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ORIGINAL ARTICLE

Cancer patients' understandings of genetic variants of uncertain significance in clinical care

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Abstract

Genetic variants of uncertain significance (VUSs) pose a growing challenge for patient communication and care in precision genomic medicine. To better understand patient perspectives of VUSs, we draw on qualitative analysis of semi-structured interviews with 22 cancer patients and individuals with cancer family history who received a VUS result. The majority of patients did not recall receiving VUS results and those who remembered expressed few worries, while respondents who were tested because of a family history of cancer were more concerned about the VUS results. Personal characteristics, medical condition, family history, expectations prior to testing, and motivations for pursuing testing influence the ways patients came to terms with the uncertainty of the VUS result. We conclude by discussing the relevance of the findings to the debate on the responsibility of the patient in checking back for VUS reclassification and to implications for genetic counseling that emphasizes tailoring the pre- and post-test discussion of VUS as appropriate to the patients' informational as well as emotional needs.

Keywords Variants of uncertain significance · Uncertainty · Genetic testing · Genetic counseling · Cancer genetics · Qualitative research

Introduction

With advances in genomic technologies, DNA sequencing is becoming faster and cheaper, increasing the availability of tests sequencing more genes, for a growing number of people, in a variety of medical settings. Inevitably, increased testing does not only reveal the presence of pathogenic or benign variants but also of variants of which little is known but which *may* be implicated in disease, referred to as variants of uncertain (or unknown) significance (VUSs). A VUS is a genetic variant that has been identified through genetic testing but whose significance to the function or health of an organism is not known (Richards et al. 2015). Geneticists' understanding of the clinical impact of VUSs may change over time. As a result, previously discovered VUSs may be reclassified as pathogenic or non-pathogenic, with most but not all downgraded (Mersch et al. 2018). There are currently no standard professional guidelines or best practice recommendations for how to best disclose a VUS result in a clinical setting other than they should not be used for clinical decision-making (Reuter et al. 2019). A European expert working group has suggested that only VUSs that are identified in genes related to the clinical question or to the patient's phenotype should be reported (Vears et al. 2018). Furthermore, VUSs should be reported in a way that distinguishes them from likely pathogenic or pathogenic mutations, such as on a separate page of the report, and that any reported VUS, along with phenotypic data, should be shared in a relevant database, such as ClinVar, to assist the diagnosis of other patients (Vears et al. 2018).

How do patients perceive and relate to such uncertain genetic results? This presents an important challenge to the practice of genetic counseling. The disclosure of uncertain results has been linked to patients' frustration and lack of trust in expert practice (Makhnoon et al. 2019; Atkinson 1984; Newson et al. 2016; Han et al. 2011; Han et al. 2017). VUSs have been described as a challenge for both patients

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and health care professionals (HCPs) (Medendorp et al. 2020, 2021; Zhong et al. 2021; Stivers & Timmermans 2016; Timmermans et al. 2017). This challenge, however, varies across medical settings and clinical indications (Clift et al. 2020). In the context of prenatal genetic diagnosis, where uncertainty about future prospects is perhaps most acutely felt, some prospective parents have reported anxiety after receiving a VUS result and even considered the uncertain and unquantifiable risks as "toxic knowledge" that caused lingering worries about their child's development (Bernhardt et al. 2013). Yet, another study found that following the initial shock, parents had no enduring concerns about VUS results (van der Steen et al. 2016). Cancer patients, who were more worried about the course of their disease, tended to disregard their VUS results (Clift et al. 2020). Finally, patients with undiagnosed symptoms reacted positively to VUS findings which were considered a potential hint that may lead to future diagnosis (Kiedrowski et al. 2016; Skinner et al. 2017).

