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Exploring relatives' perceptions of participation, ethics, and communication in a patient-driven study for hereditary cancer variant reclassification

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Abstract

Effective communication of genetic information within families depends on several factors. Few studies explore intra-familial communication of variant of uncertain significance (VUS) results or active collaboration between family members to classify VUS. Our qualitative study aimed to describe the experiences of individuals asked by family members to participate in the FindMyVariant study, a patient-driven family study which aimed to reclassify a clinically identified familial VUS in a hereditary cancer gene. We collected feedback from 56 individuals from 21 different families through phone interviews and written correspondence, transcribed the interviews, and performed thematic analysis on all text. We describe themes from three main

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Author Contributions

Ginger J. Tsai provided substantial contributions to the conception and design of this work, and to the acquisition, analysis, and interpretation of data; drafted and critically revised the work for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work including accuracy and integrity. Annie T. Chen provided substantial contributions to the acquisition, analysis, and interpretation of data; drafted and critically revised the work for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work including accuracy and integrity. Lauren T. Garrett provided substantial contributions to the conception and design of this work; critically revised the work for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work including accuracy and integrity. Wylie Burke provided substantial contributions to the conception and design of this work; critically revised the work for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work including accuracy and integrity. Deborah J. Bowen provided substantial contributions to the conception and design of this work; critically revised the work for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work including accuracy and integrity. Brian H. Shirts provided substantial contributions to the conception and design of this work; drafted and critically revised the work for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work including accuracy and integrity.

Conflict of Interest Statement

Ginger J. Tsai, Annie T. Chen, Lauren T. Garrett, Wylie Burke, Deborah J. Bowen, and Brian H. Shirts 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 responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all participants for inclusion in the study. The study was approved by the University of Washington Institutional Review Board (#50616).

Animal Studies

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

topics: participation, ethical considerations, and study impacts. Participation in the FindMyVariant study, defined as returning a sample for targeted genotyping, was motivated by convenience and a desire to help the family, oneself, and science. Relatives were generally responsive to invitations to participate in FindMyVariant from another family member. Those who declined to participate did so due to concerns about research program confidentiality rather than family dynamics. No major ethical issues arose in response to the patient-driven study structure, and no major changes in stress and anxiety, medical care, or behavior occurred. Participation in patient-driven familial VUS classification studies has a neutral or positive impact on family health communication. While it is important to design studies to minimize familial coercion, intra-familial confidentiality breaches, and misinterpretation of genetic results, these were not major concerns among relatives in this study. Clinicians and laboratories may consider encouraging familial communication about genetic variants using family members as liaisons.

Keywords

Variant of Uncertain Significance (VUS); qualitative research; family studies; patient-driven; family communication; genetics communication; Genetic Counseling; health communication; attitudes; qualitative study; perceptions; Attitudes; Communication; Family; Family History; Genetic Testing; Health Behavior; Risk Perception; Variant Classification

Introduction

Communication of cancer genetic risk information within families can depend on a number of factors, including the perceived disease risk of a genetic variant, the relationship between the giver and recipient of information, cultural expectations of family relationships, and the anticipated psychosocial consequences of giving or receiving a genetic test result (Behavioral Working Group of the Colon Cancer Family Registry et al., 2014; Claes et al., 2003; Forrest, Simpson, Wilson, Van Teijlingen, et al., 2003; Harris et al., 2010; Li et al., 2018; Stoffel et al., 2008; Vos et al., 2011). Previous studies have suggested that first- and second-degree relatives are more likely to receive information than more distantly related relatives due to differing degrees of emotional closeness and logistical issues such as availability of contact information (Forrest, Simpson, Wilson, Van Teijlingen, et al., 2003; Stoffel et al., 2008). Female relatives are more likely to receive information than male relatives, particularly for genetic information associated with “female” diseases like breast and ovarian cancer (Daly, Montgomery, Bingler, & Ruth, 2016; Hallowell et al., 2005; MacDonald et al., 2007; Patenaude et al., 2006; Wilson et al., 2004). Personal pre-judgments about the timing and emotional impact of information disclosure, as well as the recipient’s anticipated understanding of genetic test results, can also affect communication, particularly in a parent-child relationship (Bowen, Hay, Harris-Wai, Meischke, & Burke, 2017; Hallowell et al., 2005; Li et al., 2018; Patenaude et al., 2006).

