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REVIEW

Patients' views on variants of uncertain significance across indications

Kristin Clift[1] · Sarah Macklin[2] · Colin Halverson[3] · Jennifer B. McCormick[4] · Abd Moain Abu Dabrh[5] · Stephanie Hines[6]

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Abstract

As genomic sequencing expands into more areas of patient care, an increasing number of patients learn of the variants of uncertain significance (VUSs) that they carry. Understanding the potential psychosocial consequences of the disclosure of a VUS can help inform pre- and post-test counseling discussions. Medical uncertainty in general elicits a variety of responses from patients, particularly in the growing field of medical genetics and genomics. It is important to consider patients' responses to the ambiguous nature of VUSs across different indications and situational contexts. Genetic counselors and other providers ordering genetic testing should be prepared for the possibility of their patients' misinterpretation of such results. Pre-test counseling should include a discussion of the possibility of VUSs and what it would mean for the patient's care and its potential psychosocial impacts. When a VUS is found, post-test counseling should include additional education and a discussion of the variant's implications and medical management recommendations based on the results. These discussions may help temper subjective interpretations, unrealistic views, and decisional regret.

Keywords Variants of uncertain or unknown significance (VUS) · Affective response · Uncertainty · Genetic counseling · Qualitative research

Introduction

As genomic sequencing expands into more areas of patient care, an increasing number of patients learn of variants of uncertain significance (VUSs) that they carry. Based on recommendations from the American College of Medical Genetics and Genomics, genetic variants can be classified into five different categories: pathogenic, likely pathogenic, variant of uncertain significance, likely benign or benign (Richards et al. 2015). A VUS is a genetic change with unclear implications for gene function. Multiple VUSs may be reported on any clinical genomic test (Lazaridis et al. 2016). The relevance, if any, of the VUS to a patient's clinical history is not known due to a lack of sufficient scientific evidence to determine the biological and medical significance of the variant. It therefore cannot be unequivocally stated whether the variant is clinically causal, and potentially actionable, or benign. Clinicians from a variety of specialties will increasingly encounter genetic test results, but many at this time lack the understanding and resources necessary to discuss VUSs with patients (Macklin et al. 2018a).

For research purposes, VUSs can provide a wealth of opportunities for discovery, especially if the biological significance of the gene itself is unknown. However, in a clinical context, they can complicate matters. There remains no robust consensus on how to handle VUSs in the clinical setting (Howard and Iwarsson 2018; Han et al. 2017; Ackerman 2015). Any given VUS could be pathogenic or completely benign. Additional research is needed in order to guide reclassification of the variant. Unless further instances of the same VUS are found, studied, and validated, reclassification is difficult to achieve with any degree of confidence (Richards et al. 2015). ClinVar, for

✉ Kristin Clift
Clift.kristin@mayo.edu

[1] Mayo Clinic Center for Individualized Medicine, Jacksonville, FL, USA

[2] Mayo Clinic Department of Clinical Genomics, Jacksonville, FL, USA

[3] Center for Bioethics, Indiana University School of Medicine, Indianapolis, IN, USA

[4] College of Medicine, Pennsylvania State University, Hershey, PA, USA

[5] Mayo Clinic Department of Family Medicine, Jacksonville, FL, USA

[6] Mayo Clinic Center for Breast Health, Jacksonville, FL, USA

instance, is an online database that aggregates information on variants from different laboratories in an effort to aid in reclassifications and create agreement in variant classification. For rare and novel variants, robust data for reclassification may not be feasible for a significant amount of time without costly functional analysis or until more individuals are sequenced and phenotypic and genotypic information is shared on platforms such as ClinVar (Landrum et al. 2017; Rehm et al. 2015).

Some experts have argued that a VUS should be ignored during clinical decision making stating that it is inappropriate to report patients' VUSs due to the uncertainty regarding clinical significance (Berg et al. 2013). Disclosure to a patient could possibly suggest some latent significance, even if clinicians explicitly qualify them as uncertain. Over-estimation of the clinical significance could be misleading or stand as a distraction, and resources could be wasted on analyses that do not have any medical relevance (Resta 2014; Berg et al. 2013).