Patients' understanding of VUS is also influenced by personal factors. Following genetic results disclosure (including VUSs), patients often convert objective risks into personally relevant feelings about susceptibility based on their own experiences (e.g., of family history of cancer), expectations, and informational needs (Vos et al. 2008; Vos et al. 2011). While the meaning of a VUS result is no different whether identified on single-gene testing, a multigene panel, or exome sequencing, different pre- and post-test counseling styles may influence patient understanding of a VUS result due to differing informational needs in the genetic testing consent or disclosure processes (Esteban et al. 2018). Patients' responses to VUSs, therefore, are not simply a direct function of the abstract uncertainty itself. Rather, they are shaped by the contingent meanings given to that uncertainty within the subjective, inter-personal, medical, and bureaucratic contexts of a diagnostic odyssey (Werner-Lin et al. 2016; 2018). To provide much needed empirical evidence on patients' perspectives of their VUSs, this paper draws on interviews with cancer patients and individuals with cancer family history, whose genetic sequencing results included VUSs.

Methods

Study design

Thematic qualitative inquiry was conducted using semi-structured interviews with cancer patients and individuals with a cancer family history to investigate their recall and understanding of VUSs as part of genome-wide sequencing (GWS) in clinical care.

Recruitment and sample

Patients were recruited through the Genetics Institute at Hadassah Medical Center in Israel. Eligibility criteria required patients to (a) be 18 years of age or older, (b) have undergone DNA testing (multigene panels or exome testing) for hereditary cancer syndromes, and (c) have a VUS disclosed as a finding, in the absence of a pathogenic variant. We recruited patients who had a VUS disclosed in person or writing' between 1 and 2 years prior to the period of the study (in 2019–2021) to maximize likelihood participants would be able to recall past events and allow enough time for cognitive and emotional processing following results disclosure. Following ethics approval, we contacted patients whose medical records met enrollment criteria. Initially, 52 individuals met enrollment criteria, and a recruitment letter with a description of the study was mailed to them. Twenty-two of these candidates consented and completed an interview, resulting in a total response rate of 42%.

Procedures

Based on relevant literature and the clinical experience of the fourth co-author (a genetic counselor), the research team (composed of two male researchers and two female researchers) prepared the semi-structured interview guide that included questions addressing the following topics: (a) how patients perceived the disclosure of VUSs in terms of recall, satisfaction, the HCP's message, and the patient's understanding of it; and (b) if and how did the uncertainty impact on the patient's sense of coping with their medical condition and motivation for follow-up (the interview guide is provided as a supplemental file). Additional questions concerning raw data and incidental findings which were part of the guide are not discussed here. If a participant did not recall receiving information about any VUS, we adjusted the interview guide to ask the questions in a more hypothetical way. Considering the manageable amount of data, we did not use a specific software program for qualitative analysis. Participants were given the opportunity to receive their interview transcripts for comment and/or correction, yet none of the participants requested this.

Data analysis

All interviews were conducted in Hebrew by the first author (a PhD student in medical sociology with training in qualitative methodology), audio recorded, and transcribed. Interviews lasted between 30 and 60 min, and given the COVID-19 pandemic restrictions, were mostly conducted via telephone or zoom. No one else was present in the

interview besides the participants and researcher. None of the researchers or the participants expressed a need to carry out repeat interviews. Where needed, the interviewer made field notes after the interview, elaborating for example on the interview data, setting, and circumstances. To maintain anonymity, codenames were used. Each interview received a code comprising the first letters of the respondent's personal and family name, gender, age, and health status (S-sick, A-asymptomatic). The sick/asymptomatic distinction pertains to the presence or absence of diagnosed symptoms of cancer. The transcripts were analyzed thematically to uncover discursive themes and categories of themes recurring within and across groups of respondents (Butler-Kisber 2010). We followed an interpretive methodology which is particularly appropriate for the current investigation, which is aimed at advancing existing theory using unstructured, open-ended data. This iterative, reflective practice enables to inductively distill meaningful themes reflecting the participants' points-of-view and to extend existing theory on issues that have been largely understudied (Timmermans & Tavory 2012).

