, interpretation of the data, and revision of the manuscript. Weiyi Mu contributed to the conception of the study, acquisition of the data, and revision of the manuscript. Julie S. Cohen contributed to the conception of the study, acquisition of the data, and revision of the manuscript. Lori Erby contributed to the conception and design of the study, interpretation of the data, and revision of the manuscript.

CONFLICTS OF INTEREST

Julie S. Cohen is a consultant to Invitae Laboratory. Ahna Neustadt, Jill Owczarzak, Weiyi Mu, and Lori Erby declare that they have no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the Institutional Review Boards of the National Institutes of Health and Johns Hopkins School of Public Health, as well as the Helsinki Declaration. Informed consent was obtained from all participants included in the study.

ANIMAL STUDIES

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

found between the experiences of those who received negative results versus those who received VUSs. Our findings may inform clinical practices of informed consent and disclosure of negative results and VUSs through a greater consideration of patients' reactions, concerns, and challenges with adaptation to uncertainty.

Keywords

undiagnosed; exome sequencing; uncertain; variant of uncertain significance (VUS); negative; attitudes; beliefs; genetic counseling; lived experience

INTRODUCTION

Exome sequencing (ES) as a diagnostic tool is being incorporated into clinical care arguably much faster than the scientific community can keep pace with. While the clinical utility of ES has been sufficiently demonstrated to justify its place in clinical care (Retterer et al, 2016), there are still many reasons why the majority of ES results are non-diagnostic: (1) technical limitations of mass parallel sequencing technologies may leave some pathogenic genetic changes undetected, (2) incompleteness of variant databases and other interpretive tools may delay or prevent sound variant interpretations, (3) a lack of ethnically diverse populations sequenced and included in research hinders the diagnostic utility of genomic sequencing in these groups, (4) and many diseases are simply not Mendelian. ES has been reported to only provide conclusive diagnoses to about 25% of patients with undiagnosed conditions, leaving the majority with unresolved diagnostic uncertainty (Berg, 2014; Sawyer et al, 2016; Yang et al, 2013).

Patients with undiagnosed conditions may have rare or unexplained illnesses that elude a definitive molecular diagnosis. These patients have often endured diagnostic odysseys characterized by chronic uncertainty (Basel & McCarrier, 2017). For undiagnosed patients, ES is often part of a "last ditch" effort to attain a diagnosis (Sawyer et al, 2016). This patient population's experience with chronic illness uncertainty makes them a relevant population to study regarding responses to unresolved uncertainty from ES.

At the outset of ES in clinical care, trios of undiagnosed children and their parents were typically those receiving the service because trio testing increases diagnostic yield (Sawyer et al, 2016). Adults with undiagnosed conditions have just recently become a significant group of ES users, and so their response to unresolved uncertainty from ES is still a relatively new phenomenon that requires exploration.

What we do know about perceptions and responses to unresolved illness and genomic uncertainty comes mostly from studies of parents of undiagnosed children, adult cancer patients, and healthy adults participating in genomic sequencing studies. Adult cancer patients receiving negative results or VUSs from germline cancer gene panels and parents receiving the same non-diagnostic results from their child's chromosomal microarrays (CMAs) report incongruent recall and understanding regarding these results (Kiedrowski et al, 2016; Makhnoon et al, 2019; Reiff et al, 2017; Richter et al, 2013; Solomon et al, 2017; Vos et al, 2008; Wilkins et al, 2016). In parents of undiagnosed children, traits like optimism

and resilience contribute to and may even predict perceptions of and coping strategies for uncertainty (Macnamara et al, 2014; Madeo et al, 2012). Similarly, prior expectations about genomic sequencing from healthy adult research participants may influence their appraisals of and coping strategies for uncertainty (Biesecker et al, 2014; Jamal et al, 2017). Diagnostic uncertainty usually negatively affects parental coping, yet may sometimes facilitate a strengthened focus for parents to identify more positive outcomes for their child (Rosenthal et al, 2001; Graungaard et al, 2006; Lipinski et al, 2006). Genomic uncertainty may have similar effects, as receiving VUSs from ES has been shown to contribute to feelings of empowerment and a desire to advocate for further research and peer support in parents of undiagnosed children (Li et al).

There are few studies that have examined adult patients with undiagnosed conditions in the context of ES. Khan and colleagues have demonstrated that illness uncertainty can influence perceptions of the benefits of ES and hopes about the types of information to be learned from ES (Khan et al, 2016). One qualitative study of adult patients and parents of pediatric patients who received negative results from ES demonstrated that most felt either reassured that there was no genetic cause found or felt promise around the potential for future technologies to discover a genetic cause (Skinner et al, 2016). A similar study involving the same populations but regarding variants of uncertain significance (VUSs) and other types of uncertain variants from ES demonstrated that most understood their result was uncertain yet had various levels of recollection about the degree of uncertainty or type of result. Overall, participants reported feeling prepared for an uncertain result and most regarded their result as having potential value in the future (Skinner et al, 2018).

Uncertainty pervades genetic medicine and will continue to be experienced by patients who receive non-diagnostic results from genetic tests. How patients appraise such illness and genomic uncertainty is directly associated with their coping and adaptation (Mishel, 1990). Understanding how patients with undiagnosed conditions respond to unresolved uncertainty from ES may inform providers' practices around informed consent for ES and the disclosure of these result through a greater consideration of patient concerns and challenges with adaptation. One might anticipate certain differences in the ways adult patients with undiagnosed conditions experience unresolved uncertainty from ES compared to parents of undiagnosed children, perhaps because the adult patients are living with illness themselves. The dearth of research about this newly significant group of ES users, in combination with existing studies not parsing out potential differences in experiences between adult undiagnosed patients and parents of undiagnosed children, warrants a more detailed characterization of the perceptions of and responses to unresolved uncertainty from ES in adults themselves. We sought to contribute to this necessary characterization, as well as investigate potential differences in responses to two types of ES results that do not provide a molecular diagnosis and therefore may result in unresolved diagnostic uncertainty: a negative result or a result with one or more VUSs. Our study explored and compared the experiences of adult patients with undiagnosed conditions who have received one of these two types of non-diagnostic ES results that may result in unresolved diagnostic uncertainty. We define a negative result as one with no reported clinically relevant variants and a VUS as a variant for which there is not enough known to classify it as disease-causing or benign.