Others have called for more detailed and widely accepted guidelines for the assessment of VUSs (Dewey et al. 2014). Until that time, when a VUS is discovered, the ethical and psychosocial implications of returning these variants must be debated, assessing the situation subjectively and more or less ad hoc.

Medical uncertainty in general elicits a variety of responses from patients (Mishel 1988), particularly in the growing field of medical genetics and genomics (Pyeritz 2017; Newson et al. 2016; Han et al. 2017; Howard and Iwarsson 2018; Biesecker et al. 2014). Understanding the psychosocial consequences of disclosing a VUS can inform pre- and post-test counseling discussions. To this end, this review article explores the spectrum of responses from patients regarding inconclusive test results across different indications.

The literature described here includes articles with qualitative (interviews and free-text response) and quantitative (questionnaire response) data exploring the range of reactions that patients have when receiving a VUS result from genetic testing. Several factors seem to influence patients' responses, including the clinical indication, their personal health, prognosis, and level of clinical suspicion regarding the VUS. Some examples of the positive reactions described were hope for future VUS reclassification, beneficence derived from participating in research, relief, empowerment, and validation. Positive reactions sometimes occurred from misinterpretation of the result, i.e. over-interpretation of a VUS. Poor comprehension also led to some negative reactions. Negative feelings described included sadness, disappointment, isolation, hopelessness, frustration regarding the uncertainty, and regret (see Tables 1 and 2).

Positive affective response

When receiving a VUS result or when presented with a hypothetical VUS, many participants (specifically tumor profiling oncology, cardiomyopathy, and undiagnosed disease genetic testing patients), expressed the positive feeling of beneficence stemming from furthering scientific understanding by contributing to research (undiagnosed disease: Skinner et al. 2017; Werner-Lin et al. 2018. Cardiomyopathy: Lawal et al. 2018; Burns et al. 2017. Tumor profiling: Marron et al. 2016; Makhnoon et al. 2019) (Table 2).

Some patients expressed positive attitudes toward their result if they believed that the VUS would be reclassified or could potentially lead to an answer in the future (hereditary breast cancer: Kaphingst et al. 2016; undiagnosed diseases: Skinner et al. 2017; VUS patients seeking to be in reclassification research: Makhnoon et al. 2018; chromosome array prenatal setting: Jez et al. 2015). In cases of rare or undiagnosed diseases, some participants viewed a VUS positively because they interpreted it as causal or likely pathogenic (prenatal: Kiedrowski et al. 2016; undiagnosed disease: Skinner et al. 2017). This view sometimes led participants to feel empowered and validated (prenatal: Kiedrowski et al. 2016; undiagnosed disease: Skinner et al. 2017; Werner-Lin et al. 2018). Furthermore in the prenatal setting, some participants felt that the result would help them access more therapeutic amenities and assistance from the government, school systems, and providers (Reiff et al. 2012; Kiedrowski et al. 2016; Wilkins et al. 2016; Turbitt et al. 2015).

Other patients viewed VUSs optimistically, because they accurately interpreted their results as specifically indefinite, thus as a better outcome than had a pathogenic test variant been found (Lynch syndrome: Solomon et al. 2017; breast cancer: O'Neill et al. 2009; reclassification research participants: Makhnoon et al. 2018). However, some participants with a VUS result chose to pursue increased cancer screenings or enhanced medical monitoring despite the admitted ambiguity of the result (Lynch syndrome: Solomon et al. 2017; breast cancer: Lumish et al. 2017; undiagnosed disease: Werner-Lin et al. 2018).

Many of the research participants who were presented with the hypothetical option of receiving a VUS wanted to receive such results because they saw some value in the information (breast cancer: Kaphingst et al. 2016; tumor: Marron et al. 2016; Yushak et al. 2016; research: Jamal et al. 2017; Biesecker et al. 2014).