While several studies focus on the communication of genetic risk information with respect to pathogenic variants, few specifically address communication about variants of uncertain significance (VUS) or about inconclusive negative results, defined as a negative result which still leaves a personal or family history of cancer unexplained. Li et al. (2018) described a cohort of Asian women who did not proactively share VUS results with family so as to

prevent confusion and panic. Similarly, Hughes et al. (2002) and Patenaude et al. (2006) found that women tested for *BRCA1/2* were less likely to share inconclusive results and VUS with sisters compared to positive results about a pathogenic variant. Baar et al. (2016) found that in a similar cohort, most women who had inconclusive *BRCA1/2* test results felt it was their responsibility to communicate the results to their daughters and sisters; however, after that initial communication, they generally did not follow up and discuss the results in-depth or discuss related screening recommendations.

There is little literature addressing relatives' experiences in receiving cancer genetic risk information from another relative. Most literature focuses on the experience of the "information giver": the patient who receives results from clinical genetic testing and then must decide how and when to share that information with relatives; few studies address the experience of the information recipients. Leenen et al. (2016) found that individuals who received information about a genetic Lynch syndrome diagnosis from a relative tended to be informed of results by a first-degree relative with whom they were already in contact. While most individuals were generally satisfied with receiving this information through a relative, over half reported that this approach gave them some degree of burden. A minority of recipients, primarily women, also felt that the genetic information should be provided by a health care professional instead of a relative (Leenen et al., 2016). Daly et al. (2016) found that in their cohort of relatives, approximately 20% of relatives reported that the family proband who received clinical testing for *BRCA1/2* did not share results despite the proband saying otherwise. Daly et al. (2016) also found that while the majority of relatives were able to interpret test results correctly, approximately 10% remembered receiving a result but were not able to remember what the result actually was. Those who received true positive or true negative results experienced distress at receiving results, but for many relatives, hearing about results – even if they were true positive – led to a decrease in perceived cancer risk (Daly et al., 2016).

Family communication plays a vital role in facilitating patient-driven family studies for VUS reclassification, in which families provide a unique source of phenotypic and genotypic information that increases the rate and impact of VUS reclassification (Tsai et al., 2018). Previous studies have addressed the extent, methods, and impact of family communication of genetic test results to relatives, along with the communication of associated genetic risks and medical management recommendations (Baars et al., 2016; Behavioral Working Group of the Colon Cancer Family Registry et al., 2014; Claes et al., 2003; Daly et al., 2016; Forrest, Simpson, Wilson, Teijlingen, et al., 2003; Hughes et al., 2002; Leenen et al., 2016; Patenaude et al., 2006; Stoffel et al., 2008; Vos et al., 2011). However, none have addressed family communication in the context of a patient-driven family variant study, in which one relative actively solicits the participation of other relatives for research genetic testing of a family-specific variant. Additionally, to our knowledge, no studies have addressed the impact of genetic information communicated to relatives extending beyond the first or second degree.