THEORETICAL FRAMEWORK

Our theoretical framework is composed of three different theories, each described below. Mishel's theory of uncertainty in illness defines illness uncertainty and describes how unresolved uncertainty may affect the coping and adaptation processes for patients with undiagnosed conditions. While Mishel provides context for the struggles that unresolved uncertainty may pose to undiagnosed patients, Taylor's theory of cognitive adaptation outlines how undiagnosed patients may successfully adapt to unresolved uncertainty. These two theories inform the role of uncertainty in our participants' diagnostic journeys. In order to define the many facets of unresolved uncertainty from ES, as well as characterize how our participants described their experiences with this uncertainty, we also included the taxonomies of genomic uncertainty into our theoretical framework.

Theory of Uncertainty in Illness

In Western society, certainty, predictability, and control are often the expected and desired outcomes of medicine. Healthcare providers are expected to use scientific methods to provide accurate diagnoses and information on effective treatment. When uncertainty is the outcome, the medical endeavor is seen as deficient, disrupting an individual's sense of control. As Mishel explains, uncertainty is "the inability to determine the meaning of illness-related events and occurs in situations where the decision maker is unable to assign definite values to objects and events and/or is unable to accurately predict outcomes because sufficient cues are lacking" (Mishel, 1990).

The theory of uncertainty in illness describes how individuals process uncertainty related to their illness and how they create meaning around uncertain events. Mishel describes that undiagnosed patients appraise illness uncertainty as either an opportunity or threat. Adaptation occurs when coping strategies manipulate uncertainty in the desired direction based on the appraisal. Undiagnosed patients who experience continual illness uncertainty may have different appraisals throughout their diagnostic odyssey, making it difficult to process uncertainty. If uncertainty is never resolved, it may ultimately be evaluated as opportunistic. However, this re-evaluation will change their thinking to be more probabilistic and conditional, as certainty and predictability are now viewed as unrealistic (Mishel, 1990).

Theory of Cognitive Adaptation

Taylor's theory of cognitive adaptation outlines how individuals may successfully adapt to a threatening event. Her theory states that the adaptation process occurs in three steps: "a search for meaning in the experience, an attempt to regain mastery over the event in particular and over one's life more generally, and an effort to restore self-esteem through self-enhancing evaluations" (Taylor, 1983). Meaning-making is achieved through an understanding of what caused the threatening event and how it has changed one's life. Regaining mastery centers on beliefs about personal control and requires an understanding of how one can manage the threatening event and prevent it from reoccurring. Restoring self-esteem is achieved by self-enhancing evaluations, or social comparisons in which the object of comparison allows for positive self-perceptions (Taylor, 1983).

Taxonomies of Genomic Uncertainty

Han's *Taxonomy of Medical Uncertainties in Clinical Genome Sequencing* identifies sources, issues, and loci of genomic uncertainty. The three sources are *probability,* or the indeterminacy of future outcomes that comes with genomic information; *ambiguity*, or the imprecise, conflicting, or missing information regarding genomic interpretation; and *complexity*, or genomic information that is challenging to understand (Han et al, 2017). Babrow's forms of uncertainty describe how individuals experience uncertainty from genomic information. For example, *inherent uncertainty* arises from the genetic test or condition itself, such as the accuracy and reliability of the specific test or the complex genetic cause(s) of an illness. *Structuring of information* describes how an individual organizes or integrates genomic information into their existing beliefs and values (Babrow et al, 1998).

METHODS

Participants

Participants were recruited from Johns Hopkins Hospital (JHH) and Kennedy Krieger Institute (KKI). This study was approved by Institutional Review Boards from Johns Hopkins Bloomberg School of Public Health and National Institutes of Health and approved as human subjects research. Eligible patients were identified from clinic databases by genetic counselors from each site. Participants must have had endured a diagnostic odyssey of at least six months before receiving ES. A diagnostic odyssey was operationalized as (1) having a set of clinical symptoms but no diagnosis, (2) having a clinical diagnosis of a broad category of disease (i.e. ataxia, muscular dystrophy) but no specific molecular diagnosis, or (3) having a clinical diagnosis composed of psychosomatic and/or descriptive diagnoses that individually define single or groups of symptoms (i.e. joint pain, migraines, fatigue) but do not explain the entire phenotype. Each participant had ES in an attempt to attain a molecular diagnosis and received either a negative result or one or more VUSs. The operational definition of a VUS relied on the JHH and KKI genetic counselors' agreement with the VUS classification provided by the genetic testing laboratories. Participants were 18 years or older when they received their results, which were returned by genetic counselors one week to seven years prior to being recruited. Patients were excluded if ES provided a molecular diagnosis, they could not speak or understand English, or they had a cognitive disability that prevented them from comprehensibly answering interview questions.

Procedures

Eligible patients were mailed, emailed, or verbally shared information about the study purpose and procedures. Interested patients were sent consent and protected health information release forms. All participants gave their informed consent prior to their inclusion in the study. When informed consent was obtained, JHH and KKI genetic counselors provided the first author (AN) with the following clinical information: VUS or negative result, number of days between date of ES and date of result disclosure, and month and year of result disclosure. Participants completed two questionnaires, the *Intolerance of Uncertainty Short Form Scale* (Carleton et al, 2007) and the *Perceptions of Uncertainties in Genome Sequencing (PUGS) Scale* (Biesecker et al, 2017), before their interviews.

Each participant completed an approximately 60-minute semi-structured phone interview. All interviews were conducted by AN between August-October of 2018 and were audio-recorded and transcribed. The interview guide was composed of open-ended questions with follow-up prompts that addressed motivations for ES, the result disclosure process, recall and understanding of results, perceptions of uncertainty, perceptions of the relationship between the result and the cause of their condition, affective and behavioral responses to receiving results, and coping strategies. A pilot interview guide was developed prior to recruitment and modified after six pilot interviews. A codebook was developed based on the interview guide and revised in an iterative process.