Negative affective response

One of the most reported negative effects of a VUS result on patients is stress and distress, particularly for breast cancer, tumor profiling, and cardiomyopathy patients (breast cancer: Kaphingst et al. 2016; O'Neill et al. 2009; Lumish et al. 2017. Bradbury et al. 2012; tumor: Makhnoon et al. 2019; cardiomyopathy: Wynn et al. 2018a. reclassification research: Makhnoon et al. 2018.). One article found that the distress score measured in the

Table 1 The optimistic and negative attitudes from the literature are extracted and organized by indication in Table 1. (Studies where the participants were asked about what they thought about VUSs, but they did not have a VUS result, are defined as "hypothetical")

Indication	Positive affective response to VUS themes	Negative affective response to VUS themes
Undiagnosed disease 3 articles, Combined $N = 77$	• Potential answers in the future • Optimism • Contributing to research • Empowerment • Gratitude	• Disappointment at not receiving a diagnosis • Distress over uncertainty • Frustration • Disappointment
Prenatal /chromosome array parents 4 articles, Combined $N = 64$ 1 hypothetical article, $N = 147$	• Relief • Comfort • Happiness • Validation • Acceptance • Extra information • Preparedness	• Hopelessness • Guilt • Isolation • Feeling of permanence • Distress from uncertainty • Lack of answers
Cardiomyopathy 3 articles Combined, $N = 93$	• Contributing to research • Contributing to future knowledge • Useful information • Sense of self awareness	• Dissatisfaction from uncertainty • Decisional regret of learning about their result • Lack of understanding and recall
Fabry-associated c.427G > A (p.A143T) variant in *GLA* 1 article, $N = 27$	• Ability to plan for the future • Inform clinical care	• Frustrated by lack of clear information • Decisional regret of learning about their result
Lynch syndrome 1 article, $N = 27$ 1 hypothetical article, $N = 19$	• Relief • Empowerment • Hope • Viewed not as definitive diagnosis, therefore better than a positive test result	• Sadness • Conflict • Disappointment • Shocking • Decisional regret
Breast cancer (of the articles reviewed) 5 articles combined $N = 246$ 1 hypothetical article, $N = 60$	• Viewed not as definitive, therefore better than a positive test result • Potential answers in the future	• Frustration about uncertainty • Isolation • Disappointment • Distress • Greater sustained distress
Tumor 1 article $n = 11$ 2 Combined hypothetical, $N = 458$	• Participation in research • Hope for the future	• Distress • Uncertainty • Worry about increased medical costs • Confusion
Research participants 1 article, $N = 26$ 2 hypothetical articles combined, $N = 241$	• Optimism that it would be reclassified • Opportunity • Furthering scientific knowledge	• Uncertainty • Pessimism • Fear • Distrust • Misunderstanding

paper was approximately the same (higher than those who received a negative result) for VUS recipients as for those parents of patients who received a pathogenic result from diagnostic exome sequencing (undiagnosed disease: Wynn et al. 2018b). However, a more recent article about breast cancer patients showed that worry levels among patients who received a VUS was more similar to those who received a negative result (less worry than those who received a pathogenic result) (Katz et al. 2018). Another study found that while distress decreased from before testing to 1 month after disclosure for participants who received a definitively negative result, participants with a VUS result reported stable distress from before testing through 6 months after disclosure, only decreasing at 12 months (breast cancer: O'Neill et al. 2009). Distress is not only a concern for patients who receive a VUS result from testing, but also for those who receive such a result about their offspring (breast cancer: Bradbury et al. 2012).

Symptoms and affected status contributed to negative attitudes regarding the disclosure of a VUS. Those without symptoms and those who had been told their VUS would likely turn out to be benign expressed regret or had lower satisfaction with testing than those with symptoms and those who had been told their VUS would more likely end up being reclassified as pathogenic (cardiomyopathy:

Table 2 Affective responses to variants of uncertain or unknown significance results broken down by article and organized by indication

