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Parental attitudes, values, and beliefs toward the return of results from exome sequencing in children

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Abstract

Exome sequencing is being offered for children with undiagnosed conditions to identify a primary (causative) variant. Parental preferences for learning secondary (incidental) variants are largely unexplored. Our objective was to characterize values and beliefs that shape parents' preferences for learning their children's sequencing results. We conducted semi-structured interviews with 25 parents of 13 minor probands with a variety of rare genetic conditions. Parents were asked to discuss their preferences to receive four types of results from exome sequencing. Many parents preferred to receive all types of results. Parents had the most positive attitudes toward learning about variants that predispose to disorders treatable or preventable in childhood. They had reservations about learning about predispositions for untreatable adult-onset conditions and carrier status for recessive conditions. Parents described their success in coping with their child's condition as evidence for an ability to manage any additional negative health information. They felt responsible for learning about secondary variants, desiring a gain in control over their child's health. Our findings suggest that investigators should incorporate parents' perceptions of the value in receiving secondary variant information about their children when designing studies employing exome sequencing.

Keywords

genome sequencing; incidental findings; patient preferences; Theory of Reasoned Action

Introduction

Exome sequencing is a powerful tool that provides unprecedented opportunities to learn personalized genomic data. As an emerging technology, exome sequencing pushes many existing boundaries in the realms of privacy and confidentiality, personal decision-making, and the ethical obligations of researchers and clinicians with respect to anticipated and

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unanticipated findings. Debates about these topics are not novel (1, 2) and an emerging ethical consensus favors a qualified disclosure policy (3–5).

Despite a robust discussion in the literature that includes several consensus statements (6–8), there is a relative dearth of studies assessing the attitudes and expectations of research participants about learning information generated by exome sequencing. When these preferences have been assessed, attitudes toward learning results of all types are generally positive (9–11). However, much remains unknown about the values and beliefs inform participants' attitudes and whether they pertain to parents of affected children undergoing exome sequencing to identify genetic contributions to their child's condition.

In the pediatric population sequencing provides a powerful way to elucidate the molecular causes of rare conditions and multiple congenital anomaly syndromes (12). Early evidence suggests that parents of children with undiagnosed conditions view sequencing as the next step in attempting to identify a genetic cause for their child's condition (10). Yet parents find themselves in uncharted territory facing decisions about whether to learn secondary variants and which type of findings to receive. Researchers and clinicians seek evidence to guide them in identifying effective ways to facilitate such choices(13–15). Understanding parental preferences for receiving exome sequencing results for their children and related values and beliefs are key to designing interventions to facilitate informed choice.

To address these issues, we conducted a semi-structured qualitative interview study to assess parents' values, beliefs, and attitudes toward receiving exome sequencing results for their children. This study aims to assess the ways in which parents conceptualize genomic data and factors that contribute to their decision-making.

Materials and Methods

Participants were recruited from an exome sequencing study at the National Institutes of Health (NHGRI protocol 10-HG-0065). The parent study has two main goals: 1) to determine the molecular etiology of rare conditions, and 2) to study and develop best-practices approaches regarding the return of individual genetic variant results generated by exome sequencing. Participants may opt to learn both "primary" variant results (causative variants for the condition under investigation) and "secondary" variant results (genetic variants that cause or are associated with human disease other than the primary condition, also known as incidental findings). This protocol, which had broad eligibility, typically employed a "trio-based" approach. The National Human Genome Research Institute Institutional Review Board reviewed and approved the study.

English-speaking mothers and fathers of children 18 years old or younger who were enrolled in the parent study were eligible and invited to participate. Verbal consent was obtained by telephone for the interview study, which took place before an in-person informed consent session where written consent for their participation in the exome sequencing study(with parents consenting on their child's behalf) was obtained. It is important to note that in consenting for the sequencing study, all participants agreed to receive potentially life-saving

genetic test results, were they to be discovered. However, the structured interviews took place before this consent took place.