Data Analysis

Interview transcripts were explored by AN using thematic analysis, in which coding was highly inductive and analysis combined deductive and inductive approaches (Elo & Kyngas, 2008). Coding was conducted using NVivo, a qualitative data analysis software. A preliminary codebook of a priori codes was created based on topics from the interview guide, such as ‘hopes and expectations,’ ‘coping,’ and ‘recall and understanding.’ This preliminary codebook was applied to several initial transcripts. While applying the a priori codes to the first set of transcripts, some emerging codes were identified and added to the codebook, such as ‘motivations,’ and ‘feeling differently about cause of condition.’ Once the initial codebook of a priori and emerging codes was established from coding the initial transcripts, sub-codes were created for various codes and the initial coded transcripts were re-coded to include the sub-codes. The final codebook was then used to code the remaining transcripts. AN met periodically with co-authors LE and JO during the coding process to discuss the development and organization of codes. Code saturation was confirmed by the final codebook remaining stable during the process of coding the remaining transcripts (Hennink et al, 2017).

Once coding was completed, findings were interpreted via thematic analysis. Potential themes were both elucidated from the data itself (inductive approach) and informed by the theoretical framework (deductive approach). For example, when analyzing the data to answer our aim of how participants experienced and perceived uncertainty, themes were developed within the context of the taxonomies of genomic uncertainty with the purpose of discovering how the data reflected these known taxonomies. Themes were refined by providing clear names and definitions and assessing how each theme was related to the overall data set and the specific aims of the study. Themes were analyzed within the context of participants’ diagnostic odysseys. Coded data within each theme was reviewed to select illustrative quotes.

The data were also analyzed comparatively by dividing the data into groups and analyzing it side-by-side to detect possible differences in emerging themes. These groups were: participants with VUSs vs. negative results, “high” vs. “low” responses to the two uncertainty questionnaires, and shorter vs. longer time since result disclosure. “High” and “low” groups for uncertainty questionnaire responses were based on the median score for each questionnaire (*PUGS* median = 30, “low” = 10–29, “high” = 30–50; *Intolerance of Uncertainty* median = 36, “low” = 12–35, “high” = 36–60). Shorter time since result

disclosure was defined as one week to 12 months, and longer time was defined as greater than 12 months.

RESULTS

Thirty-two patients were contacted during recruitment, with an ultimate response rate of 72% (23/32). Twenty-seven were reached during recruitment, expressed interest in participation, sent consent forms, and had interviews scheduled. Four of the 27 either did not return their consent form or could not be reached for their interview. Of the 23 total participants, 12 were from JHH and 11 were from KKI. Fourteen participants had received VUSs and nine had received negative results. One interview from a participant with a VUS was dropped from data analysis because the interview revealed that ES provided a molecular diagnosis.

Participants had ES between 2014–2018. The sample was mostly Caucasian, highly-educated, and over half were male. Participants widely varied in their intolerance for and perceptions of uncertainty and had a range of symptomatology (Table 1).

All participants had unique stories about receiving ES. Some self-referred to a genetics clinic after searching online for recommendations, while others were referred by a provider after exhausting all other diagnostic avenues. No thematic differences were detected during comparative analysis. Interviews uncovered three major themes that are further divided into sub-themes: taxonomies of genomic uncertainty, acclimation to illness uncertainty, and hope and optimism.

Taxonomies of Genomic Uncertainty

Participants generally had accurate understandings of their results. Those with negative results could articulate that there were no reportable findings through conveying that ‘the test found nothing’ or that they had not learned anything new about their condition. Twelve of the 13 participants with VUSs could describe that ES detected something their genetics providers could not say with certainty explained their condition at the current time.

Sources of Genomic Uncertainty—Participants experienced and were able to describe various aspects of genomic uncertainty including its sources, known as probability, complexity, and ambiguity (Han et al, 2017). Participants identified *probability uncertainty* through their understanding that their result did not provide prognostic information. One expressed this when describing how her hope for a prognosis was not met:

> *“I was hopeful that I would have an explanation and that we would be like, ‘Well, this is it, and this is what’s going to happen, and this is how your life is going to be.’ But that didn’t happen.”* (P1, VUSs, Neurologic/Ataxia)

Ambiguity uncertainty was marked by many participants’ understanding that there is currently a lack of genomics knowledge necessary for the complete interpretation of ES data to provide a diagnosis. One participant, while describing what he learned during result disclosure, demonstrated this ambiguity uncertainty:

> *"Although they don't know what they don't know, either. There's always a possibility there could be something there, but they just don't know."* (P19, Negative, Neurologic/Ataxia)

Some perceived a nonexistent recurrence risk for their undiagnosed condition based on their result. They did not demonstrate an understanding that despite not having a molecular diagnosis by ES, there is still the possibility for hereditary transmission of their condition. For instance, when asked about what implications his result had for family members, one participant said about recurrence risk:

> *"Well, I was concerned about family members, and how it might affect any nieces or nephews, brothers or sisters, and I was assured that that would not be the case based on what they learned from the exome sequencing. So that was good. That was a relief."* (P9, VUSs, Myopathy)

This misunderstanding of a more nuanced genetics concept may reflect *complexity uncertainty.* However, it may also reflect a desire for their result to have some useful meaning or a realization that their result rules out some number of known heritable conditions.

