Experiences of patients seeking to participate in variant of uncertain significance reclassification research

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Abstract

Patients' understanding of a genetic variant of unknown clinical significance (VUS) is likely to influence beliefs about risk implications, consequent medical decisions, and other actions such as involvement in research. We interviewed 26 self-selected participants with a clinically identified VUS before they enrolled into a VUS reclassification study. Semi-structured interviews addressed topics including motivation to get genetic test, experience with the VUS result, affective responses to receiving VUS, and perceived effect of VUS and reclassification on medical care. We found that family and personal history of disease were the most prevalent motivators for getting a genetic test. Participants demonstrated mixed understanding of VUS. Most expressed negative effect on learning of their VUS result and uncertainty about its impact on clinical management. Most expected reclassification efforts to benefit their family members but not themselves. Some expressed distrust of their providers following a VUS result. Participation in the VUS reclassification study appeared to be motivated by four factors for patients with VUS—negative effect about VUS, uncertainty about its impact on clinical management, concern for family members' well-being, and to advance science. Perhaps the direct acknowledgement and appraisal of uncertainty as a means of coping was missing in some pre-test counseling experienced by our participants and thus they were not psychologically prepared for atypical VUS results. The finding of VUS-induced provider distrust suggests a need for careful consideration of appropriate pre- and post-test counseling about VUS.

Keywords Affective response · Cancer · Oncology · Reclassification · Uncertainty · Understanding · VUS

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Introduction

Variants of uncertain clinical significance (VUSs) are a common type of uncertainty introduced by genomic medicine (Han et al. 2017). A variant is classified in this way if the variant does not fulfill criteria for pathogenic or benign classification, or the evidence for benign and pathogenic classification is conflicting (Richards et al. 2015). The number of reported VUS in a genetic test result is usually proportional to the number of genes sequenced in the test (Shirts et al. 2016). These inconclusive test results are difficult for patients to interpret and recall correctly (Vos et al. 2008), which may lead to inaccurate risk perception, and medical decisions which may or may not be appropriate (Culver et al. 2013; Garcia et al. 2014; Murray et al. 2011), causing significant increase in patient distress (O'Neill et al. 2006; O'Neill et al. 2009; van Dijk et al. 2006).

Genetic counselors prefer to know about their patients' VUS test result and feel comfortable explaining VUS results, but they are less confident when discussing medical management options in connection with VUS and are unsure about how well

patients understand VUS (Scherr et al. 2015a; Scherr et al. 2015b). The American College of Medical Genetics recommends that VUS results not be used to modify clinical care, so counselors use their own professional judgment in how they describe strategies for handling VUS information, causing variability in clinical management of VUS (Kurian et al. 2017; Petrucelli et al. 2002). Non-genetics specialists who use genetic results are often unsure about the clinical implication of test reports containing VUS (Eccles et al. 2015).

Risk beliefs of patients are shaped by various cognitive and affective heuristics (simplified judgments that influences decision) as well as biases (Slovic et al. 2002). Perceived risk of disease and (in)tolerance for uncertainty can together explain why patients engage in various types of coping behavior in order to reduce distress (O'Neill et al. 2006). A survey of patients who received a Lynch syndrome-related VUS result suggests that participants incorrectly appraised their variant as dangerous, a position that was assumed by patients to be safer than interpreting their result as harmless (Solomon et al. 2017). Recognizing such beliefs and biases that underlie them will yield insights into patients' motivation for engaging in risk-reduction behaviors. These findings can then lay the groundwork to create tailored counseling messages that can most benefit patients.

VUS patients also benefit from having an action plan (Solomon et al. 2017). VUS reclassification, i.e., the process through which a variant classified as uncertain is later reclassified as benign, likely benign, pathogenic or likely pathogenic, is not uncommon (Turner et al. 2018) and is often a suggested action plan for patients with VUS. Family studies and other research options for variant classification are offered to eligible patients by many clinical laboratories, but eligibility criteria vary (Garrett et al. 2016). Unlike VUS results, reclassified VUS results can lead to better clinical decisions (Eccles et al. 2015), improve the clinical utility of cascade testing in relatives (Eggington et al. 2014), and perhaps offer resolution for the patient.

The purpose of this study was to explore the experiences and expectations of patients who received a VUS test result and were seeking research studies for variant reclassification. The study explored: motivations to get genetic test, patients' experience with the VUS result, affective responses to receiving VUS, and perceived effect of VUS on medical care. Learning about VUS understanding of patients who chose to participate in a variant classification research study may shed light on the cognitive and affective beliefs and associated heuristics underlying their motivation to participate in such research.

