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Author Contributions

CMS made substantial contributions to the conception and design, acquisition, analysis and interpretation of data for the work, drafted the work, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KL and EGK made substantial contributions to the conception and design, acquisition, analysis and interpretation of data for the work, revised it critically for important intellectual content, and approved the final version to be published. CGSP and JSS made substantial contributions to the conception and design, analysis and interpretation of data for the work, revised it critically for important intellectual content, and approved of the final version to be published.

Conflict of Interest

Courtney M. Studwell, Kimberly LeBlanc, Emily G. Kelley, Christina G. S. Palmer, and Janet S. Sinsheimer declare that they have no conflict of interest.

Human Studies and Informed Consent

This research was approved by the NIH General Medicine 1 Institutional Review Board (protocol 15-HG-0130) and by the Boston University School of Medicine Institutional Review Board (protocol H-38163). All participants provided their informed consent.

Animal Studies

No non-human animal studies were performed by the authors for this research.

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Family Genetic Result Communication in Rare and Undiagnosed Disease Communities: Understanding the Practice

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Abstract

Genetic results have implications not only for the individual, but also for their family members. Research on family communication of genetic results has primarily focused on families affected by adult-onset, dominant conditions as well as more common genetic conditions such as familial hypercholesterolemia, cardiomyopathies, and genetic hearing loss. This study therefore aimed to characterize genetic result communication in families with rare and undiagnosed conditions and identify factors that influence communication. 142 individuals who received a diagnosis from the Undiagnosed Diseases Network (UDN), a study focused on providing diagnoses to individuals with undiagnosed conditions, were eligible to complete a survey assessing genetic results communication. Survey items assessed if communication was discussed with healthcare providers, with whom participants communicated genetic testing, why they chose to communicate with these family members, and what information they communicated. All respondents (5 adult UDN participants, 38 parents/guardians of UDN participants, and 2 identifying as both) shared genetic results with at least one family member. Individuals who identified as both were considered exclusively adult participants for the purpose of these analyses. Adult participants and parents/guardians of participants reported high levels of understanding (96%), utility (96%), and comfort communicating genetic results (89%). Additionally, parents/guardians were more likely to disclose genetic results due to a general desire to share (60% of parents/guardians vs. 14% adult participants), while adult participants reported that they shared results to communicate risk to family members (86% of adult participants vs. 24% of parents/guardians). Many respondents did not recall discussing with a healthcare provider how (64%) or what (42%) to communicate about results. The results of this study provide insight into the practice of result communication by individuals with rare and previously undiagnosed conditions, which can ideally inform development of more effective counseling strategies and guidelines to aid family communication.

Keywords

family communication; genetic results; undiagnosed disease; genetic counseling; communication; family

Introduction

Genetic results have implications not only for the individual, but also for their family members. Research has shown that patients believe it to be the responsibility of the family, not the healthcare providers, to communicate this information (Forrest K et al., 2003). As genetic counseling involves "..the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease", there is a natural role for genetic counselors to help facilitate this process (Resta et al., 2006). To do this effectively, family communication of genetic results in different populations must be understood.

To date, research on communication of genetic results has primarily focused on families affected by adult-onset, dominant conditions (Mendes et al., 2016; Wiens et al., 2013; Wilson et al., 2004; Wiseman et al., 2010). In particular, there is an abundance of research in the realm of cancer, specifically hereditary breast and ovarian cancer. These studies reveal that a variety of factors impact family communication, including condition status, level of worry, interest in genetic information, and availability of treatment for at-risk relatives (Elrick et al., 2017, Mendes et al., 2016; Wiens et al., 2013; Wilson et al., 2004; Wiseman et al., 2010). Additionally, research shows that individuals are more likely to disclose genetic results to first-degree relatives and that social factors, such as the specific personal relationships with relatives, play a role in communication (Finlay et al., 2008). Aside from cancer-specific research, studies have been conducted on family communication in specific areas such as genetic hearing loss, inherited cardiomyopathies, familial hypercholesterolemia, balanced translocation carriers, and X-linked conditions like Duchenne muscular dystrophy (Blase et al., 2007; Hayes et al., 2016; Shah & Daack-Hirsch, 2018; Wurtmann et al., 2018). Research in these areas has shown that family communication is a complex process, regardless of the condition or context.