Illness Beliefs and Identity—Uncertainty was also experienced as a 'lack of identity,' which falls under *person-centered issues of uncertainty* (Han et al, 2017). For many, being undiagnosed was isolating because a significant part of their identity was undefined. Receiving a diagnosis would mean regaining that missing identity and being able to join an identifiable group of people with the same known condition, which has certain benefits such as access to support groups and the ability to qualify for participation in research. When asked directly about participation in support groups and research, many expressed that they desired these opportunities, but their undiagnosed status made them difficult to find. For example, one participant described the challenge of finding the right support group:

> *"As far as support groups or whatever it's kind of difficult because I don't fit in with anyone. I'm unique."* (P5, Negative, Ambiguous)

Babrow's *structuring of information* also describes how our participants experienced the uncertainty from their result (Babrow et al, 1998). Regarding the effects of ES results on beliefs about the cause of their undiagnosed condition, most reported that their result reinforced their previous belief that their condition had either a genetic or non-genetic cause. In other words, ES results were seen as consistent with participants' prior beliefs about the etiology of their conditions. For instance, one participant's VUS reinforced her belief that her undiagnosed condition had a genetic cause. She described her VUS as being in only one allele of a gene known to cause an autosomal recessive condition that is similar to her constellation of symptoms. She believes she has a milder version of this recessive condition, and that in the future, geneticists will learn that a milder form can be caused by a single pathogenic variant. She explained:

> *"I guess it makes me more confident that there is a genetic explanation, as strange as that sounds. I do think that it's not a coincidence that I have this one defective gene that's related to [condition]. Even though they don't think that the*

characteristics are expressed if you only have one gene, I think that maybe there's something that they just don't know, maybe [I] don't have the full [condition]. So to me it confirms that there's something there; they just haven't quite figured it out yet." (P18, VUSs, Connective Tissue)

On the other hand, other participants' results reinforced the belief that their condition has a non-genetic cause. For example, one spoke about how his result reinforced his belief that his condition was caused by rare side effects of a cholesterol medication he once took (P3, VUSs, Myopathy). Another participant shared how his VUS reinforced his belief that Lyme disease explained his undiagnosed condition (P12, VUSs, Cardiovascular). Finally, a participant spoke about how her result reinforced her belief that her condition is non-genetic because no one else in her family has similar symptoms:

"I think it's most likely not genetic because nobody else that I've ever heard of in a hundred relatives has ever had it. And I know it can be a spontaneous genetic issue, that this can start with me-- I understand that-- but for some reason I just don't think it is." (P20, Negative, Neurologic/Ataxia)

Responses to Inherent Uncertainty—Most participants reported that their result reminded them of the *inherent uncertainty* of their undiagnosed condition, specifically the uncertainty around cause, prognosis, and treatment or cure. The response to remembering this inherent uncertainty during result disclosure was described by most as disappointment or frustration. For example, one described how each inconclusive test result received during her diagnostic odyssey makes her feel frustrated:

"I'm kind of used to the frustration, but it is a little frustrating that every time I go in, they're like, 'Oh, you've got this, this, this, this,' but they don't really know." (P14, Negative, Ambiguous)

Another participant described her disappointment about ES not resolving the inherent uncertainty of the cause of her condition:

"I was totally disappointed because I wanted an answer and I thought, you know, I don't even care if I'm diagnosed with something, I just want to know what this is…" (P13, Negative, Cardiovascular)

Acclimation to Illness Uncertainty

Our participants' expectations about ES relieving some illness uncertainty align with Mishel's theory of uncertainty in illness (Mishel, 1990). All expressed a belief that ES was unlikely to relieve illness uncertainty. While many mentioned that their genetics provider discussed the small likelihood of a diagnostic result during pre-test counseling, participants mostly attributed their expectations about their results to having a history of receiving inconclusive or non-diagnostic clinical test results during their diagnostic odysseys. One participant illustrated how her diagnostic odyssey influenced her expectations:

"What I think of in the course of battling this for almost 20 years I've kind of learned to lower my expectations and not expect a lot." (P5, Negative, Ambiguous)

This expectation of continued illness uncertainty was also revealed when participants were asked about their initial emotional response to receiving their result. Some expressed having a neutral response because they expected an inconclusive or non-diagnostic result and were used to receiving them from clinical tests. For example, one described his response to his result as:

> *"I didn't have a huge reaction to it because it said what I expected it to say… But it didn't upset me; it didn't really have any negative effects, nor a positive effect because it didn't really tell me anything. So I guess I'd say I had a fairly neutral reaction to it."* (P11, VUSs, Myopathy)

Being acclimated to illness uncertainty allowed participants to more easily accept and move on from the additional uncertainty added by this most recent ES result. In fact, many reported the use of acceptance when asked about coping strategies. Participants expressed being able to "move on" from their result disclosure experience relatively quickly because their result had little impact on their lives or understanding of their condition. This minimal impact of their result explains why most did not report feeling differently about their results over time.

Hope & Optimism

Motivations—Despite participants universally expecting that it was unrealistic for ES to relieve illness uncertainty, all still hoped that it would. Participants' primary motivation for electing ES was a residual hope that the test could provide a diagnosis. How a diagnosis could specifically relieve illness uncertainty was different for different participants. Some wished that a diagnosis could provide clarity about recurrence risk. When describing his motivations for electing ES, one participant said:

> *"It was just knowing that this condition that I have wouldn't be passed on to my children. That was basically-- for me, that's what I was hoping to hear from it…"* (P19, Negative, Neurologic/Ataxia)

Others anticipated that a diagnosis would relieve prognostic uncertainty or provide specific guidance for treatment or management of symptoms. For example, when describing his hopes for what ES could provide, one said:

> *"I think information that […] could help me have a better idea of what might be going on with me and help plan for the current and the future I think would be beneficial."* (P9, VUSs, Myopathy)

Finally, some desired that a diagnosis would make them eligible to participate in clinical trials related to their condition, which meant contributing to efforts aimed at relieving uncertainty about their undiagnosed condition.