Participants completed a 30–45 minute semi-structured telephone interview designed to capture parental attitudes toward exome sequencing for their children. With one exception, all interviews were conducted by one investigator (DD), recorded, and transcribed. This investigator did not participate in any consent or results discussions with the participants nor did she code the results.

The Theory of Reasoned Action, a health behavior model that posits the importance of attitudes in predicting behavioral intentions, was used as a framework for the interview (16). Key constructs of interest included attitudes toward learning results and the values and beliefs that defined them. Questions were designed to elicit these constructs related to sequencing. Types of results from sequencing were grouped into categories derived from the literature and clinical experience and the interview guide was piloted and revised as needed. To facilitate understanding of various types of results, an example of a result from each category was provided as displayed in Table 1. Parents were asked about if they would want to learn their child's specific results in each category and then to explain their preference.

Transcripts of the first several interviews were analyzed to assess the need for additional questions. A codebook was developed based on the interview guide and revised in an iterative process. LEI and CS coded each transcript using NVivo™ software. Coding discrepancies were discussed and when appropriate, resolved, yielding a final Kappa score of 0.7. The interview guide and the final codebook can be found in Supplementary Materials.

Results

Study Population

Twelve fathers and thirteen mothers (thirteen families) with an average age of 39 years participated; Table 2 describes participants' and probands' demographic and phenotypic information. Each family had one affected child except for one family with four affected children. Table 3 summarizes parental preferences for receipt of secondary variant information, major themes that emerged as they described the rationale behind their preferences, and selected exemplar quotes.

Prospect of Learning Primary Variant

All twenty-five participants held positive attitudes towards learning their child's primary variant. This finding was anticipated given that a frequently cited motivation to participate in the parent study was the prospect of learning the cause of their child's condition. The most common reasons cited for their hope of learning of a primary variant were the opportunity for an explanation for their child's condition and having a distinct preference to learn any health information. The opportunity to prepare for their child's future healthcare and the potential for better management of their child's condition were also cited as reasons to learn results.

Secondary Variants for Treatable and Preventable Genetic Conditions

All twenty-five participants also conveyed positive attitudes toward learning secondary genetic variants for conditions that are treatable or preventable in childhood. The majority of parents (17) wanted this information to help guide their child's healthcare but six also valued this information for its own sake.

Secondary Variants for Untreatable and Unpreventable Genetic Conditions

Attitudes toward learning variants that confer genetic susceptibility for health conditions not actionable in childhood were more varied. Ten parents wanted to learn these results, six did not, and the remaining nine were either ambivalent (6) or placed constraints on learning this information (3). When explaining their attitudes toward these results, many participants discussed the importance of being aware of health risks to their child, even if these risks would be realized in adulthood. They cited hope that means to mitigate adult health risks may become available in the future and relayed plans to stay abreast of new information that might affect their child's future risks. Other parents expressed more hesitation about this prospect and were ambivalent or had outright negative attitudes toward learning variants in this category. These parents expressed the need to consider this decision further and were concerned that learning information of this nature could cause additional worry or uncertainty.

Carrier Status for Recessive Genetic Conditions

Thirteen participants expressed a desire to learn about variants for recessive disorders their child carries because of this information's potential to inform their child's future reproductive risks. The remaining twelve participants' attitudes were either ambivalent or conditionally positive. These parents acknowledged that learning these variants would have little impact on their children in the near term. Fourteen participants mentioned a desire to share the information with their child when he or she was older or allowing for the child to make his or her own decision in the future.

Values and Beliefs

Explicit values and beliefs underlying participants' attitudes emerged and fell into five themes.

Parental Responsibility—Woven throughout participants' explanations for their desire to learn their child's sequence variants in all categories was a strong feeling of parental responsibility. Parents described their diagnostic odyssey and their desire to do the best that they could as parents in understanding their child's condition; they viewed pursuing the most extensive testing available to them as part of their obligation to care for their child. Further, they cited the notion that new information, both related and unrelated to their child's condition, was not likely to cause them significant additional distress given what they have already lived through.