Given the increased utilization of more comprehensive genetic testing strategies like exome and genome sequencing, it is important to understand communication of results in families undergoing these types of tests (Prokop et al., 2018; Krier, Kalia, & Green, 2016). Research focused on parental perceptions of exome sequencing in an undiagnosed pediatric population showed that the majority of study participants openly discussed testing with family members and healthcare providers, but some reported that the complicated nature of this information made communication difficult (Rosell et al., 2016). These findings provide a glimpse into the experiences of the undiagnosed disease community when communicating complex genetic results to family members but leave other factors to be explored, such as the impact of uncertainty, comfort communicating genetic results, and perceived importance of genetic results on communication.

The Undiagnosed Diseases Program (UDP) at the National Institutes of Health (NIH) was launched in 2008 with the goal of providing diagnoses to individuals with undiagnosed conditions (Gahl & Tifft, 2011). In 2013, the NIH Common Fund elected to support the expansion of the UDP into a network of clinical research centers across the United States called the Undiagnosed Diseases Network (UDN) (Gahl et al., 2015). Since the launch of the UDN, there have been several studies exploring the unique experiences of individuals in the undiagnosed disease community with the goal of improving the quality of care for these individuals (McConkie-Rosell et al., 2018; Palmer et al., 2018; Spillmann et al., 2017). There has yet to be a study specifically characterizing the process through which individuals in the undiagnosed disease community communicate genetic results to extended family members.

Studying genetic result communication in the undiagnosed and rare disease community will ideally highlight factors uniquely impacting communication in this population including perceived uncertainty, understanding, and utility of genetic results. This understanding is expected to inform effective genetic counseling practice. This study therefore aimed to: (1) characterize the practice of genetic result communication to extended family members by participants and parents of participants in the undiagnosed and rare disease community, and (2) identify factors that influence communication.

Methods

This research was approved by the NIH General Medicine 1 Institutional Review Board (protocol 15-HG-0130) and by the Boston University School of Medicine Institutional Review Board (protocol H-38163).

Participants

UDN participants and parents/guardians of participants unable to provide consent were invited to take part in this study. To be eligible, participants were required to have undergone evaluation and genetic testing through one of six UDN clinical sites (Baylor, Harvard, NIH, Stanford, UCLA, Vanderbilt) and received a genetic diagnosis before November 1, 2018. In the UDN, genetic testing is performed in CAP-accredited, CLIA-certified clinical diagnostic laboratories. At the conclusion of the evaluation, participants or parents/guardians of participants are provided with copies of genetic testing reports and a letter summarizing relevant findings (UDN Manual of Operations, n.d.). If a genetic diagnosis is made through the evaluation, this information is included in the letter, discussed during a genetic counseling session, and communicated to the referring provider.

In order to participate, individuals were also required to have a documented email address and have indicated that English was their primary language. An online survey was electronically distributed to all participants and parents/guardians who met the inclusion criteria.

Instrumentation

The survey was specifically designed for this study and is not a validated measure (see Supplemental Materials). The survey was developed by the study team, which included

certified genetic counselors, and reviewed by the UDN Survey Committee, which included physicians, researchers, and allied health professionals. The survey was piloted with three UDN participants to ensure clarity and ease of completion. In response to feedback, questions were modified before the survey was administered to study participants. The survey consisted of 18 questions and was created and distributed through Qualtrics.com.

Demographic and result communication questions were asked in multiple-choice and multiple-selection formats. Demographic information gathered included age, gender, and race/ethnicity. Information collected about result communication included: (1) if communication was discussed with healthcare providers, (2) with whom participants communicated genetic results, (3) why they chose to communicate with these family members, and (4) what information they communicated. Questions addressing factors that may be associated with communication practices, such as reported understanding of genetic results, uncertainty, and comfort communicating this information, utilized a 5-point Likert scale ranging from “Strongly agree” to “Strongly disagree”.