Promise of Advances in Genomics—Participants also expressed hope regarding the promise of future technologies or advances in genomics knowledge relieving illness uncertainty. This hope was expressed in two different ways. First, it was expressed in the context of participants understanding the limitations associated with ES. While many described ES as being the most comprehensive genetic diagnostic test available, some

demonstrated the additional understanding that the test's diagnostic utility only stretches as far as the current state of genomics knowledge. In other words, some understood that there may still be a genetic explanation for their condition that has yet to be discovered and so ES could not detect it at this time. For example, one participant demonstrated an understanding of this concept when discussing what he learned during pre-test counseling:

> *"Just because it's not there, there's other genes that we haven't unlocked yet that may be causal."* (P23, VUSs, Neurologic/Ataxia)

This more nuanced understanding of a limitation of ES may be explained by detailed pre-test counseling or the sample majority having at least a college education. Nevertheless, this understanding reflects hope in advances in genomics knowledge producing a future diagnosis. Second, hope was expressed in the context of motivations for electing ES. Specifically, some participants were motivated to have ES because they knew their genetics provider could reanalyze their genomic data in the future. For instance, one recalled learning about reanalysis from her provider:

> *"Sometimes new medical science goes on, they get new, more information about causes of ataxia or places it can be, genes it can be in, and sometimes they like to retest things, and sometimes they actually get a diagnosis on the second testing…"* (P20, Negative, Neurologic/Ataxia)

This motivation demonstrates hope that reanalysis may provide a molecular diagnosis in the future. Participants who expressed hope in these two ways illustrate how a desire for a diagnosis may persist despite the disappointment and frustration that is associated with receiving a non-diagnostic result or despite acclimation to illness uncertainty. This persistent hope was often reported as a coping mechanism for dealing with the unresolved uncertainty from ES and their undiagnosed condition.

Self-Enhancing Evaluations—Participants described optimism as another coping strategy for dealing with the uncertainty of their result and undiagnosed condition. Many explicitly mentioned having positive attitudes, while others demonstrated optimism through self-enhancing evaluations, which Taylor states can help restore self-esteem and self-control (Taylor, 1983). For example, one explained how surviving many cardiac events helped him to learn to be grateful for each day, a lesson that he feels not many people learn:

> *"I'm just trying hard to be a glass-half-full guy-- but I consider this whole episode to be an absolute gift to me because I'm a healthy, active, middle-aged guy, and I've had these near-death experiences and I walked away, and I'm still a healthy, active, middle-aged guy, and I can do everything that I want to do, and I've been reminded that […] tomorrow is not promised, and live for today, and I wake up in the morning every morning and I'm happy just because I wake up, and I think a lot of people don't get to enjoy that."* (P12, VUSs, Cardiovascular)

Another consistently brought the conversation back to his optimistic spirit when describing his response to his result, saying:

> *"I just stay positive about life. There's enough bad stuff and, like I said, a lot of people are dealt some unfortunate things, much worse than me."* (P9, VUSs, Myopathy)

"Healthier" Perspective—Participants also demonstrated optimism when describing their emotional responses to and perceptions of the meaning of their result. For example, positive attitudes were expressed when participants, like these two, reported feeling relief or happiness that ES, while not providing a diagnosis, at least did not detect a terminal diagnosis or ruled out some terminal or severe diagnoses:

> *"I mean, I guess I would rather not have an explanation for what has happened to me than to say, 'Oh, you have brain cancer,' or 'You have this.' So I was very happy in a way…"* (P1, VUSs, Neurologic/Ataxia)

> *"…it's good to rule out all the really bad stuff and no causative mutations."* (P13, Negative, Cardiovascular)

While a negative result or VUS does not directly relieve diagnostic uncertainty, optimism is employed by some to feel that ES somehow indirectly relieves some illness uncertainty by ruling out certain diagnostic possibilities or confirming some level of healthiness. These types of positive responses to unresolved diagnostic uncertainty reveal how optimism can be used as a coping strategy to reduce some of the associated uncertainty (Mishel, 1990).

DISCUSSION

Experiences and perceptions of uncertainty related to participants' ES result and undiagnosed condition reflected categories of Han's and Babrow's taxonomies of genomic uncertainty (Babrow et al, 1998; Han et al, 2017). Our participants were acclimated to illness uncertainty due to their ongoing diagnostic process, which resulted in realistic expectations about and acceptance of their results. However, participants still hoped that ES would end their diagnostic odyssey, and many remain hopeful that future technological advances will provide a diagnosis. Hope and optimism were used as coping strategies for the unresolved uncertainty.

There were no thematic differences between the experiences of participants who received negative results versus those who received VUSs, suggesting that adult undiagnosed patients may have similar affective and behavioral responses to unresolved diagnostic uncertainty after ES regardless of the type of ES result. The type of non-diagnostic result may have little influence on perceptions and coping strategies for genomic and illness uncertainty because in all cases the results do not provide diagnoses or prognoses.

Responses to the *Intolerance of Uncertainty* and *PUGS* scales revealed a wide variance in reported levels of intolerance for and perceptions of uncertainty related to their results. While there were no thematic differences when comparing participants who scored "high" vs. "low" on either measure, our sample may be too small to detect significant differences between these groups. Nevertheless, this finding suggests that intolerance for and perceptions of uncertainty may not influence the ways adult undiagnosed patients cope with and adapt to unresolved uncertainty after ES, perhaps because of their acclimation to

illness uncertainty. This suggestion differs from what we know from other qualitative studies involving healthy individuals, which find that perceptions of uncertainty about genome sequencing results influence attitudes and coping (Biesecker et al, 2014).

The responses of parents of undiagnosed children to receiving VUSs and negative results from their child's CMA have been extensively described (Desai et al, 2018; Hayeems et al, 2016; Kiedrowski et al, 2016; Jez et al, 2015; Reiff et al, 2017; Wilkins et al, 2016). Many similarities can be seen between our participants and that of parents described in this literature. For instance, parents of children with autism spectrum disorder who received negative results or VUSs from CMA shared that their child's result reinforced prior beliefs that their child's condition had either a genetic or non-genetic cause. Specifically, family history of autsim was a strong factor for the persistent belief of a genetic etiology, and vaccination was a common belief for non-genetic etiology (Reiff et al, 2017). It is perhaps not surprising that both our participants and parents of undiagnosed children integrated their non-diagnostic results in a way that was consistent with prior beliefs, as people tend to interpret genetic information about their condition within the context of their own experiences and beliefs (Kiedrowski et al, 2016; Sankar et al 2006).

Both parents and our participants were left feeling frustrated by unresolved diagnostic uncertainty (Hayeems et al, 2016), and worried about continued prognostic uncertainty (Kiedrowski et al, 2016; Wilkins et al, 2016). However, like our participants, parents also understood the limitations of genomic knowledge and were hopeful that future advances in the field would offer more information about their child's condition and treatment (Hayeems et al, 2016; Kiedrowski et al, 2016; Reiff et al, 2017; Wilkins et al, 2016).