Disease	Study	Regret	Distress/ anxiety	Poor comprehension/ recall	Altruism	Potential answers	Other
Cardiomyopathy	Lawal et al. 2018 VUS, $n = 79$	x			x		Overall sense of health awareness
	Burns et al. 2017 VUS, $n = 9$ patients			x	x		
	Wynn et al., 2018a VUS, $n = 5$ patients	x	x				
Fabry	Macklin et al. 2018 VUS, $n = 27$ patients	x				x	Interest in it being reclassified
Lynch syndrome	Solomon et al. 2017 VUS, $N = 27$ patients	x	x				Better than being positive, empowered to take precautions, increased cancer screening, hope for reclassification
	Hitch et al. 2014 $N = 19$ hypothetical						Better than being diagnosed with cancer, interest in it being reclassified
Tumors or other cancers	Yushak et al. 2016 $N = 413$ hypothetical	x					Concern over increased medical costs and additional testing
	Marron et al. 2016 $N = 45$ hypothetical				x		
	Makhnoon et al. 2019 VUS $n = 11$		x	x	x		Confusion
Breast cancer	Richter et al. 2013 VUS, $n = 36$ patients			x			decreased perceived risk; intermediate level of worry
	Kaphingst et al. 2016 $N = 40$ hypothetical		x			x	Would not want to know about it until it is reclassified
	Lumish et al. 2017 VUS, $n = 34$	x	x	x			Increased cancer screening
	O'Neill et al. 2009 VUS, $n = 19$ patients		x				Better than receiving a pathogenic result
	Katz et al. 2018, VUS $n = 134$		x				Low worry, higher in less educated, younger, and minorities
	Bradbury VUS, $n = 23$ parents of 43 children		x				Neutral, useful
Prenatal	Kiedrowski et al. (2016) VUS $n = 14$		x			x	Over-interpretation (view VUS as pathogenic); access more therapeutic amenities and assistance
	Jez et al. 2015 VUS, $n = 30$					x	Access more therapeutic amenities and assistance
	Wilkins et al. 2016 VUS, $n = 9$						Access more therapeutic amenities and assistance
	Turbitt et al. 2015 $n = 147$ hypothetical						Access more therapeutic amenities and assistance
	Reiff et al. 2012 VUS, $N = 11$		x	x			Access more therapeutic amenities and assistance
Undiagnosed disease	Skinner et al. VUS, $n = 32$				x	x	Over-interpretation (view VUS as pathogenic), empowered and validated
	Werner-Lin et al. 2018 VUS, $n = 10$ patients		x		x	x	Frustration, disappointed, minimalized, normalized, more informed, empowerment, gratitude
	Wynn et al. 2018b	x		x			Frustration; affect non-medical care
Research	Biesecker et al. 2014 Hypothetical, $N = 39$		x		x	x	Normalized, expected, information, a loss
	Jamal et al. 2017 Hypothetical, $n = 202$						Increased screening, no value, surprise, neutral
	Makhnoon et al. 2018 VUS, $n = 26$		x			x	Better than pathogenic

Wynn et al. 2018a; Lawal et al. 2018. Fabry: Macklin et al. 2018b; Lynch syndrome: Solomon et al. 2017; breast cancer: Lumish et al. 2017).

A negative outcome of receiving a VUS is that participants had a greater lack of understanding and recall regarding a VUS than those who had received a definitive test result (cardiomyopathy: Burns et al., Richter et al. 2013; breast cancer: Lumish et al. 2017; Makhnoon et al. 2018; Kaphingst et al. 2016; Reiff et al. 2012; undiagnosed disease: Wynn et al. 2018b).

Other negative sentiments expressed in the literature included shock, guilt, isolation, frustration and hopelessness and worry about increased medical costs.

Discussion

Despite some variability of specific responses, several themes repeated across indications between the different types of clinical scenarios and the way patients or families viewed the VUS result. Some patients viewed VUSs optimistically, others negatively, and sometime expressed a nuanced combination of both. This heterogeneity of positive and negative attitudes does not seem to correlate with the type of indication but rather with the patient's own interpretation of the result within the context of their life.

The literature has shown that patients often misinterpret VUSs (Grover et al. 2009; Lumish et al. 2017; Richter et al. 2013; Makhnoon et al. 2018). This misunderstanding contributes to patients' overall attitudes (either positive or negative) toward the result and how they act upon it. The difficulty in successfully communicating the clinical uncertainty characteristic of a VUS is not limited to any particular indication.