Materials and methods

Recruitment Twenty-six self-selected participants who had expressed interest in classifying their VUS were interviewed for the study. We informed genetic counselors about our VUS classification study for patients through a poster at the October

2015 National Society of Genetic Counselors (NSGC) annual educational conference, and through a NSGC Cancer Specific Interest Group e-mail in March 2017. Genetic counselors were given study contacts and informed that interested patients needed to contact the study directly. In addition, we placed an announcement on the FORCE (Facing Our Risk of Cancer Empowered) web site in July 2016. Study announcements stated that the study was designed to “help individuals and families find more information about the VUSs that are unique to them” and “identify and collect DNA samples from their family members in order to learn more about their VUS.” Participants from across the USA contacted the study directly by e-mail or phone between February and October 2016. Eligibility criteria limited the study to English-speaking adults (18 years or older) from the USA who had sought genetic testing as a part of routine clinical care and received a laboratory report listing a VUS in any gene as a result, and who had access to telephone or e-mail. Although the study recruited through genetic counselors, eligibility was not limited to patients who had received genetic counseling prior to the study. The first sequential 26 eligible participants who contacted the study and participated in the interviews are included in this report.

Data collection Soon after, initial study enrollment interviews were conducted over the telephone about participants' experience with past genetic testing and VUS results. No VUSs were reclassified at the time the interviews were conducted. A semi-structured interview guide was designed to elicit participants' feelings of VUS result, their understanding of the medical implications of this result, and their expectations about reclassification. The text of questions from study interview guide used for this analysis can be found as a supplemental document. Each interview lasted between 16 and 30 min. Interviews were recorded and transcribed; transcripts were de-identified using study numbers to protect confidentiality. The study was approved by the University of Washington Institutional Review Board (no. 50616).

Data analysis All transcripts were uploaded into the qualitative analysis software Atlas.ti 8 for coding and content analysis. An inductive thematic analysis approach was used to interpret the interview data (Pope and Mays 2006). To identify emerging concepts, analysis began by independent review of interview transcripts to develop a preliminary code book. The code book was modified in an iterative fashion, by adding, refining definitions, and collapsing codes as patterns in the data became apparent. A second analyst independently applied this codebook to code the transcripts. Codes were discussed and clarified between the two analysts, and adjustments were made until inter coder consensus was achieved. Reliability was established by inter-coder agreement of 89%. Discrepancies were resolved by discussion. Quotations illustrating main themes were identified during the coding process.

Results

Sample

Twenty-six patients who were interested in variant reclassification self-selected as volunteer participants of this study. Respondents had VUS in 19 genes (*APC*, *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *COL3A1*, *ENG*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *RAD51C*, *STK11*, and *TP53*), 17 of which were cancer-risk genes, 1 related to hereditary hemorrhagic telangiectasia, and 1 with Ehlers-Danlos syndrome. One participant had two separate VUSs in two different genes, and another participant had three VUSs in three separate genes. All but two study participants were eligible for increased screening based on family history of disease. Four of 30 VUSs were in a gene inconsistent with the initial indication for testing. Participants were mostly educated, married, and had high socioeconomic status, although there was some diversity in income and education (Table 1). Most participants had European

ancestry. All except 1 participant was female, while only 11 VUSs were in genes with phenotypes that predominantly affect women.

Initial motivation for genetic testing

Family history of disease and personal history of disease were two of the most common reasons for undergoing genetic tests. Some participants stated that they intended to use test results to inform disease prevention, to follow up on screening results, and to help family members. Participants either proactively pursued genetic testing because they were curious about genetic causation or testing was recommended by a clinician. Most, but not all, patients expected a definitive “yes or no” result from their test but had received a VUS instead. Other participants were prepared to receive an uncertain result through pre-test genetic counseling.

Uncertainty about VUS

Not surprisingly, participants expressed uncertainty about the uncertain (i.e., VUS) test result:

PARTICIPANT: “Wondering why with the technology the way it is because they were able to look at 24 genes and only one of them. And yet they were able to identify the gene and then just couldn’t check whether or not that this has any relationship to having cancer. Just kind of wondering if the results are unknown, why are they unknown”

Uncertainty was also expressed as an unclear interpretation of VUS. For example, one participant explained her VUS from a gene panel test as

PARTICIPANT: “Well, it sounded good for the other ones [genes] because it seems like the indication for all the other genes analyzed came out on the positive [good] side except for this one. So it’s just like having one sitting there. It’s got a variance to it and I just want to know—but when it says “unknown significance,” does it mean then that it’s meaning on the positive [good] side also? Or is that negative [bad] saying, “No, it could be,” if there is a possibility.”