Our participants had particularly good recall and understanding of their ES results. In contrast, inconsistent recall and understanding have been reported in adult patients with cancer who received negative results or VUSs from germline cancer gene panel testing (Makhnoon et al, 2019; Richter et al, 2013; Solomon et al, 2017; Vos et al, 2008). Patients with cancer may have more confusion about their negative or uncertain genetic results due to the acute nature of the disease and less exposure to illness uncertainty than our study participants. Patients with cancer who have a strong family history of cancer might also have higher expectations for receiving definitive results from their germline cancer genetic testing and these higher expectations may interfere with their ability to understand results that are negative or uncertain. Parents of children with a variety of phenotypes also reported inconsistent understanding about their children's uncertain CMA results. Parents were more likely to interpret VUSs as causal while still acknowledging the clinical uncertainty associated with the results (Kiedrowski et al, 2016; Reiff et al, 2017; Wilkins et al, 2016). This interpretation of a VUS as causal may be influenced by how the genetics provider described the result to the parents. Some genetics providers may believe the VUS to be causal based on the gene's close phenotypic match to that of the patient (while still accepting that the laboratory must interpret and report the variant as uncertain based on standard and accepted guidelines). Another reason parents may perceive their child's VUS as being the cause of their child's condition is to cope with their child's illness uncertainty. This explanation of incongruent recall and understanding is a method of coping that results from a threat appraisal of illness uncertainty (Mishel, 1990).

Given this previous observation, one might have expected to observe the same phenomenon among undiagnosed adults. However, this was not apparent in the interviews. Adults with undiagnosed conditions may be more comfortable living with their own illness uncertainty, and therefore do not need to reduce it in this way, thus resulting in both accurate recall and understanding of their result. Parents, on the other hand, may not be as comfortable or acclimated with illness uncertainty because they are experiencing it related to their child's health rather than their own health. It may also be that there are arguably more years of uncertainty ahead in a child's life when compared to an adult. As ES becomes more prevalent among adult patients, future studies should explore this in a more diverse population of undiagnosed adults.

Our findings were consistent with recent studies that demonstrated participants' unresolved illness uncertainty from ES results that fail to reveal a molecular diagnosis. Specifically, expectations for non-diagnostic exome results due to acclimation to illness uncertainty, as well as persistent hope that uncertainty will be resolved by future scientific advances, have been previously described in our population, as well as in healthy individuals, cardiology patients, and parents of undiagnosed children (Jamal et al, 2017; Skinner et al, 2016; Skinner et al, 2018).

Study Limitations

Our findings are not representative of all adult undiagnosed patients who receive non-diagnostic results from ES. Our participants were generally well-educated, which may influence their ability to more accurately recall and understand their results. Our sample was also enriched for participants with neurologic or ataxic phenotypes. While our interviews did not include questions regarding disease-specific influences on perceptions of ES results, it is possible this enrichment influenced the data in a particular direction. The variety of symptomatology of undiagnosed conditions among our sample surely allowed us to capture over-arching themes, but perhaps more nuanced differences would be detected from studying a sample of adult patients who all had similarly presenting undiagnosed conditions. Recruitment from two different sites allowed for some diversification in understanding the influences of different types of post-test counseling; yet, genetic counseling practices at other sites may differ from the practices at our recruitment sites and would perhaps alter findings. It should also be noted that as ES is offered earlier in the diagnostic process in the future, reactions to uncertain genomic information may differ.

Practice Implications

Our findings have implications for the clinical practice of genetics providers. This study demonstrated the range of emotional responses adult undiagnosed patients may have from receiving a negative result or one or more VUSs from ES. Genetics providers should remain prepared to help patients process the variety of emotions they may feel during result disclosure.

Adult undiagnosed patients experienced and perceived the uncertainty of their result in a variety of ways. Genetics providers should explore the ways in which their patients perceive this uncertainty to facilitate appropriate meaning-making of their result. Assessing

the client's prior beliefs for the cause of their undiagnosed condition and eliciting the experience of their diagnostic odyssey may also help in this process, especially if these conversations begin during pre-test counseling.

Reanalysis was acknowledged by participants as an important benefit of undergoing ES and was a source of hope. In fact, knowledge of VUS reclassification and promise of provider re-contact in the event of reclassification has been reported as an important coping mechanism for uncertainty in adult cancer patients (Makhnoon et al, 2019; Solomon et al, 2017). Providers and laboratories should do what they can to facilitate reanalysis for their patients and overall practice. As ES becomes more broadly available, genetics clinics and laboratories should consider developing systematic plans for conducting reanalysis for all patients who consent to it. The process may become more easily automated with the development of reanalysis functionalities of genomic databases.

Many participants mentioned they would like to participate in support groups or research but are unable to find opportunities for which they qualify or fit in. While most research opportunities require a diagnosis to qualify for participation, providers may be equipped with referrals to studies which focus on undiagnosed patient populations. In addition, genetics providers may consider developing and/or facilitating support groups for their undiagnosed patients within their institutions. They may also offer to connect their undiagnosed patients who express a desire to speak with others who are undiagnosed.

Research Recommendations

The purpose of this study was to provide a preliminary understanding of how adult undiagnosed patients recall, perceive, and cope with unresolved uncertainty from ES. This patient population and their responses to genomic uncertainty remain ripe for future studies. Larger-scale studies on the affective and behavioral impacts of unresolved uncertainty from ES may provide more generalizable information and target specific challenges in coping and adaptation that may inform intervention studies. As ES is offered earlier in the diagnostic process in the future, comparative studies may be warranted. Future studies may also focus on the impact of other types of ES results that may leave patients with unresolved diagnostic uncertainty, or the typical practices of genetics providers in providing pre- and post-test genetic counseling to those seeking ES and receiving non-diagnostic results.