Procedures

An email was sent to the primary email address recorded in the UDN participant database with a letter describing the study and instructions to complete the survey (see Supplemental Materials). The letter indicated that a $200 donation, funded by the Boston University School of Medicine, would be made to the National Organization for Rare Disorders (NORD) on behalf of survey respondents. The survey was open January 1, 2019 – January 31, 2019 and one reminder email was sent two weeks after initial contact. Each eligible participant received a unique email link, which allowed for the manual linkage of the survey response to the UDN participant.

Data Analysis

Quantitative data were analyzed using descriptive statistics including calculation of percentages and means. A difference of proportions was calculated when appropriate and when there was a sufficient sample size using Fisher exact tests. Regression analysis could not be performed due to small sample size.

Results

Demographics

Of the 142 UDN participants and parents/guardians eligible and contacted for this study, 49 started the survey, yielding a 35% response rate. Forty-five of these 49 individuals completed the survey in its entirety, yielding a 92% completion rate; the 45 submitted surveys are the focus of analyses reported below.

Cohort demographics are summarized in Table 1. One respondent opted not to complete the demographic questions. The average age of respondents was 45 years (+/− 11 years) and the majority of respondents identified as female (82%, 36/44). Of note, one respondent indicated that they were a parent/guardian of a UDN participant but reported their age to be 15, which was the age of their child. This response was not included in age calculations. The majority

(86%, 38/44) of participants self-identified as White; 11% (5/44) identified as Asian and 7% (3/44) identified as Hispanic or Latino. This racial and ethnic distribution is similar to that of the larger UDN population (Splinter et al., 2018).

Most respondents indicated that they were the parent/guardian of a UDN participant (84%, 38/45) with 11% (5/45) identifying as an adult participant. Four percent (2/45) selected that they were both the parent/guardian of a UDN participant and an adult participant themselves; these individuals were considered exclusively adult participants for the purpose of these analyses due to the likelihood that their diagnostic experiences are more similar to adult participants as they are affected with the condition themselves. The percentage of adult participants who completed the survey (15.5%, 7/45) is significantly lower than the percentage of adult participants in the eligible population who did not fill out the survey (36%, 44/91) (p=.0006), with a correspondingly greater proportion of parents/guardians of UDN participants completing this survey than those who did not fill out the survey. Of all participants who met inclusion criteria, 36% (51/142) were adult participants. This corresponds with approximately a 14% response rate for adult participants compared to an approximate response rate of 42% for parents/guardians.

Impressions of Genetic Testing Results

The majority of respondents indicated that they “Strongly agree” or “Agree” with the following statements: *I understand the genetic testing results* (96%, 43/45), *Information from the genetic testing results is useful to me* (96%, 43/45), *It is important to me to share the genetic testing results with family members* (93%, 42/45), and *I am able to explain genetic testing results to family* (89%, 40/45). The majority of respondents (82%, 37/45) noted they “Strongly disagree” or “Disagree” with the statement *I am still unclear about what the genetic testing results mean for me*. Seventy-six percent (34/45) chose “Strongly disagree” or “Disagree” when asked to respond to the statement *I am still unclear about what the genetic testing results mean for family members* (Table 2).

Family Communication Practices

All survey respondents indicated that they shared genetic results with at least one family member. All adult respondents who indicated they had a spouse or partner (n=7) shared their results with their spouse or partner (100%) and all adult participants with children (n= 6) shared their results with their children (100%). All parents/guardians who indicated that their child had an aunt or uncle (n=35) responded that they shared their child’s results with their child’s aunt or uncle (100%). Most parents/guardians who indicated that their child had a grandparent (n=33) shared their child’s results with their child’s grandparent (97%).

Respondents indicated that they chose to share genetic results with family members because of a close personal relationship (76%, 34/45), a general desire to share information (60%, 27/45), and family member(s) asking for information (56%, 25/45). Some respondents also noted that they shared this information to assist family members in reproductive planning (36%, 16/45), to inform them about genetic information that may influence their health (33%, 15/45), and to receive emotional support (22%, 10/45).