Effect of this uncertain result on medical care was explained by one participant who was about to undergo prophylactic oophorectomy:

PARTICIPANT: “Well, having to remove ovaries before menopause is a pretty significant impact to my life and...to have a test come back [inconclusive] that is providing more uncertainties but also more fear”

Table 1 Demographic characteristics of participants (*N* = 26 individuals)

Variable	Number	Percent
Age		
Mean age (years)	55	
Range (years)	34–78	
Sex		
Male	1	3.8
Female	25	96.2
Marital status		
Single	1	3.8
Divorced	4	15.4
Married/partner	21	80.8
Widow/widower	0	0.0
Parenthood		
Parent	23	88
Not a parent	3	12
Higher education		
< High school	1	3.8
High school or GED	2	7.7
Some college	6	23.0
College graduate	5	19.2
Advanced degree	12	46.1
Insurance status		
Insured	25	96.1
Uninsured	1	3.8
Annual household income		
Less than \$50k	1	3.8
\$50k to \$100k	12	46.1
Greater than \$100k	13	50

Several people worried for the future of their children and grandchildren. They were dismayed at not being able to help their family “the way they want to” i.e., with a genetic explanation of disease:

PARTICIPANT: “Why was I the one who got cancer? Well, because it was my job to go through this and I’m the strong one to figure it out, and now I can save everybody else. So it [VUS] kind of ruined my whole reason”

Accurate understanding of VUS

A few patients demonstrated an accurate understanding of the meaning of VUS and that this finding should not cause them to alter their medical care. In the words of one participant, the VUS was “[not] a time bomb”; these participants expressed the intention to remain in a state of heightened awareness about their health care. Some were distressed about medical care as they felt a lack of guidance moving forward, despite understanding the meaning of VUS. Participants, who did not qualify for increased screening based on family history, pointed out that VUS has hindered their efforts to get more rigorous preventative measures—it was difficult to convince clinicians to recommend tests and to get insurance to cover preventative screening. Some expressed worry about whether VUS increases their risk for a different disease and were upset that VUS makes them ineligible to receive aggressive high-risk gene tailored screening. For example, one patient described feeling

PARTICIPANT: “[VUS] was a little upsetting to me thinking that I was not going to get the additional screening that I would be getting if I had a variant that had been identified as one that causes Lynch....Not that I want the label, the label is just a label. I want the treatment if I need it”

A participant with good understanding of VUS reported how the result had a positive influence on her participation in routine health protective behavior, such as screening:

PARTICIPANT: “I don’t really think that there has been much that has changed [as a result of VUS] except that I am perhaps a little more responsible about getting a [routine] colonoscopy. I shared that with my primary care physician and you know she’s on board with that as well”

After learning the test findings, many participants resented that their family members would not qualify for diagnostic testing or increased preventative measures because of the

VUS. Patients even showed understanding of the complexities in the process variant of classification. One participant pointed out that

PARTICIPANT: “...I also found out that you could have a result from one lab saying that it is a variant of uncertain significance, and then another lab did the testing, they may say that there is a different result with that same mutation because they do not share information. And that was very upsetting to me that is still upsetting to me. I don’t understand that, I think that should be shared for the common good of anybody having these kinds of tests done.”

Misunderstanding VUS

Most participants either misunderstood or were not clear about management recommendations that VUS findings should not alter their medical care. Some were under the impression that VUS was used by clinicians for clinical decision making. Others hoped that VUS would inform their disease prevention in future. Many participants clearly reported not understanding the meaning for VUS:

PARTICIPANT: “Honestly I didn’t know how to interpret it and there has always been this way in my mind if this is a factor in increasing or decreasing my cancer risk?”