> "We've already been through the process of thinking the worst, so finding out, you know, some of this information, I've already been down that road of thinking

> [name of child] may only live to be 10. You know, I've been down that road so at this point, I could handle this." [M/6y][1]

> "I mean, we've already been through a ton of stuff, I don't think any type of answer that you can give us is going to hurt our feelings…I mean, we're already living and he already is what he is." [F/2y]

Need to Know, Preference for Knowledge—All participants expressed a need to know or a preference for having available information about their child. Many participants expressed deep discomfort with the idea of **not** learning information. One participant said:

> "My husband and I have talked about it extensively; we'd rather know than not know. We'd rather prepare than just throw it up in the air and see where the coins lay." [M/1y]

Control—Eleven participants specifically expressed their desire for control as they explained their interest in learning their child's variant information. The majority expressed having little control over understanding their child's condition prior to diagnosis. Even when the variant information discussed was in the "untreatable/unpreventable" category, these parents still cited ways that they could use or act upon this information, such as keeping abreast of research or taking other steps that they perceived would make a difference for their child.

> "I think it's probably good information to know, because maybe even if we can't do certain things, maybe there are small things we could to do to help be aware of – not leave us in the dark by not knowing."[F/7y]

> "There might not be a cure for it now, but in 10 years, you know, there might be some things we can do to prevent or treat it. So…you know, I'm kind of, of the mind that I might want to know anyway, but, you know, I think this is the kind of thing that we would need to think about more." [M/3y]

Most participants viewed their decision to undergo exome sequencing as an active choice to provide an opportunity to advance and improve their child's healthcare. They acknowledged the extensiveness of this testing and were optimistic that receiving their child's results could empower them to identify novel ways to control aspects of their child's condition.

> "Well, if we're going to go this far, we might as well take it as far as we can…my overall idea is, you know, you wouldn't go through this process, as I said earlier, trying to find out what the future might be medically speaking, you wouldn't go through the process of that without at least, personally, I wouldn't go through it without saying "Well, we might as well find out what we can find out and deal with it if possible." [F/1y]

Faith—Several participants discussed a belief in God or how their faith informed their moral or ethical considerations as they elaborated on their thoughts about the rationale for

[1]Participants are identified by gender ("M" for mother, "F" for father) and the age of their oldest affected child (years(y) or months(m)) at the time of the interview.

their participation in exome sequencing, and presented their preferences for receiving results.

> "God wouldn't have given us the technology to do this if he didn't want us to have it." [M/1y]

One father, in explaining his rationale for wanting to learn about variants related to adult-onset conditions in his daughter said:

> "Well, I guess as she got old enough to understand and we knew that, basically [we'd] just encourage her to enjoy life and not worry about what might happen and, you know, the reality is we're all going to have some ailment probably if we live long enough. So, you know, the reality is just take it as it goes and if it happens, it happens, and you know, the good Lord will take care of you." [F/1y]

Another father took comfort in his children's faith in God as he considered the possible health information that they could learn about themselves as a result of participating in the study.

> "I guess we bring our girls up, they're Christians and believe in God and believe that God is Almighty, all powerful all healing, that all be left in his hands…" [F/5y]

Finally, two families shared their awareness that they may be participating in research that could ultimately be used in a prenatal or preconception setting.

> "I mean the ethical and the moral issue that I'm not comfortable with is I don't want to contribute to, you know, it's out of my control, but I do not want to feel like I'm directly contributing to people having embryos tested for genetic, you know, problems and then terminating them, but I also realize that's going to happen regardless of what our family chooses to do with this study." [M/6y]

Altruism—Based on a previous study of ClinSeq® participants and studies of cancer research participants (9,11,17), it was anticipated that altruism would emerge as one reason for positive attitudes toward learning results. Participants often expressed a desire to help others interlaced with their desire to learn more about their child. One mother reflected:

> "Hopefully the information will help us to understand more about the genetic issue and so other kids that have this can also benefit from that." [M/9m]

Discussion

This study represents one of the first explorations of parents' preferences to learn not only primary variants from exome sequencing, but also secondary variants. Significant values and beliefs behind parents' preferences were illuminated through these interviews and the themes were consistent. Parents of children with undiagnosed genetic conditions demonstrated their willingness to learn and assimilate new information from exome sequencing, regardless of its relationship to the child's primary problem, although the primary variant was their main interest. While there was further interest in learning most types of secondary variants based largely on values of parental responsibility and the importance of knowing, there were limitations to what some parents wanted to learn and

parents' attitudes were not uniformly positive. Regardless of their relative enthusiasm for information, they did not express interest in receiving any and all information. Parents distinguished secondary results in terms of actionability and weighed the possible benefits and consequences of learning their children's results. Many expressed feeling naïve and needing to know more information to make a decision about receipt of results. Notably, all 25 participants voiced a preference for the return of secondary results for treatable disorders. Sorting results by their perceived usefulness and a strong desire to learn information perceived to be useful have been demonstrated parental values in other studies examining parental attitudes toward genetic testing in children (18,19).

Overall, parents were not intimidated by unexpected information, based on their experience of having lived with a child with a rare, undiagnosed condition. They felt that having adapted to an affected child, they had managed to cope successfully with uncertainty and health-threatening circumstances. They expressed confidence in their ability to manage the stress of learning of secondary variants and were able to express that many of them would not likely be worse than what they were already living with or what they had imagined may be in their future. Some turned to their religious beliefs to guide their preferences and voice the limitations to their interest.

Interestingly, parents of children with rare undiagnosed conditions did not appear to hold exceptional or different values and beliefs toward receipt of secondary variants in their children when compared to adults making choices about the types of secondary variants they would like to learn (9,11,20). These findings challenge assumptions that parents are unlikely to be interested in information beyond the primary variant, are unprepared to manage or would be overwhelmed by additional health information about their child. These parents believed that it was their personal responsibility to learn the information coupled with the value of being able to convey their preferences for what information they wanted to learn about their child and themselves. These parents described differences among the types of results by discriminating on clinical actionability, and some parents expressed significant uneasiness with the notion of receiving results pertaining to disorders with few available treatments or prevention and wished to preserve their child's autonomy, consistent with views of many bioethicists and clinicians writing about this issue(21, 22). While the value of knowing whatever information they can about their child trumped the majority of their other concerns these residual concerns should not go unheeded.

Informed consent of parents for exome sequencing of their children should help parents to distinguish the types of results they may learn and preserve their opportunity to choose among the information they want to learn. Consistent with other studies (20, 23, 24), these parents valued having a choice and welcomed the opportunity to consider the options and their implications.

This study was limited by its size and exploratory methods. Our findings cannot be generalized to all research or clinical populations of parents consenting to genomic sequencing for their children.

The parents in this study were actively making choices about what exome sequencing variants they wanted to learn, thus providing some of the first data on preferences among those undergoing sequencing. While larger studies are needed for replication, these early results can be used to design such studies and to challenge some of the assumptions made by clinicians and investigators. Parents of affected children had overall interest in learning information beyond the primary variant for their child's condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Categories of Secondary Variant Results

Categorization of Secondary Variant Result	**Clinical Example**
Variant related to a disease that is actionable in childhood	*Early-onset colorectal cancer*
Variant related to a disease that is not treatable or preventable in childhood	*Alzheimer disease or adult-onset cancer*
Carrier status for an autosomal recessive disorder	*Cystic fibrosis or sickle cell anemia*

Table 2

Demographic Information of Research Participants

Average Age of Parent (years/range)	39.1(26–54)
Gender	
Male	12
Female	13
Age of Proband(years/range)	7.25(9 months –12 years)
Education Level	
High School	1
Some College	1
College Graduate	7
Post-Graduate	10
Declined to Answer	6
Income	
$50,000–$74,999	5
$75,000–$100,000	5
More Than $100,000	3
Declined to Answer	12
Proband's Diagnosis	
Dubowitz Syndrome	3
Overgrowth Syndrome	2
Dysmorphic Features	3
Congenital Anomaly/Developmental Delay	5