In previous work, we found that actively involving patients as collaborators in charge of family communication for their own VUS reclassification studies led to reclassification of approximately 60% of variants, with an average time to classification of less than one year

(Makhnoon, Garrett, Burke, Bowen, & Shirts, 2018; Tsai et al., 2019, Tsai et al., 2018). Unique aspects of this process included conveying uncertainty related to the clinical significance of the variant, patients' and relatives' involvement in aspects that might be considered research activities, and communication with relatives extending beyond the first and second degree of relationship. Patients were motivated to engage in the patient-driven process to and appreciated the opportunity to proactively manage their uncertainty about their variant, connect with relatives during the study, and advance scientific research (Makhnoon et al., 2018; Tsai et al., 2019). This qualitative study describes the experiences of relatives who were asked to participate in the FindMyVariant study, a patient-driven family variant study that aimed to reclassify a familial VUS in a hereditary cancer gene that was initially identified in another relative (Makhnoon et al., 2018; Tsai et al., 2019, Tsai et al., 2018). We interviewed relatives to explore motivators and deterrents to participation, the ethical implications of patient-driven research, and the impact of participation on health care, family communications, and behavior.

Methods

Participants

Eligible participants for the interviews were English-speaking adults (18 years or older) who had enrolled as a relative of a family member in the FindMyVariant study (Makhnoon et al., 2018; Tsai et al., 2019, Tsai et al., 2018), a patient-driven study for reclassification of VUS in hereditary cancer genes. Individuals were asked to participate in the FindMyVariant study by a family proband, defined as a family member found to have one or more VUS through clinical testing who had contacted the FindMyVariant study for further VUS reclassification efforts (Tsai et al., 2018). Individuals were eligible for the FindMyVariant study if they had a VUS in one or more hereditary cancer genes (*AXIN2, APC, ATM, BAP1, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CHEK2, CDKN1C, CDK4, EPCAM, KIT, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, POLE, POLD1, PTEN, RAD50, RAD51C, RAD51D, RUNX1, SMAD4, STK11, or TP53*); those with VUS in non-cancer genes were accepted on a case-by-case basis. Individuals could choose to be genotyped through a saliva kit sent directly to their residence with the aim of classifying the proband's VUS, and they could choose to receive their VUS results and share the result with the family proband.

Returning a sample for genotyping, sharing results with the proband, and testing positive for the family-specific VUS were not requirements for doing an interview.

Instrumentation

A semi-structured interview guide (see Supplementary Information) was used to explore relatives' perceptions of the FindMyVariant study and the study's impact on family relationships, family communications, and each individual's behavior, stress, medical care, and genetics understanding. Interview guide sections included Participation, Family Communication, Genes and Health, and Family Member Elicited Input on Ethics of Patient Driven VUS Classification.

Procedures

From May 2017 to February 2018, relatives were contacted for interviews after the familial VUS had been classified or after the family proband decided to end family studies without reclassification. Relatives scheduled and completed phone interviews or sent written responses to interview guide questions at their own convenience. The study genetic counselor (G.T.) conducted the majority of phone interviews, while an experienced interviewer conducted interviews when the genetic counselor was not available. Interviewers audio-recorded phone interviews using telephone recorders. A non-affiliated transcription service transcribed phone interviews verbatim. Written answers to interviews from letters and emails were saved and stored directly without changes. All transcripts and written data were de-identified to protect participant confidentiality.

Relatives were specifically recruited for interviews if their relationship to the proband extended past the first or second degree. Additionally, we made a large effort to contact relatives who did not return a sample for genotyping after they told the proband that they were interested in participating in the FindMyVariant study and received a saliva kit. Relatives were each contacted three times with invitations to give an interview. Participation in the FindMyVariant study was defined as returning a saliva sample for genotyping; this was separate from participation in the interviews. Individuals were not invited to do an interview if they never informed the proband or the study of their contact information.

Informed consent was obtained and documented prior to the interview. The study was approved by the University of Washington Institutional Review Board (#50616).

Data Analysis

An inductive thematic analysis approach was used to analyze interview transcripts (Braun & Clarke, 2006). The codebook was developed iteratively by two coders. The primary coder (G.T.) developed a preliminary codebook by identifying common themes that emerged in participant responses, and a second coder (A.C.) independently applied the codes to a subset of transcripts over successive iterations. After each iteration, the two coders discussed disagreements and revised the codes to increase consistency and ensure that the intended meaning was captured with each code. The codebook was finalized after 5 iterations and applied to all transcripts. The qualitative data analysis software Atlas.ti 8 was used to perform data analysis.