The research team discussed the first few interview transcripts together, examining the relevance of the themes and agreeing on needed modifications and reclassifications. The first author then continued with the coding, discussing new findings as they appeared and their relationships to the codes in team meetings, where agreements were reached to prevent the potential bias of a single rater. The iterations stopped when all authors agreed on all the themes and no new themes were identified, suggesting that theoretical saturation of the sample was achieved (Corbin & Strauss 2008). Each of the themes is described below and illustrated with quotes from respondents, who are given pseudonyms. These quotes were translated by the first and second authors from Hebrew to English. Quotes were selected because they were noted by at least two of the authors as examples that best captured the identified themes. We did not conduct participant checking since in studies that are not participatory or collaborative there is little evidence that member checks improve research findings (Thomas 2017). We focus here on views presented concerning patients' perceptions of VUS disclosure.

Results

The sample comprised 20 women and 2 men, with an age range of 30–73 (mean 57) (see Table 1). Eighteen of them were already diagnosed with cancer and 4 were healthy individuals who were referred to genetic testing following a family history of cancer.

The demographics of the study population are representative of the patient population in the clinic who had a VUS. The two men (9%) who completed the interview were the only men in the patient population. The proportion of healthy respondents in the sample (4/22, 18%) was similar to that of healthy individuals in the Genetics Institute's patient population who underwent genetic testing because of cancer family history and received a VUS in their tests (7/52, 13%). All respondents received pre- and post-test consultation with genetic counselors. In the pre-test consultation, all counselees were counseled on the probability of detecting a VUS, to empower them to receive uncertain test results that might otherwise be unexpected and confusing. All signed a consent form, which does not offer opting out from receiving VUSs. In the post-test consultation, all respondents were informed that they have a genetic change that cannot be interpreted (a VUS) but may be later re-categorized as potentially disease-causing or harmless, and it is recommended that they check back in once a year. Three thematic domains surrounding patient perceptions of their VUS emerged from the analysis of the interviews: lack of recalling the VUS and no worries; concerns associated with VUS recall; and attitudes toward follow-up on reclassification. Out of the 22 participants, 7 (32%) did not recall any VUSs; 11 (50%) recalled the disclosure of VUSs but were largely indifferent about it. Only 4/22 (18%) expressed concerns regarding their VUS.

Table 1 Participants' demographics

Demographics	Value (*N*)
Health status	
Sick (cancer patients)	18
Asymptomatic (family history of cancer)	4
Age	30–73 (mean 57)
Gender	
Male	2
Female	20
Total	22

Lack of recall and few worries

About one third of the respondents had no recollection of their VUS disclosure. The following quote typically captures this lack of recall:

> No, I do not remember [that I received] such things… as soon as you are told that there is nothing to continue then you, ah ... how to say, you do not burden your mind to remember all the subtleties (SN-F-67-S)

Half of the respondents recalled the disclosure of VUS with very minor or no concerns. As the following respondent explained:

> It is written [in the letter with the test results], and she [the genetic counselor] explained to me the meaning of

it, said that it is not so relevant and... I'm not worried about it. (DL-M-47-S)

Other respondents expressed being tired of what they saw as an overload of test results concerning their disease:

She [the genetic counselor] gave me the results and that's it. [...] I, for my part, am already tired of information, I have already done enough, I don't check too much, because the clinicians already check too much, and find too much [...] If there are no [pathogenic] results and it [meaning the VUS] is not clear, then I just leave it like that. (MD-F-47-S)

Some respondents were dissatisfied with the VUS disclosure because they felt it was futile to spend time on having the meaning of the VUS explained, as the following quote illustrates:

I know I have a variant in some gene. [interviewer: What does it mean?] That's exactly the point, not knowing what it means. [...] She [the clinician] sent me to genetic counseling, but it really was nonsense I think, I came, I sat with her and I just wasted my time because they do not know, they just do not know. [...] I really didn't feel that the uncertain finding left me hanging in the air or made me look for information elsewhere. […] After all, if scientists sequence more genes, they will find more uncertain things [...] Okay, I have cancer. It's not that I found out about it from genetics. (DML-F-48-S)