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REFERENCES

Babrow AS, Kasch CR, & Ford LA (1998). The many meanings of uncertainty in illness: toward a systematic accounting. Health Commun, 10(1), 1–23. doi:10.1207/s15327027hc1001_1 [PubMed: 16370987]

Basel D, & McCarrier J. (2017). Ending a Diagnostic Odyssey: Family Education, Counseling, and Response to Eventual Diagnosis. Pediatr Clin North Am, 64(1), 265–272. doi:10.1016/j.pcl.2016.08.017 [PubMed: 27894449]

Berg JS (2014). Genome-scale sequencing in clinical care: establishing molecular diagnoses and measuring value. JAMA, 312(18), 1865–1867. doi:10.1001/jama.2014.14665 [PubMed: 25326641]

Biesecker BB, Klein W, Lewis KL, Fisher TC, Wright MF, Biesecker LG, & Han PK (2014). How do research participants perceive “uncertainty” in genome sequencing? Genet Med, 16(12), 977–980. doi:10.1038/gim.2014.57 [PubMed: 24875302]

Biesecker BB, Woolford SW, Klein WMP, Brothers KB, Umstead KL, Lewis KL, . . . Han PKJ (2017). PUGS: A novel scale to assess perceptions of uncertainties in genome sequencing. Clin Genet, 92(2), 172–179. doi:10.1111/cge.12949 [PubMed: 27925165]

Boyatzis RE (1998). Transforming Qualitative Information: Thematic Analysis and Code Development. Thousand Oaks, CA: Sage Publications.

Carleton RN, Norton MA, & Asmundson GJ (2007). Fearing the unknown: a short version of the Intolerance of Uncertainty Scale. J Anxiety Disord, 21(1), 105–117. doi:10.1016/j.janxdis.2006.03.014 [PubMed: 16647833]

Desai P, Haber H, Bulafka J, Russell A, Clifton R, Zachary J, . . . Chung WK (2018). Impacts of variants of uncertain significance on parental perceptions of children after prenatal chromosome microarray testing. Prenat Diagn, 38(10), 740–747. doi:10.1002/pd.5323 [PubMed: 29956345]

Elo S, & Kyngas H. (2008). The qualitative content analysis process. Journal of Advanced Nursing, 62(1), 107–115. Doi:0.1111/j.1365-2648.2007.04569.x [PubMed: 18352969]

Graungaard AH, & Skov L. (2007). Why do we need a diagnosis? A qualitative study of parents’ experiences, coping and needs, when the newborn child is severely disabled. Child Care Health Dev, 33(3), 296–307. doi:10.1111/j.1365-2214.2006.00666.x [PubMed: 17439444]

Han PKJ, Umstead KL, Bernhardt BA, Green RC, Joffe S, Koenig B, . . . Biesecker BB (2017). A taxonomy of medical uncertainties in clinical genome sequencing. Genet Med, 19(8), 918–925. doi:10.1038/gim.2016.212 [PubMed: 28102863]

Hayeems RZ, Babul-Hirji R, Hoang N, Weksberg R, & Shuman C. (2016). Parents’ Experience with Pediatric Microarray: Transferrable Lessons in the Era of Genomic Counseling. J Genet Couns, 25(2), 298–304. doi:10.1007/s10897-015-9871-3 [PubMed: 26259530]

Hennink MM, Kaiser BN, & Marconi VC (2017). Code Saturation Versus Meaning Saturation: How Many Interviews Are Enough? Qual Health Res, 27(4), 591–608. doi:10.1177/1049732316665344 [PubMed: 27670770]

Jamal L, Robinson JO, Christensen KD, Blumenthal-Barby J, Slashinski MJ, Perry DL, . . . McGuire AL (2017). When bins blur: Patient perspectives on categories of results from clinical whole genome sequencing. AJOB Empir Bioeth, 8(2), 82–88. doi:10.1080/23294515.2017.1287786 [PubMed: 28949844]

Jez S, Martin M, South S, Vanzo R, & Rothwell E. (2015). Variants of unknown significance on chromosomal microarray analysis: parental perspectives. J Community Genet, 6(4), 343–349. doi:10.1007/s12687-015-0218-4 [PubMed: 25666435]

Khan CM, Moore EG, Leos C, & Rini C. (2016). Patient hopes for diagnostic genomic sequencing: roles of uncertainty and social status. Eur J Hum Genet, 24(6), 803–808. doi:10.1038/ejhg.2015.204 [PubMed: 26395557]

Kiedrowski LA, Owens KM, Yashar BM, & Schuette JL (2016). Parents’ Perspectives on Variants of Uncertain Significance from Chromosome Microarray Analysis. J Genet Couns, 25(1), 101–111. doi:10.1007/s10897-015-9847-3 [PubMed: 25983052]

Li X, Nusbaum R, Smith-Hicks C, Jamal L, Dixon S, Mahida S. (2019). Caregivers’ perception of and experience with variants of uncertain significance from whole exome sequencing for children with undiagnosed conditions. J Genet Couns, 28(2), 304–312. doi: 10.1002/jgc4.1093. [PubMed: 30680845]

Lipinski SE, Lipinski MJ, Biesecker LG, & Biesecker BB (2006). Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling. Am J Med Genet C Semin Med Genet, 142C(4), 232–240. doi:10.1002/ajmg.c.30107 [PubMed: 17068805]

Madeo AC, O'Brien KE, Bernhardt BA, & Biesecker BB (2012). Factors associated with perceived uncertainty among parents of children with undiagnosed medical conditions. Am J Med Genet A, 158A(8), 1877–1884. doi:10.1002/ajmg.a.35425 [PubMed: 22711240]

Maheu C, & Thorne S. (2008). Receiving inconclusive genetic test results: an interpretive description of the BRCA1/2 experience. Res Nurs Health, 31(6), 553–562. doi:10.1002/nur.20286 [PubMed: 18449940]

Makhnoon S, Shirts BH, & Bowen DJ (2019). Patients' perspectives of variants of uncertain significance and strategies for uncertainty management. J Genet Couns, 28(2), 313–325. doi:10.1002/jgc4.1075 [PubMed: 30636062]

Mishel MH (1990). Reconceptualization of the uncertainty in illness theory. Image J Nurs Sch, 22(4), 256–262. [PubMed: 2292449]