Inter-rater reliability was performed as in Burla et al. (Burla et al., 2008), using percent agreement and Cohen's kappa for the most frequently occurring codes across a subset of transcripts (n=5). On the last iteration, Cohen's kappa reached moderate (0.4–0.6), substantial (0.61–0.8), and almost perfect agreement (0.81 or above) (Viera & Garrett, 2005) for all codes for which it was calculated. The overall kappa coefficient was 0.81 (Supplementary Table).

Results

Study Participants

One hundred and ten individuals were eligible and approached for interviews. Fifty-six individuals from 21 different families were interviewed (51% response rate). Fifty-three individuals completed interviews over the phone, and three provided written feedback due to health reasons after receiving the phone interview questions through email or mail.

Demographic information was collected by self-report. The median age was 62 years (range: 22–87 years). 25/56 (44%) reported male gender and 31/56 (56%) reported female gender. Most interviewees (54/56, 96%) were of European ancestry, and two (4%) reported Mexican ancestry. Twelve interviewees (21%) from 8 different families had a personal history of gene-related cancer or polyposis. Eighteen interviewees were distant relatives, defined as being related to the proband by three degrees or more (32%). 47 of 56 (84%) interviewees elected to participate in the FindMyVariant study by returning a saliva kit to the study and receiving genotyping. Of those, all (47/47) chose to share results with the family proband. Interviewees were related to family probands who had a VUS in one or more hereditary cancer genes (*AXIN2*, *APC*, *BARD1*, *BRCA1*, *BRCA2*, *BRIPI*, *CDHI*, *CHEK2*, *CDKN1C*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *POLE*, *PTEN*, *RAD51C*). Interviews were conducted a median of 31 days (range: 0–228 days) after reclassification of the familial VUS or after the family proband decided to end family studies without VUS reclassification.

Topic 1: Participation

Motivations for participation

Help family: Relatives were motivated to participate in the variant classification study to help the proband or their other family members solve a problem related to the variant. Some joined the study because they wanted to support the proband, particularly after seeing the proband undergo cancer treatment, and others agreed to join the study simply because the proband was a family member. Several wanted to pinpoint the genetic cause of cancers affecting the proband and other relatives:

“It was one of those things where it just kind of -- like it kept coming down the line of the grandma, mom, older sister, you know, in a way...like it’s trying to pick on us. So the genetic testing was in defense.” (P52, male, 26–35 years old, sibling, sample not returned, VUS not reclassified)

Many also wanted to help other family members, focusing on the benefits of variant reclassification for their children and grandchildren, including clearer risk assessment and medical management recommendations that might prevent the onset of cancer:

“You are talking about your gene makeup and this is something you can’t change. And it is passed on from generation to generation and it is not like you can decide: Oh, I am not going to do that...I thought that would be a good idea to allow them [kids] to understand what their DNA heritage is so they can be prepared.” (P15, male, 56–65 years old, parent, positive for VUS, VUS reclassified)

Contribute to science: Another factor driving study participation was the possibility of contributing to scientific research, adding to the knowledge base, and helping others who might have the same variant. Some interviewees also described feeling a moral obligation to participate, in particular to share genetic data that may help others:

“I feel strongly that if there is something going on in this vein that I can contribute to, whether it is research of any kind or whatever...I really feel a responsibility to participate to tell you the truth. Because there may be things here that people can find out that will be useful now and in the future, as far as battling what may be cancer genes.” (P46, female, 66–75 years old, sibling, negative for VUS, VUS reclassified)

Self-interest: Self-interest also motivated relatives to participate. One relative reported that he participated because everyone else in the family was doing it and he did not want to feel left out. Some relatives wanted to know whether or not they had the variant even if the variant remained a VUS, either to satisfy their own curiosity or help with their own future risk assessment:

“It’s good to know about what’s going on inside my body so I can deal with it accordingly.” (P32, male, 46–55 years old, sibling, positive for VUS, VUS reclassified)

Convenience: Several individuals participated because they could not see how the study would negatively impact their lives, and many also participated simply because it was convenient to do so:

“I had done ancestry testing before, so spitting in a tube and sending it through the mail was no big deal.” (P4, female, 56–65 years old, sibling, negative for VUS, VUS reclassified)

“I could see no reason not to. I don’t consider it an invasion of me.” (P31, male, 66–75 years old, parent, positive for VUS, VUS reclassified)

Deterrents to participation

Variant study was not a priority: Relatives sometimes did not return a sample because participating in the study was not high on their priority list. A few relatives simply forgot, preoccupied with personal issues such as moving. Some relatives did not feel the variant was relevant to them given their gender, their lack of biological children, or their lack of affected phenotype:

“My kids are all step-kids, so the results of that aren’t going to tell me anything actionable. So it is like well, okay, interesting. What am I going to do if tomorrow you come back and tell me, ‘Oh, you’ve got a 90 percent chance of having this nasty gene that is going to kill you.’ Okay. What do I do about it? Nothing.” (P17, male, 56–65 years old, 3rd degree or more, negative for VUS, multiple VUS – some reclassified, some not)

Meanwhile, one relative felt that the variant study was not useful or relevant based on her professional judgment as a health care provider:

“I actually never got around to doing it. To tell you the truth, I kind of thought that she [proband] was overreacting to her own situation.... I am aware of family history, it’s worried me a whole lot more than my own. And I felt that, you know, [proband] got anxious when she discovered she had [cancer]....And so I didn’t tell her this, but I felt that she was kind of being silly.” (P24, female, 56–65 years old, sibling, no sample returned, VUS reclassified)

Data security: The most commonly cited reasons for declining participation were concerns about data security regarding genetic information within the study database. Despite assurances about the confidentiality of research study data and the separation of research data from medical records, individuals worried that study data, in particular their variant testing results, could end up in their clinical medical record and affect future insurance policies for themselves and their children:

“I was a little leery of having all of my genetic information in some database that you don’t know the security of, pretty much everything is breachable....my thought was I am still fairly young and it is something that eventually had I been tested and if I have the mutation, even though there is nothing negative that they can say about the mutation, it still ends up in part of my medical records, and it could possibly later in life have an adverse effect on any life insurance or long-term insurance possibilities.” (P3, female, 36–45 years old, child, sample not returned, VUS not reclassified)

Topic 2: Ethical Considerations

No major ethical issues for patient-driven variant reclassification study – with contingencies: While some relatives were concerned about the security and confidentiality of genetic data outside of the study, most did not have concerns about the patient-driven structure, in which the proband shared information about their genetic variant and requested testing from their family. A few stated that sharing genetic information was an important part of caring for your family:

“I just think that everybody should be informed. I don’t think there’s been any ethics to it. It’s just a matter of ‘should’, it is the right thing to do.” (P48, female, 56–65 years old, 3rd degree or more, positive for VUS, VUS reclassified)

Some expanded upon this idea, stating that they preferred to receive information about the familial VUS from another relative instead of a health care provider:

“If anything it probably comes better from whoever is the mutant is as opposed to the doctor. You know your family, you don’t know who Dr. A, B, C is. If you are going to get told your family is a bunch of mutants, well, hell, let it be somebody from your family.” (P3, female, 36–45 years old, child, sample not returned, VUS not reclassified)

A couple of relatives also stated that it was important to be cautious of how genetic information was presented in the family, particularly with regards to cancer risk and cascade testing:

“You’re sharing information that you had this variant and that has some potential to give it [cancer] to your family, but it doesn’t necessarily mean that everybody should panic and run and do this testing. It just means that everybody should be on the lookout.” (P40, male, 56–65 years old, sibling, sample not returned, multiple VUS – some reclassified, some not)