Respondents expressed dissatisfaction with the VUS disclosure, complaining that it was "a waste of my time"; "results that are not really results"; and "reading aloud to me what is already written in the letter while I can read it for myself." The VUS consultation was seen by these respondents as "not a big deal," especially when considered against the difficult reality of coping with cancer. The following quote is representative of this opinion:

Medicine has not yet developed enough to interpret what they have found, and I was not too worried about it [...] What worried me was how do I keep my hand from having a tissue swelling... How to regain functionality slowly again, how do I go back to things I did before, how do I keep myself from getting fat because of the medicines I take, how do I do more exercises [...] The variant made no difference to me. (GK-F-48-S)

While respondents understood the need for following-up on the VUS, in the context of their cancer, the uncertainty of the variant gave them few worries and some even found positive aspects in it, for example in terms of being able to relax and mitigate family members' concerns:

Overall, I realized that I could relax but I need to continue following-up, but this is not a big deal [...] I was happy to find out that it does not surely lead to sickness and this also calmed my children. [...] I think it helped me because I realized that the result is more in the negative direction than in the positive direction ... I mean, not that I fully understood the doctor and I may have misunderstood her, but she said it did not look like Lynch and for me that was okay, it's reassuring [...] It's definitely reassuring to hear that maybe it's negative. (MG-F-47-S)

Taking advantage of the VUS as a precautionary signal for family members was also mentioned by respondents as a positive outcome of being informed about their VUS:

In genetic counseling they told us that there are things that are not clear. [...] That did leave me with questions. […] Look, we listened, one of my daughters already had two lumps removed from her breast. [...] Had the VUS not been found, her follow-up would not have been so in-depth, there would have been less attention. (NM-F-70-S)

Concerns regarding VUSs

Respondents who were worried by the VUS qualified it with a personal inclination of becoming stressed when confronted with uncertainty and described how the initial worry diminished over time:

There was a sentence there [in the summary letter sent by the genetic counselor] that worried me a bit, even though they said everything was fine, and it means nothing, there is nothing to do about it. I got rid of the worry, I said come on, they do not know, and it isn't clear and there is nothing to do and all that, everything is from God [...] This sentence [about the VUS] made me a little worried [...] I'm already all stressed up and there was some sentence saying it does not mean anything, but it sounded to me as if there is a chance that you can get something […] So at first I was stressed and then I started thinking come on there is nothing to do if they don't know then that's enough. (HZ-F-61-S)

Some respondents also related their worries to a broader dissatisfaction with the medical system, which they saw insufficiently responsive:

My results show that I am negative to all the BRCAs, but I have one variant […] the clinician told me, it's like they write, they don't think it is significant. But for me, it's a question mark [...] My sister who is an ob/gyn read it and also said it was not... I will not say nothing, but she said it isn't something important. [...]

> When I came back and asked, they said it's not serious and that's it, but I did not get an answer […] I can suppress my worries, it's actually a denial, the fact that I did not continue to investigate the variant that you are now bugging me about, sorry for the language, asking me about, okay? So actually, now it comes back to worry me why I didn't continue to research on this variant, okay? It really raises very big question marks. But I have no one to turn to. (RS-F-63-S)

Overall, cancer patients described being less worried about the VUS because of fears about the real dangers of their diagnosed disease, saying that the VUSs worried them less compared to what they "went through in the disease itself." In contrast, for half (2/4) of the asymptomatic respondents who were tested because of family history, the VUS was perceived with moderate concerns:

> The results showed that they tested eighty-four cancers [genes] so in eighty-three, everything came out clean, and one came out gray [...] The truth is I was a little worried because maybe it will develop into something bad (EM-F-66-A)

Asymptomatic respondents also described how the VUS disclosure motivated them to go online to find out more, which resulted in more fears. In addition, the VUS was described as interfering with life plans:

> The genetic counselor told me there were unclear results, and I didn't understand, so I said: What does this mean? so she told me, it is not clear yet, but we see some findings, maybe breast or ovarian cancer will develop at a later time [...] I read a lot about it. In Google. […] It bothers me because I keep thinking let's say about having children, I'm 31 […] if I'm told, God forbid, that I will have ovarian cancer when I'm 35, just as an example, then it means I should change my plans about my life, right? But [they just] leave you hanging in the air and tell you that it's not certain. (MO-F-31-A)

Attitudes toward follow-up and hypothetical reclassification

When asked "who should be responsible to follow-up on the VUS?" nine respondents said it should be the clinician; five respondents said it should be the genetic counselor; four said it should be a common responsibility of the patient and the HCPs; and only three said it should be the sole responsibility of the patient. Overall, only a minority of the respondents saw themselves as sharing the responsibility for follow-up.

When asked if they would like to know about any VUS re-classification in the future, the majority welcomed revisiting the VUS if more information became available. Seven respondents said they would like to know about any re-classification; six respondents said they would like to know, providing that such re-classification is actionable; one respondent said that she is not sure about it. The rest did not recall their VUS disclosure.

Respondents who wanted to know about any future re-classification of their VUSs were motivated by prevention, namely a potential for action (for them and for their family members), but they did not pose it as a pre-requirement for knowledge:

> I think you need to know everything. […] Why not? Yes. I think you should know. (EM-F-66-A)
>
> Of course, if they found out I'm a BRCA carrier it's terribly significant, if it's possible to treat before a tumor develops, is it not better? Preventive? (GK-F-48-S)
>
> Yes, even though I'm afraid of it... afraid of being put under stress and pressure, you understand? But overall, I am going to ask for it, maybe, yes, there is something to do. (HZ-F-61-S)
>
> I did all of this to be aware and all the tests I do, the results of the tests, I pass on to my children and to my sister. […] The health of my children and grandchildren is very important to me. (NM-F-70-S)

In contrast, some respondents insisted that they wanted to know only about reclassifications that are actionable, or in their words: "only if there is something to do with it."

> If it has consequences then yes, but not if it doesn't require follow-up or treatment or anything. Or it is just a cause for concern. (DL-M-47-S)
>
> I do not want to know, necessarily. Only if there are clear and concrete results, then yes, I would like to know. (MD-F-47-S)

Discussion

Genetic variants of uncertain significance (VUSs) are a challenge for patient communication and care in precision genomic medicine. Our study provides insight into how patients interpret VUS results. We found that many patients did not recall receiving a VUS result and few worried about such results. Only 4/22 (18%) expressed concern regarding their VUS. Similar lack of recall (and lack of distress) regarding VUSs was described in the context of cancer patients who received the results of VUS *re*classification, irrespective of whether the VUS was upgraded or downgraded (Halverson et al. 2020). This relative lack of concern may suggest that patients with hereditary cancers are often overwhelmed by numerous tests and by coping with the disease itself, making it difficult to muster the emotional

energy to attend to all relevant new information about their health care (Halverson et al. 2019). This is in line with our finding that cancer patients were less worried about the VUS because of worrying about the real dangers of their disease, while for half (2/4) of the asymptomatic respondents who were tested because of family history, the VUS was perceived with moderate worries.

Our findings show that most patients understood that while the presence of a VUS did not provide an explanation for the cancers in themselves or those in their family, the absence of a pathogenic variant did not rule out a genetic etiology for their cancers and the cancers in their family. Moreover, our data suggest that patients perceive the significance of their VUS result through the lens of their personal experiences. Our results illustrate that factors such as personal characteristics, medical condition, family history, expectations prior to testing, and motivations for pursuing testing influence the way patients come to terms with the uncertainty of the result, more than the factual information provided.

This presents an opportunity for genetic counselors to apply their unique counseling skill set to tailor disclosure and results discussion in light of these personal factors. Genetic counseling is meant to supplement information-focused "teaching" with listening to the patient (Meiser et al. 2008). Genetic counselors are used to practicing the Reciprocal-Engagement Model (REM), which proposes a balance of educating and counseling to deliver patient-centered care (Hartmann et al. 2015). Moreover, with the mainstreaming of genetic testing in cancer care (George et al. 2016; Scheinberg et al. 2021), physicians outside of genetics are increasingly referring cancer patients to genetic testing and also provide them with the tests' results. Developing pre-test education tools and clinical decision support tools for VUS disclosure may assist both clinicians and patients (Mighton et al. 2021).