The most frequent choices for what specific information was shared with family members were diagnosis name (78%, 35/45), information about the diagnosis (78%, 35/45), inheritance pattern (58%, 26/45), and chance of family member(s) developing the same condition (51%, 23/45). Individuals who indicated that they did not share information with all family members selected reasons for not sharing. These selections included age of family member(s) (45%, 5/11), not in regular communication (45%, 5/11), did not see a reason to (27%, 3/11), and wanted to maintain privacy (27%, 3/11).

Sixty-four percent (29/45) of respondents indicated that they had not talked with a healthcare provider about *how* to tell family members about the genetic results and 42% (19/45) indicated that they had not talked with a healthcare provider about *what* to tell family members about the results.

Differences Between Adult and Parent/Guardian Responses

When indicating reasons for sharing genetic results, a higher percentage of adult participants selected *wanted to inform them about genetic information that may influence their health* compared to parents/guardians (86% (6/7) vs. 24% (9/38), p = 0.004). In contrast, a higher percentage of parents/guardians selected *general desire to share information* compared to adult participants (68% (26/38) vs. 14% (1/7), p = 0.015) (Figure 1). When asked what information they communicated, a greater proportion of adult participants selected *chance of family member(s) developing the same condition* (100% (7/7) vs. 42% (16/38), p = 0.009) while a greater proportion of parents/guardians indicated that they shared *information about the diagnosis* (84% (32/38) vs. 43% (3/7), p = 0.035) (Figure 2).

Discussion

Communication with at-risk family members is an essential outcome of the genetic testing process. Although family communication of genetic results has been studied, communication practices specifically in the undiagnosed and rare disease populations have not been well described. The purpose of this study was to (1) characterize the practice of genetic result communication to extended family members by participants and parents of participants in the undiagnosed and rare disease community, and (2) identify factors that influence communication. All participants indicated that they communicated genetic results with at least one person, which suggests that participants in the UDN who have received a diagnosis value this communication. This is consistent with prior research showing that the majority of study participants undergoing exome sequencing share genetic results with at least one or two close family members (Daly et al., 2016; Rosell et al., 2016). Our study found that respondents reported a high degree of understanding of results, believed the results to have utility, and felt comfortable communicating these results. Adult participants and parents/guardians reported unique motivations for communication and different content of the information disclosed to family members. Many respondents did not recall discussing with healthcare providers how and what to communicate to family members. These findings provide insight into how genetic counselors can continue to support members of the undiagnosed and rare disease community as they discuss results with their relatives.

The majority of respondents reported a high level of comprehension of results despite their complex nature. The results from exome and genome sequencing for UDN participants often involve novel variants or variants in genes without a previously known disease association. Frequently, resources do not exist to aid in result or diagnosis communication. The complexity of results has previously been identified as a possible barrier to result communication (Rosell et al., 2016); however, this does not appear to be the case in our cohort. This observation could be due to the extensive amount of genetic testing that respondents may have experienced prior to their enrollment in the UDN (Splinter et al., 2018). This may result in a greater familiarity with the genetic testing process and, subsequently, a greater understanding of results. In general, respondents also agreed that it is important to share genetic results with family members and were clear about what the genetic results meant for them and their family members. These findings further support a high level of confidence regarding the meaning of results despite their complicated nature and perceived importance of family communication. This high level of comprehension could be due to a motivation to take ownership of their genetic results and diagnosis given a long diagnostic odyssey.

Interestingly, a high proportion of respondents (96%) indicated that the information from the genetic results was useful to them. This finding is noteworthy, particularly given that many of the diagnoses received by UDN participants do not have immediate treatment implications (Splinter et al., 2018). This perceived utility of genetic results despite lack of treatment has been shown in prior research exploring the perspectives of parents of children with undiagnosed disease undergoing exome sequencing. In that study, parents whose child received a diagnosis shared that they experienced less worry and more focused medical care despite the lack of treatment (Rosell et al., 2016).