One participant intentionally withheld information from her providers about her test result as her variant was initially understood to be likely pathogenic but had been later reclassified to a VUS. She had not conveyed information about her reclassified variant to all her health care providers because she wanted to continue to receive the frequent screening tests. She understood that these screening tests would be covered by insurance only if her variant was classified as pathogenic, not VUS. In reality, her family history alone made her eligible for increased screening, which she believed she benefitted from:

PARTICIPANT: “I did not correct them that it had been reclassified as a VUS because the screenings that they were doing would not have been made possible otherwise. And that’s when they found that I have a cerebral aneurysm”

Affective responses to VUS

Negative affect

Most participants reported a negative effect upon receiving their VUS result. Some reported feeling general distress—scared, stressed, frustrated, helpless, frightened, or annoyed.

Others were frustrated because they could not “get something definite started for their family”, that the test was unable to find any causal variant when “...obviously, there is something that’s not right”. Many participants expressed confusion and disappointment at not having a definitive answer. For example:

PARTICIPANT: “...Just getting more and more vague information where they didn’t really have the evidence of whether or not it was potentially going to be harmful or not was not really helpful...it felt disappointing”

PARTICIPANT: “Why was I the one who got cancer? Well, because it was my job to go through this and I’m the strong one to figure it out, and now I can save everybody else. So it [VUS] kind of ruined my whole reason”

Feeling distrust towards provider Many participants felt unsatisfied and bothered by their clinical experience. Some strongly disapproved their clinical experience and described it as a “dreadful way to present information to any layman.” Others questioned their providers’ competencies:

PARTICIPANT: “The physician really didn’t seem to know what to do with the results. Yeah, she was kind of confused by it as well”

PARTICIPANT: “I am not really happy with my oncologist and he (had) totally dropped the ball...”

At times, participants felt that their providers were dismissive of their VUS-induced worries, and as a result, some dissatisfied participants got second opinions. Feelings of distrust persisted even when providers made the correct clinical decision.

PARTICIPANT: “I was really trying to be vigilant about getting my colonoscopy and getting on top of this and he [the provider] was just like, ‘This is ridiculous’.”

PARTICIPANT: “The lack of helpful constructive genetic counseling response made it quite a bit worse because I also just plain didn’t know what was a sensible way to proceed”

Positive affect

Some participants reported positive effect in response to a VUS result. For example, some participants expressed relief that it was not a known pathogenic variant that they suspected.

PARTICIPANT: “I was so relieved that the breast cancer part was negative. That was all I paid attention to”

Others felt reassured to have “some clue” even if it was not a definitive answer. A different group of people felt fascinated at learning something new about themselves and were scientifically intrigued. One felt that it was “cool to have the information”.

Indifference to VUS result

A small number of participants felt indifferent. They were either expecting or prepared for a VUS or very understanding of the fact that genetics is a developing field and VUSs will be clarified as we gather more evidence. Another small group of participants reported feeling unflustered and one calmly asked, “What do we do now?”

Importance of reclassification

Majority of participants felt participation in VUS reclassification study would be more beneficial for their family members than for them. Patients already suffering from a disease generally did not feel that a reclassified VUS (to benign or pathogenic) would change their medical management. On the other hand, their family could use the reclassified variant information for disease prevention. A minority (one-third) of patients hoped that a reclassified variant would help inform their care—e.g., decision to undergo preventative surgery. Another large group of altruistic participants hoped to advance science and help future patients through their VUS reclassification. They were hoping to contribute to the “large databank of knowledge”.

Discussion

This study sought the views of a very specific subset of genetics patients—those who seek more information about a clinically identified VUS. Patients in our study sample demonstrated mixed understanding of VUS. They seemed to be motivated to participate in a VUS classification study due to four major reasons—negative affect about VUS, uncertainty about its impact on clinical management, concern for family members’ well-being, and to advance science. These data confirm previous reports suggesting that patients may misunderstand (Jamal et al. 2017; Lumish et al. 2017; Solomon et al. 2017) or understand (Solomon et al. 2017) the clinical implication of VUS results. We demonstrate uncertainty experienced by patients around VUS, which may be reasonable in response to an uncertain result, but problematically, also elicits negative affective responses. This highlights the need to develop effective VUS management strategies that can reduce negative affective emotions experienced by patients and help them cope with their test result.