In some scenarios, patients assigned meaning and greater classificational specificity to their VUS on a likely pathogenic to likely benign scale. Sometimes, breast cancer patients viewed VUSs as more similar to a negative result than to a positive result (Richter et al. 2013). Conversely, undiagnosed patients were more likely to view a VUS as pathogenic, because they perceived it as a potential answer for their health history (Skinner et al. 2017). Parents were more likely to present optimistic views of their child's uncertain chromosome microarray results if the parent considered it to be causal or likely pathogenic (Kiedrowski et al. 2016). The subjective nature of VUS interpretation is important to consider upon disclosure. Over-interpretation of a VUS has the potential to lead to harm through unwarranted surveillance or inappropriate treatment. Furthermore, if a family member tests negative for a familial VUS, they may wrongly interpret that to mean they have no increased risk for the associated condition.

Patients' interest in reclassification was also shown to be contextual. In the Fabry-associated case, the severity of patient's reported symptoms correlated with the value they saw in the variant being confirmed as pathogenic (Macklin et al. 2018b). In an article about cardiomyopathy-associated VUSs, patients were informed whether their result was more likely benign or more likely pathogenic. Patients who were told that the VUS was more likely pathogenic perceived more value in the disclosure of a VUS. On the other hand, patients who received a result that was described as more likely benign saw less value in the disclosure of the VUS (Lawal et al. 2018).

In cases of undiagnosed disease, VUSs are often seen by the patient as a potential indication of future diagnosis that could help them get access to care and social and clinical validation (Skinner et al. 2017; Makhnoon et al. 208). This finding is important, because uncertainty about a diagnosis in general has been found to correlate with negative attitudes (Madeo et al. 2012). However, for undiagnosed diseases, an uncertain result is seen as a partial answer and therefore leads to optimistic views (Kiedrowski et al. 2016; Skinner et al. 2017). Patients' responses to uncertainty, therefore, are not simply a function of the uncertainty itself but of that uncertainty within the specific context of their own diagnostic odyssey. The return of variants of uncertain significance cannot merely be valued in the abstract. The likelihood of mis- and over-interpretation varies based on the diverse psychosocial needs for evidence to legitimize particular patients' suffering within their own clinical course.

Decisional regret is often mentioned in the literature. In one paper related to Lynch syndrome, the only people with VUSs that expressed regret regarding testing were unaffected patients (Solomon et al. 2017). Patients who received a cardiomyopathy VUS that was described as more likely benign indicated more decisional regret (Lawal et al. 2018). From these studies, it appears that if a VUS result is less likely to inform health care decisions, patients may express more regret in learning the inconclusive result. Further studies of people who communicate regret after receiving a VUS need to be conducted in order better to understand what prompts this feeling. By learning more about these patients, we may eventually be able to predict and help prevent such regret.

Conclusion

Genetic counselors and other providers ordering genetic testing should be prepared for the possibility of their patients' expressing regret or therapeutic misconception (Appelbaum and Lidz 2008). Pre-test counseling should include a discussion of the possibility of VUS and what it would mean for the patient's care (Daly et al. 2001). When a VUS is found, post-test counseling should include a discussion of the variant's implications and what patients should and should not do with the results. The discussion should facilitate patient consideration of this result in the long term (Johnson et al. 2016).

Development of shared decision-making tools may facilitate patient–clinician conversation and support better understanding of the results, and subsequently a better response to potential long-term psychosocial consequences, allowing ultimately for a truly informed decision-making process (Hargraves et al. 2016).

Genetic counselors could also provide patients with educational information that can be shared with other providers who may not be as familiar with genetics. Furthermore, genetic counselors could send an annotated note to other providers to explain in general what a VUS is, but also what it might mean specifically in the patient's context considering the patient's medical and familial history. Laboratories and genetic counselors could also offer resources for patients to become involved in reclassification research or variant registries, such as the PROMPT Registry. They should also provide specific details for how they will recontact the patient if the variant gets reclassified as pathogenic or benign but also recommend that the patient follow-up every few years as well. These resources and discussions emphasizing uncertainty may help temper subjective interpretations, unrealistic views, and decisional regret.

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Compliance with ethical standards

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Ethical approval All procedures performed in the referenced 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 was obtained from all individual participants included in the referenced studies.

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