Parents/guardians of participants showed a universally high rate of communication, with 100% indicating that they shared results with their child's aunt or uncle, 97% with their child's grandparent, and 94% with their child's parent. The lowest rate of communication was for their child's sibling (77%), which was likely due to the age of these family members. When noting factors that influenced their decision to share results, a higher percentage of parents/guardians (68%) selected a general desire to share information when compared to adult participants (14%). A higher proportion of parents/guardians also chose to disclose information about the diagnosis (84% vs. 43%) and inheritance pattern (66% vs. 14%) compared to adult participants. Of note, a high percentage of adult participants indicated that they wanted to inform family members about genetic information that may influence their health (86%), compared to just 24% of parents/guardians. All adult participants (100%) indicated that they shared the chance of family member(s) developing the same condition when communicating their genetic results, compared to 42% of parents/guardians. Overall, these results suggest that adult respondents were motivated to communicate their genetic results because of perceived risk and health implications for their family members. This could in part be influenced by the inheritance pattern of their diagnosis, since a large proportion of genetic diagnoses in pediatric patients have been found to be *de novo* (Deciphering Developmental Disorders Study, 2017).

Results from this study also show that many participants did not recall speaking with a healthcare provider about how (64%) or what (42%) to communicate about genetic results with family members. These results are an interesting insight into UDN participants' perceived support from healthcare providers. Studies have shown that patients often do not have perfect recall after genetic testing result disclosure, the cause of which may include the large volume of information or levels of patient anxiety, so it may be possible that conversations surrounding this topic did occur at a higher frequency than recalled and reported in this survey (Kessels, 2003; Michie et al., 1997). There have been many studies describing genetic counseling strategies to support genetic result communication, which include direct contact with a proband's at-risk family members and specific interventions involving ongoing contact with patients (Hodgson et al., 2016; Mendes et al., 2016). Other research has suggested that healthcare providers should discuss family communication before, during, and after genetic testing in order to promote successful disclosure to relatives (Derbez et al., 2017). The utilization of unique genetic counseling strategies for facilitating result disclosure could benefit patients participating in genetic testing, such as those surveyed in this study.

Study Limitations

This study had several limitations. First, the small sample size and overrepresentation of parents/guardians of UDN participants limits generalizability of the results. The lower response rate of the adult UDN participants could be due to a variety of factors, such as a busy schedule, direct impact of the condition on their physical health, or a decreased perceived importance of participation in research after the UDN evaluation. This study did not evaluate the time from result disclosure to survey distribution. It is possible that the time since result disclosure impacts communication. This study also did not collect information on age of the affected UDN participant or whether a genetic diagnosis was inherited or *de novo.* Additionally, this study assessed perceived understanding of results and did not concretely measure this understanding.

In addition, respondents largely identified as White and female. Although the majority of participants evaluated by the UDN are also White, it impacts the generalizability of the results. This study also excluded non-English speaking participants, who may have different experiences sharing results with family members given the additional barriers to communication with healthcare providers or communication with relatives that may reside in other countries. This survey was administered via email as the majority of the targeted population had a recorded email address. However, this means of distribution may have excluded participants without access to a computer or of lower literacy. The respondents to this survey may also be more likely to report a high level of genetic result communication as a result of their willingness to participate in this study, while those who did not respond may be more averse to sharing information with their family.

Practice Implications

The results of this study provide insight into genetic result communication by participants who have undergone genetic testing including exome and genome sequencing. These findings can be utilized to inform genetic counseling practice when facilitating the process

of family communication after discussing results of this testing. This study showed that there are a variety of motivations for communicating that may necessitate different genetic counseling approaches or resources. In particular, it seems adult patients and parents/guardians of pediatric patients have different motivations to share results, which could be incorporated into genetic counseling discussions. It may be beneficial for providers to ask focused questions during result disclosure to identify motivators or barriers of communication with family members. Additionally, the results of this study show that many participants do not recall having discussions with healthcare providers about how and what to tell family members about genetic results. This demonstrates an opportunity for genetic counselors to address these topics during results disclosures or follow-up letters and to tailor counseling in response to unique patient motivators.

Research Recommendations

Given the limitations of this study, it is recommended that future research include a larger and more diverse cohort to determine statistically significant relationships between groups and increase generalizability of results. The results of this study could also be augmented by qualitative data to further explore motivations and methods for genetic result communication. This information would allow for the development of specific interventions necessary to support genetic counselors in facilitating communication in the context of undiagnosed and rare disease populations.