Although the majority of participants were aware of the possibility of getting a VUS result, many expressed negative

affective responses upon receiving an inconclusive result. It is not unusual for patients to assume that genetic testing (or any clinical test for that matter) is offered as a means to eradicate uncertainty and that coming to a “yes or no” result is the norm. Perhaps the direct acknowledgement and appraisal of uncertainty as a means of coping (Babrow and Kline, 2000) was missing in some pre-test counseling experienced by our participants and thus they were not psychologically prepared for atypical VUS results. Our findings echo prior research, which shows that knowledge after pre-test genetic counseling had no direct effect on psychological outcomes after counselees were notified of their genetic test results (Brédart et al. 2017). The negative affect was a key motivator for seeking clarity through classification studies. Other patients were justifiably relieved to receive negative test result on a gene suspected for their differential diagnosis (for example BRCA genes for patients with family history of breast cancer), despite having a VUS result on a separate gene.

Distrust towards health care providers was a novel finding from this study. When VUS result could not confirm patients’ intuition that there was a genetic cause underlying their disease, patients seemed to doubt the information that contradicted their beliefs. This was reported as frustration or distrust towards providers and their well-justified clinical recommendations. Furthermore, the inability to help family members with a confirmed answer or get insurance coverage for their genetic test likely added to their frustration. It is possible that previous studies of patient attitudes towards (O’Neill et al. 2006; O’Neill et al., 2009; Solomon et al. 2017; van Dijk et al. 2006) VUS did not identify this distrust towards providers because many previous studies of VUS were conducted by providers surveying patients tested at their own institutions.

When asked about the importance of reclassification, only a third of all participants thought it would benefit them personally. Although reclassification is not uncommon (Turner et al. 2018), most participants did not expect VUS reclassification to alter their medical management. Such expectation is not surprising for participants who were already diagnosed with disease and undergoing treatment. For those with no confirmed diagnosis, the expectation may stem from the belief that reclassification is rare; lack of the understanding that a reclassified variant may actually change their clinical management; or understanding the fact that when reclassified, VUS are commonly reclassified to benign and seldom pathogenic. It is also possible that patients understood the implications of VUS reclassification but were not expecting their VUSs to be reclassified. This observation could be a manifestation of unrealistic pessimism, i.e., patients believe that they are less likely to experience positive health outcome, VUS reclassified to benign or likely benign, than they really are (Blanton et al. 2001). Alternatively, this could be a possible exhibition of unrealistic optimism, i.e., patients believe that they are less

at risk of experiencing negative health outcomes, VUS reclassified to pathogenic or likely pathogenic, than they really are (Weinstein, 1980). Further research is needed to definitively comment on the heuristics underlying patients’ beliefs of VUS reclassification. Altruism or benefiting science was mentioned by some as an outcome they expected from this research. Patients hoped to help their family members by offering them a “definitive answer,” i.e., a pathogenic or benign variant interpretation rather than VUS. Inability to help family members caused displeasure among participants with uncertainty and understanding of VUS. Intolerance for genetic uncertainty, which is known to be higher in people concerned about their children (Skirton, 2006), could have been another motivator for participation in variant classification study. Our findings echo earlier studies which suggest that genetic research participation is fueled by social, familial, and personal motives (Hallowell et al. 2010).

Our study design targeted individuals motivated to seek help understanding their VUS and resulted in a cohort of highly educated patients. Nevertheless, participants demonstrated mixed understanding of VUS—the majority expressed some misunderstanding associated with VUS, while some patients had perfect understanding of such sequence variants. This supports the conclusions of other studies performed in broader cohorts (Solomon et al. 2017). VUS results are known to be confusing for cancer patients (Murray et al. 2011; Vos et al. 2008; Richter et al. 2013); this study adds that similar confusion is also experienced by non-cancer patients such as those with hereditary hemorrhagic telangiectasia and suggests this confusion about VUS may not be related to educational level or socioeconomic status.

The conclusions that can be drawn from this study are limited as the study focused on a small subset of patients. A more diverse participant sample would have given better understanding the full scope of patient reactions to VUS. Self-selection of study participants may have disproportionately included patients who belong to the “monitoring” style of psychological coping (Miller, 1995). We did not control for pre-study genetic counseling, so differences in pre-test genetic counseling were not evaluated and could explain some of the observed variation in patient responses to VUS. At the same time, the diverse initial counseling experienced by our study participants may be more representative than past studies performed at a single practice site, which is strength of our study. Interview questions were not designed to delve into the psychological explanations of patients’ responses around VUS which prevents us from making definitive conclusions in this area. Understanding patient reactions to VUS may become more important as genetic testing grows and additional opportunities to integrate genetics in to clinical care are identified. Future studies investigating why certain patients pursue reclassification studies and how patients who do not seek additional information respond to challenging genetic information are needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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