Similarly, some relatives emphasized the importance of assessing familial relationships before disclosing information about the VUS to certain family members:

“People have pretty strong opinions about this kind of thing. And if you’re not close to the person who is contacting you, you know, it might be seen as a violation of privacy.” (P24, female, 56–65 years old, sibling, sample not returned, VUS reclassified)

Autonomy generally respected with regards to participation decision: During the ethics discussion, several relatives stated that it was important for probands to respect each relative’s decision about participation. In practice, relatives almost always felt that the proband and other relatives respected their autonomy in deciding whether or not to participate. Most reported feeling no pressure from the proband and said that the proband presented the study as an option, not a requirement. Those who discussed study participation with other relatives also mentioned that they felt they could make individual choices about participation without negatively impacting familial relationships.

There were a few exceptions to this. A few relatives stated that they would have preferred to receive information from a genetics provider because they felt the proband was “too emotional” when discussing the VUS, and they felt that the emotional reaction infringed upon their autonomy to make a decision about testing. Along those lines, a couple relatives stated that they felt pressured to participate because of the proband’s attitude and their relationship with the proband:

“Honestly [proband] is my oldest sister and she is a bit bossy.” (P4, female, 56–65 years old, sibling, negative for VUS, VUS reclassified)

Two relatives who were both part of the same family reported that although their conversations with the proband about the study went well, other older relatives attempted to pressure them to participate and pursue screening under the misguided notion that the VUS was pathogenic:

“They could have just respected it [the variant information] but they decided to call and make demands for me to go to the doctor which I already was...I [felt] very talked down to.” (P28, female, 26–35 years old, 3rd degree or more, positive for VUS, VUS reclassified)

Topic 3: Study Impacts

Mixed impact on stress and anxiety, medical care, or behavior: Relatives reported mixed changes in medical care and health behavior in response to learning about a familial genetic variant and being asked to participate in a VUS reclassification study.

A few individuals had other health concerns that took priority over potential cancer risk conferred by the VUS. Some also believed lifestyle choices and preventative management had a greater effect on cancer risk than genetic testing. Others felt that they were already getting sufficient medical care, including cancer screening, based on their age and personal and family health histories, and so there was no point in changing their medical care for an uncertain genetic variant until the variant was reclassified. As these individuals summarized:

“The two variants that she was talking about were -- I looked in the literature and they’re of such unknown significance that had it not been sponsored by a university for research reasons, I probably wouldn’t have done it.” (P86, female, 66–75 years old, sibling, negative for VUS, VUS reclassified)

“I’ve always had insurance and I’ve always been insured and I go to the doctors every year for my annual checkup, so I don’t feel like there’s anything more I could do other than eat better.” (P33, female, 46–55 years old, 3rd degree or more, negative for VUS, VUS reclassified)

Some relatives also expressed a broader fatalistic view about the variant and cancer risk:

“It is what it is and it’s going to be what’s it’s going to be. I am not a real stressed out person and dying is easy. The living stuff is complicated.” (P16, male, 46–55 years old, 3rd degree or more, negative for VUS, VUS reclassified)

For some relatives, the study increased awareness of genetic variants, family history, and potential cancer risk. A few were inspired to search for and participate in other genetic research studies about their hereditary cancer variants or gather information about their family history and genealogy. Others were inspired to live a healthier lifestyle or pursue increased screening options based on their family history, which they had either not considered before or had neglected due to unwillingness to go through procedures:

“It is kind of a relief somehow, like okay, now I know and the scheduled colonoscopies, I don’t dread them as much. I know that they are keeping me safe. It is like I don’t ignore the scheduled time.” (P27, female, 66–75 years old, parent, positive for VUS, VUS reclassified)