Another lesson learned from this study relates to the role of the patient in checking back for VUS reclassification. There is yet no consensus and no standard policy over who is responsible whether, when, and how patients with VUSs should be recontacted for reclassification. Professional organizations such as the American College of Medical Geneticists (ACMG) generally advise that re-contact is fundamentally a shared responsibility between the ordering health-care provider, the clinical testing laboratory, and the patients themselves (Richards et al. 2015; David et al. 2019). Similarly, the European Society of Human Genetics (ESHG) recommended that recontacting patients in clinical genetics services should be commensurate with previously obtained consent, and a shared responsibility between healthcare providers, laboratories, patients (who may be asked to take the initiative to check in), and other stakeholders (Carrieri et al. 2019; Doheny et al. 2018; Otten et al. 2015). Variant classification in Israel follows the ACMG guidelines, with no guidelines in place regarding the way VUS are communicated to patients and the long-term management of reclassification and recontact of past patients with new evidence. We found that only a minority of the respondents saw themselves as sharing the responsibility for follow-up. In addition, the majority of our respondents did not recall and were indifferent about their VUS. These findings highlight the problematic implications of the suggestion, made by HCPs involved in genomic medicine, that the patient is the most suitable stakeholder to ask to follow up on VUS reclassification (Levin Fridman et al. 2021). Especially, those who are more burdened by disease, such as cancer patients, may be less likely to rise to this challenge (Dheensa et al. 2017). The findings mean that throwing the responsibility for recontact at the patient may unfortunately reinforce Tudor Hart's (1971) Inverse Care Law, namely that the availability of good medical or social care tends to vary inversely with the needs of the population served. The finding that a minority of participants see themselves as partly responsible for follow-up should be taken into consideration by centers that manage such activities. A possible practical solution is to use a patient registry such as GenomeConnect that provides genetic updates back to interested participants (Savatt et al. 2021).

There are limitations to this study. Although the participants' ages and health status contributed diversity to the sample, the sample size was small. It is difficult to draw conclusions about individuals with a cancer family history due to the small number participating in this study. Other patients with other medical conditions may express different views. Results also reflected individual recall bias, which we attempted to explain by personal characteristics. Moreover, findings may be limited to the context of the Israeli health system. Utilizing the present study's qualitative findings, future research should examine predictors of patients' uncertainty appraisal and perceptions. While our study focused on uncertain genomic findings in the context of cancer care, future research could also examine the disclosure of uncertain genomic findings in other settings exploring the possible effect of medical conditions on the ways patients manage and perceive uncertainty. Despite its limitations, the present study has identified major patterns of patients' interpretations of genomic uncertainty.

In conclusion, the data presented in this study indicate that many cancer patients, due to their medical condition, fail to recall receiving VUS results and express few and moderate worries concerning their VUSs. Patient understanding of the clinical and etiological significance of a VUS result is influenced by their medical condition, personality, and motivations for testing. It is important for clinicians involved in genetic testing to explore these characteristics to better frame the conversation around VUS results disclosure and

improve patient understanding of its significance. Under current circumstances of patients' engagement in the responsibility of recontacting the clinic for up-to-date information on VUSs, it is important to bear in mind that only the minority of patients are likely to actively recontact. Third-party tools may help both clinicians and patients in the important task of receiving updated information about VUSs.

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Code availability N/A.

Declarations

Ethics approval This study has been performed in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee of Hadassah Medical Center #0447–19-HMO.

Consent to participate Informed consent to participate in the study has been obtained from participants.

Consent for publication N/A: This MS does not include identifying details, images, or videos relating to an individual person.

Conflict of interest The authors declare no competing interests.

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