O'Neill SC, Rini C, Goldsmith RE, Valdimarsdottir H, Cohen LH, & Schwartz MD (2009). Distress among women receiving uninformative BRCA1/2 results: 12-month outcomes. Psychooncology, 18(10), 1088–1096. doi:10.1002/pon.1467 [PubMed: 19214961]

Reiff M, Bugos E, Giarelli E, Bernhardt BA, Spinner NB, Sankar PL, & Mulchandani S. (2017). "Set in Stone" or "Ray of Hope": Parents' Beliefs About Cause and Prognosis After Genomic Testing of Children Diagnosed with ASD. J Autism Dev Disord, 47(5), 1453–1463. doi:10.1007/s10803-017-3067-7 [PubMed: 28229350]

Retterer K, Juusola J, Cho MT, Vitazka P, Millan F, Gibellini F, …Bale S. (2016). Clinical application of whole-exome sequencing across clinical indications. Genet Med, 18(7):696–704. doi: 10.1038/gim.2015.148. [PubMed: 26633542]

Richter S, Haroun I, Graham TC, Eisen A, Kiss A, & Warner E. (2013). Variants of unknown significance in BRCA testing: impact on risk perception, worry, prevention and counseling. Ann Oncol, 24 Suppl 8, viii69-viii74. doi:10.1093/annonc/mdt312

Rosenthal ET, Biesecker LG, & Biesecker BB (2001). Parental attitudes toward a diagnosis in children with unidentified multiple congenital anomaly syndromes. Am J Med Genet, 103(2), 106–114. [PubMed: 11568915]

Sankar P, Cho MK, Wolpe PR, & Schairer C. (2006). What is in a cause? Exploring the relationship between genetic cause and felt stigma. Genet Med, 8(1), 33–42. doi:10.109701.gim.0000195894.67756.8b [PubMed: 16418597]

Sawyer SL, Hartley T, Dyment DA, Beaulieu CL, Schwartzentruber J, Smith A, . . . Consortium CRC (2016). Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. Clin Genet, 89(3), 275–284. doi:10.1111/cge.12654 [PubMed: 26283276]

Skinner D, Raspberry KA, & King M. (2016). The nuanced negative: Meanings of a negative diagnostic result in clinical exome sequencing. Sociol Health Illn, 38(8), 1303–1317. doi:10.1111/1467-9566.12460 [PubMed: 27538589]

Skinner D, Roche MI, Weck KE, Raspberry KA, Foreman AKM, Strande NT, . . . Henderson GE (2018). "Possibly positive or certainly uncertain?": participants' responses to uncertain diagnostic results from exome sequencing. Genet Med, 20(3), 313–319. doi:10.1038/gim.2017.135 [PubMed: 29593351]

Solomon I, Harrington E, Hooker G, Erby L, Axilbund J, Hampel H, . . . Leonard L. (2017). Lynch Syndrome Limbo: Patient Understanding of Variants of Uncertain Significance. J Genet Couns, 26(4), 866–877. doi:10.1007/s10897-017-0066-y [PubMed: 28127677]

Taylor SE (1983). Adjustment to threatening events: A theory of cognitive adaptation. Am Psychol 38(11), 1161–1173.

Vos J, Otten W, van Asperen C, Jansen A, Menko F, & Tibben A. (2008). The counsellees' view of an unclassified variant in BRCA1/2: recall, interpretation, and impact on life. Psychooncology, 17(8), 822–830. doi:10.1002/pon.1311 [PubMed: 18157792]

Wilkins EJ, Archibald AD, Sahhar MA, & White SM (2016). "It wasn't a disaster or anything": Parents' experiences of their child's uncertain chromosomal microarray result. Am J Med Genet A, 170(11), 2895–2904. doi:10.1002/ajmg.a.37838 [PubMed: 27411073]

Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, . . . Eng CM (2013). Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med, 369(16), 1502–1511. doi:10.1056/NEJMoa1306555 [PubMed: 24088041]

Table 1.

Demographics and characteristics of the study participants

Characteristic	Participants with VUSs Result (N=14)	Participants with Negative Result (N=9)
Age at Time of Recruitment	28–69 years	29–71 years
Male	79% (11/14)	33% (3/9)
White	91% (13/14)	100% (9/9)
Estimated Annual Household Income		
<$45,000	2	3
$45,000-$89,999	1	1
≥$90,000	10	5
Declined to answer	1	0
Education		
Graduate School	8	1
College Graduate	5	6
Some College	1	1
High School	0	1
Length of Diagnostic Odyssey		
6 months – 1 year	1	0
3–4 years	5	2
5–10 years	2	5
over 10 years	6	2
Approximate Time Passed Since Exome Result Disclosure, Range	1 month – 4.25 years	6 months – 2.5 years
Category of Undiagnosed Condition [a]		
Neurologic/Ataxia [b]	7	3
Myopathy [c]	3	2
Cardiovascular [d]	1	1
Connective Tissue [e]	1	0
Ambiguous [f]	2	3
Intolerance of Uncertainty Short-Form Scale [g], mean (SD); Median	25.9 (8.34); 25	30.4 (8.50); 28
Perceptions of Uncertainties in Genome Sequencing Scale [h], mean (SD); Median	36 (9.90); 37.5	32.2 (6.38); 34

[a] Based solely on participant report of their symptoms. Conditions were characterized based on a majority of symptoms fitting into one particular category; therefore, some conditions may share symptoms from other categories.

[b] Refers to unspecific ataxia/movement diagnoses, or symptoms reflecting neurologic issues such as tremors or slurred speech.

[c] Refers to unspecific muscle-related diagnoses or symptoms such as muscle weakness and pain.

[d] Refers to cardiac conditions or events such as cardiomyopathy or aortic dissection.

[e] Refers to symptoms reflective of a connective tissue condition, such as hypermobility and joint pain.

[f] Refers to a symptomatology that did not have a majority of symptoms fitting into one distinct category.

[g] Higher scores convey greater intolerance of uncertainty. Range: 16–48.

[h] Higher scores convey greater certainty in patients' perceptions of their genome sequencing results. Range: 20–50