Table 3

Preferences and Rationale Regarding Receipt of Secondary Variant Categories

Secondary Variants for Treatable and Preventable Conditions in Childhood				
Parental Preference to Learn Result	**Number of Parents**	**Rationale for Preference**	**Total References**	**Exemplar Quote**
Yes	25	Helps guide child's healthcare	17	*"You want to be able to do the best for your kid. And if it's a preventable thing or a thing that can be watched… I am more optimistic on keeping an eye out for something that's likely to happen and can be controlled through diet or medication, so I would be welcoming of that sort of information." [F/11y]*
		Need to know/prefer to know	6	
		Knowledge is important/worthwhile	5	
		Allows planning and/or preparation	3	
Conditional Yes	0			
Neutral/Ambivalent	0			
No	0			
Secondary Variants for Untreatable or Unpreventable Conditions in Childhood				
Parental Preference to Learn Result	Number of Parents	Rationale for Preference	Total References	Exemplar Quote
Yes	10	Measures can still be taken to avoid condition	10	*"If she wanted to be part of another study where they took a look at people that have the gene that predisposes them to a disease or illness like that, that might help other people. It might help [my child] depending on what they find out. There's a silver lining to everything." [M/1y]*
		Parents can keep abreast of research and identify treatments that may become available in the future	7	
		Need to know/prefer to know	4	
Conditional Yes	3	Parent wishes to learn result but will wait to share with child until an appropriate time	4	*"If something happens where it comes up and some kind of conversation has to happen, then it has to happen. I wouldn't want to just withhold it from [my child], I wouldn't want to try and hide it. I would want – whatever appropriate time that his mother and I or whoever may decide that it's right for whatever information that I have to tell him it's his right to know." [F/2y]*
Neutral/Ambivalent	6	Need to discuss/think about further	3	*"I might want to know, but I think this is the kind of thing that we would need to think about more." [M/3y]*
No	6	Adds worry		*"Well, if there's no testing for that – no, I don't think so. Then it might just give us more to keep on our heads, make us worry about something that I have no control [of] at all." [F/5y]*
Carrier Status for Recessive Genetic Conditions				
Parental Preference to Learn Result	Number of Parents	Rationale for Preference	Total References	Exemplar Quote
Yes	13	Will help with future reproductive decision making	10	*That would be a good piece of information for her to have when she is considering starting a family, at least so she is prepared going in. I don't think it should be [the] only thing [when] she decides whether or not she wants to have*

Secondary Variants for Treatable and Preventable Conditions in Childhood				
Parental Preference to Learn Result	**Number of Parents**	**Rationale for Preference**	**Total References**	**Exemplar Quote**
		Will allow for informed decisions	6	*a family later in life, butit may help her to make a better decision or at least be prepared that that could be a possibility" [F/11y]*
		Need to know/prefer to know	4	
		Knowledge is important/worthwhile	2	
		Will allow preparation for future	2	
Conditional Yes	5	Will wait until child is older or indicates a need for testing	6	*"The reason I would like to learn about them is because I think it definitely will be beneficial for my girls as they got older to understand and know what life kind of brings" [F/5y]*
		Child must make own decision to learn	6	*"She has the right to choose and the right to know it is her body and I respect that. And it's whatever DNA the Lord has given her, so it's not up to me to hide anything from her that's already hers, but as her Mom, maybe to not give her too much knowledge too soon so that it doesn't overwhelm her and lead to other problems."[M/11y]*
Neutral/Ambivalent	7	Preference depends on other factors	3	*"I think we can kind of get into a dangerous area though there where, you know, may we want to know and it might have implications for other people in our [families] but maybe they don't want to know. [F/9m]*
Negative	0			