Stress and anxiety originate from misconception of cancer risk and uncertainty: Most of the stress and anxiety mentioned by relatives seemed to originate from a misunderstanding of the definition of a VUS. These individuals assumed that a VUS conferred an increased cancer risk, even after the VUS had been reclassified as benign or likely benign. In these cases, the study genetic counselor contacted these individuals to clarify the misconception. A few individuals also mentioned that the uncertainty and the rarity of the VUS increased their stress:

“Well, you know, you just wonder what’s in your cards and what’s going to happen. You know, it is another variable. There is nothing you can do about it.” (P18, female, 66–75 years old, parent, positive for VUS, VUS reclassified)

Neutral or positive impact on family health communications: Most relatives felt that familial participation in the study had a neutral or positive impact on family health communications. Many stated that their family was already close and usually talked openly about health problems, so discussing the study was simply another extension of that dynamic. A few stated that the study temporarily facilitated a pathway for health communication by establishing a reason for the family to discuss health history:

“Our family has historically not discussed health...It was a natural conversation to have now that we were participating in the study.” (P57, male, 66–75 years old, 3rd degree or more, positive for VUS, VUS reclassified)

Discussion

Our findings indicate that relatives had varied and nuanced experiences with patient-driven familial VUS reclassification studies. Relatives share similar motivations with probands for participating in the VUS reclassification study, including a desire to increase knowledge about the variant and help their families and scientific researchers establish a link between the variant and their familial disease (Makhnoon et al., 2018; Tsai et al., 2019). Discussion of genetic information can open up health communications without impacting stress and anxiety levels, medical care, and behavior. However, per the findings in our study, it is important for individuals to assess familial relationships and dynamics, as well as the potential biases of the information source, before acting upon a family member’s suggestion to get genetic testing or participate in genetics research. Relatives in our study also emphasized the importance of respecting a family member’s autonomy by allowing each family member to respond to genetic information in their own way. Although most did not feel pressured to participate in the variant study by the family proband, a few reported paternalistic attitudes in older relatives who demanded that younger family members get tested for the variant. These older relatives may have seen themselves as authority figures, especially if they had a parent-child relationship with the younger family members.

Our findings suggest that relatives may be more responsive to discussing familial genetic information, including testing for familial variants, with another family member as opposed to a researcher or clinician. This may partially explain the success of the parent variant classification study (Tsai et al., 2018). It also contrasts with Leenen’s study, in which members of Lynch syndrome families preferred to receive genetic information from a healthcare provider over their first-degree relatives (Leenen et al., 2016). This difference may be due to our variant study’s narrowed focus, which provided testing for familial VUS instead of a diagnostic panel of genes; the chances of disclosing incidental findings such as a pathogenic variant were minimized. The convenience of sample collection for genotyping, which was performed through a saliva kit provided at no charge instead of a clinical blood draw that could incur a fee or generate insurance complications, may have also contributed to information-giver preference.

We were specifically concerned that coerced participation and miscommunication of genetic information may occur when patients recruited relatives to help classify their own variants. Even when asked explicitly about these issues, relatives generally did not express related concerns. In fact, the most common concerns expressed by relatives were not related to family communication, but to general genetic research issues such as data security and the impact of genetic testing on insurance coverage. This may have been due to specific consent form language about the risks of participating in research that was required by our Institutional Review Board.

Previous studies have explored how demographic factors such as age, gender, degree of biological relationship, and familial roles influence the timing, depth, and method of genetic information disclosure in families (Bowen et al., 2017; Daly et al., 2016; Hallowell et al., 2005; MacDonald et al., 2007; Patenaude et al., 2006; Wilson et al., 2004). Although this study was not designed to stratify communication strategies using these demographic variables, challenges in genetics communication were uncommon overall. This may have been due to online education from the [FindMyVariant.org](https://www.findmyvariant.org) website or phone and email guidance from the study genetic counselors (G.T. and L.G.), which was designed with these issues in mind. Additionally, during the interviews, a study genetic counselor (G.T.) occasionally corrected misconceptions about the disease risks and screening recommendations associated with having a VUS.