Conclusions

Family communication of genetic results should be researched in a variety of settings in order for genetics professionals to best support their patients. This study identified that adult participants and parents/guardians of participants in the UDN have high rates of result communication with their relatives. Study participants also indicated that they understood their results, thought that their genetic results were useful, and felt comfortable communicating results. Adult participants and parents/guardians noted unique motivations for sharing genetic results and may require distinct genetic counseling approaches to facilitate family communication. Finally, this study showed that there is room for improvement in the frequency and effectiveness of discussions surrounding genetic results between healthcare providers and patients. In the future, additional research on family communication within and outside of undiagnosed and rare disease populations could inform best practices for genetics professionals to help patients communicate genetic results to family members.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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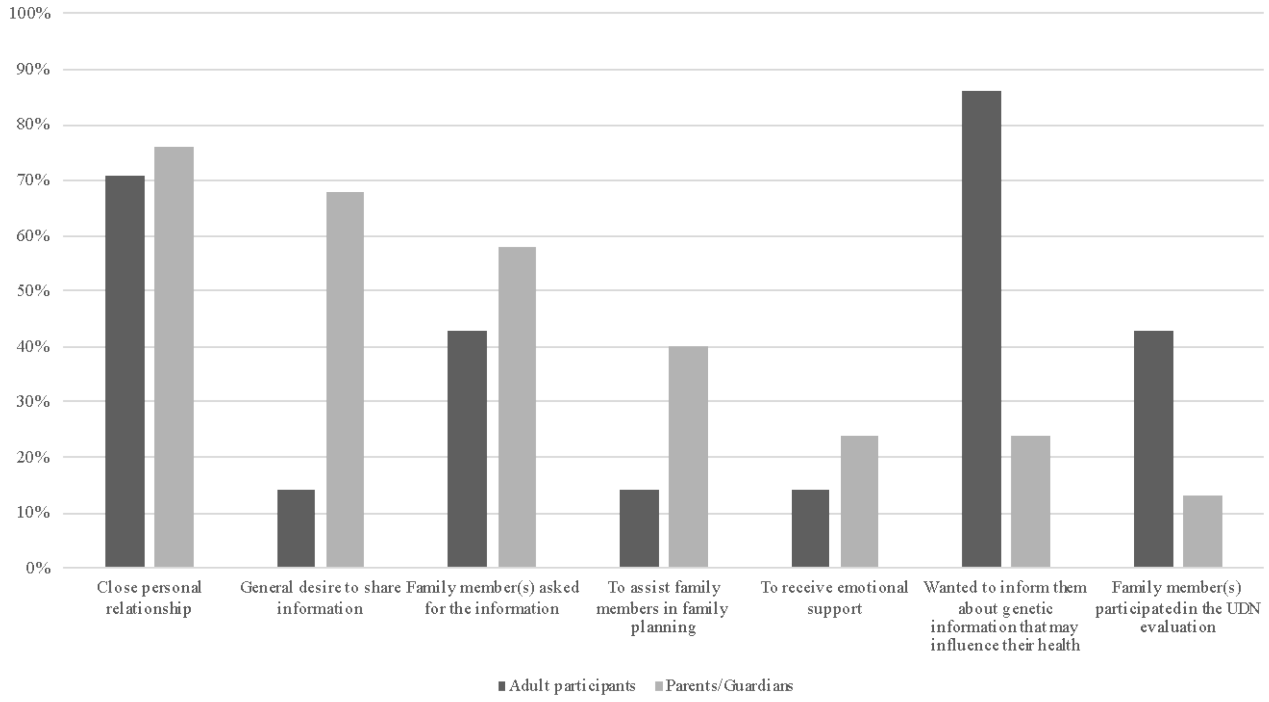
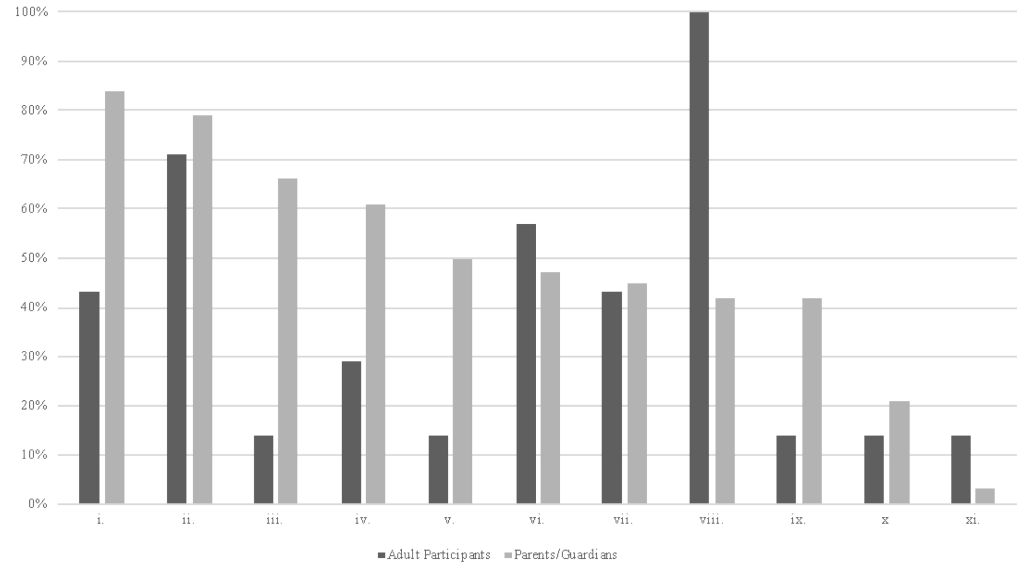