We did not see any notable patterns in responses from individuals interviewed on the day their familial variant was reclassified, or the day after their familial study ended, versus those interviewed at a later date, despite the large range of time in which interviews were conducted (0–228 days post-study-end or post-reclassification). We also did not see patterns among participants with different variant results (positive, negative, or unreturned samples). This study was not designed to stratify differences in responses among these different characteristics.

One major limitation of this study was that individuals were not invited to do an interview if they never provided their contact information to the FindMyVariant VUS reclassification study, either through the proband or by directly reaching out to study staff. It is not clear whether these individuals had interest or knowledge of the study, and it is not possible to quantify how many individuals were in this group. As such, we could not capture experiences from this group of individuals.

Study Limitations

This qualitative study has limitations. The majority of relatives (54%) were women and men of European ancestry (Table 1); thus, it is yet unclear whether relatives of other ethnic backgrounds would have similar reactions. Additionally, relatives were providing feedback specific to the patient-driven VUS reclassification study, and findings may differ for family communication within other contexts such as clinical cascade testing. As such, our findings only suggest that issues related to family communication may be mitigated by proband education; they may not be generalizable to broader cohorts or different intervention designs.

Research Recommendations

The primary purpose of this study was to explore relatives' perceptions of a patient-driven variant classification study. Our findings indicate that additional studies of strategies to implement more patient-driven VUS reclassification in broader settings are warranted, and that both close and distant relatives respond well to these efforts. This study was not designed to assess the direct impact of educational interventions from study genetic counselors on relatives' understanding of proband-provided genetic information. Future studies could investigate the retention and impact of genetic information provided by a genetic counselor or other healthcare worker as opposed to a family member. Studies that assess the correlation between demographic factors such as age, intra-familial relationships, and gender and how those affect the reception of genetic information from a family member would also be valuable contributions to the field. Finally, a study with a more diverse cohort with regards to age, ethnic background, socioeconomic status, and cultural values may deepen understanding of how patient-driven family studies may or may not be successful within particular cohorts or contexts.

Practice Implications

We have shown that relatives are generally responsive to participating in family variant studies when the request comes from another family member. While it is important to design studies to minimize concerns about familial coercion, intra-familial confidentiality breaches, and misinterpretation of genetic results, these ethical concerns may be exaggerated in a familial context. Clinicians and researchers may consider communicating genetic information to relatives using another family member as a liaison and implementing patient-driven studies to collect familial data.

Conclusion

Patient-driven efforts for variant classification and other studies may be an effective approach for communicating genetic information while respecting family dynamics and relationships. Our prior work has shown that these studies are effective in classifying VUS (Tsai et al., 2018) and that patients are motivated to engage in and lead familial genetic research (Makhnoon et al., 2018; Tsai et al., 2019). As a final piece of the puzzle, this study shows that a patient-driven strategy is not only acceptable but generally appreciated by both close and distant relatives. Patient-driven efforts may serve as a novel way to implement personalized genomic medicine in both clinical and research contexts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant Characteristics

Demographic characteristic		n (N=56)	%
Age (years)	Median: 62 years (Range: 22–87 years)		
	18–25	1	2
	26–35	8	14
	36–45	7	13
	46–55	6	11
	56–65	11	20
	66–75	13	23
	76	9	16
Gender			
	Female	31	55
	Male	25	45
Biological relationship			
	Child	3	5
	Parent	13	23
	Sibling	18	32
	Aunt or uncle	3	5
	Grandparent	1	2
	At least third degree (cousins, etc)	18	32
Ancestry			
	European	54	96
	Non-European	2	4
VUS result ^a			
	Positive	22	39
	Negative	26	46
	No sample	9	18
VUS reclassification ^a			
	Benign or likely benign	37	66
	Pathogenic or likely pathogenic	3	5
	Still VUS	23	41

^aSome families had more than one variant of uncertain significance (VUS); all VUS were counted individually for this table.