Figure 1:

Comparison of responses between adult participants and parents/guardians of participants when asked about information communicated to family members



i.	Diagnosis details
ii.	Diagnosis name
iii.	Inheritance pattern
iv.	Incidental findings
v.	Certainty about diagnosis
vi.	Gene name
vii.	Variant details
viii.	Risk to family
ix.	Technology used
x.	Family member testing
xi.	Genetic discrimination

Figure 2:

Comparison of responses between adult participants and parents/guardians of participants when asked about factors influencing the decision to share results with family members

Table 1:

Sample demographics including age, gender, race/ethnicity, and type of participant. One participant did not complete questions asking about age, gender, and race/ethnicity.

	Total (n=45)	Adult participant* (n=7, 16%)	Parent guardian of participant (n=38, 84%)
Age	**(n=43)**		
Mean	45	54	43
Median	42	53	40
Minimum	29	33	29
Maximum	72	65	72
Gender Distribution	**(n=44)**		
Female, n (%)	36 (82)	6 (86)	30 (79)
Male, n (%)	8 (18)	1 (14)	7 (21)
Race/Ethnicity	**(n=44)**		
White, n (%)	38 (86)	7 (100)	31 (84)
Asian, n (%)	5 (11)	0 (0)	5 (14)
Hispanic or Latino, n (%)	3 (7)	0 (0)	3 (8)

*The adult participant group includes two individuals who identified as both adult participants and parents/guardians of participants.

Table 2:

Distribution of participant responses to statements addressing perception of genetic testing results

Statement	Strongly agree, n (%)	Agree, n (%)	Neither agree nor disagree, n (%)	Disagree, n (%)	Strongly disagree, n (%)
Information from the genetic testing results is useful to me	30 (67)	13 (29)	1 (2)	1 (2)	0 (0)
It is important to me to share the genetic testing results with family members	24 (53)	18 (40)	2 (4)	1 (2)	0 (0)
I understand the genetic testing results	23 (51)	20 (44)	1 (2)	1 (2)	0 (0)
I am able to explain genetic testing results to family	16 (36)	24 (53)	3 (7)	2 (4)	0 (0)
I am still unclear about what the genetic testing results mean for me	2 (4)	0 (0)	6 (13)	21 (47)	16 (36)
I am still unclear about what the genetic testing results mean for my family members	2 (4)	2 (4)	7 (16)	19 (42)	15 (33)