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Evaluation of Clinical Practices and Needs about Variants of Uncertain Significance Results in Inherited Cardiac Arrhythmia and Inherited Cardiomyopathy Genes

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Evaluation of Clinical Practices and Needs about Variants of Uncertain Significance
Results in Inherited Cardiac Arrhythmia and Inherited Cardiomyopathy Genes

by

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A thesis submitted in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
with a concentration in Genetic Counseling
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ABSTRACT

The increasing numbers of genetic tests in clinical settings have identified many variants of uncertain significance (VUS) in genes associated with inherited cardiac arrhythmias and inherited cardiomyopathies. Evaluation of clinical practices including counseling strategies and medical management recommendations for patients and their families is important to improve patient outcomes and prevent over- or under-treatment that may result in morbidity or fatality. The purpose of this study is to describe provider practices related to VUS results including how they conduct risk assessments and ascertain what information and medical management recommendations they provide to patients with VUS results and the patients’ family members. Additionally, we aim to describe providers’ concerns and informational needs related to counseling about a VUS. An anonymous online survey was developed for the current study and distributed to genetic counselors through the National Society of Genetic Counselors (NSGC) listerv and to cardiologists via emails obtained from publicly available resources. The survey explored healthcare providers’ confidence in counseling about a VUS, explanation of a VUS to patients, topics covered before and after genetic testing, and recommendations for patients with a VUS and their families using clinical vignettes.

Providers (N=102) who completed the survey included 29 cardiovascular genetic counselors, 50 genetic counselors from other specialties, and 23 cardiologists. A hypothetical clinical scenario was used in which a young adult patient had a VUS in a gene causing Arrhythmogenic Right Ventricular Cardiomyopathy, but did not meet clinical diagnostic criteria for the condition. The patient’s only concerning issues included a personal history of fainting during exercising and sudden death of a 45 year old first-degree relative. Nearly 9% of all providers incorrectly described the VUS as likely pathogenic, while 15% would downplay the
finding by indicating the VUS is more likely to eventually be reclassified as benign. Genetic counselors feel more confident about counseling about VUS results (p<0.001). Both cardiovascular genetic counselors and cardiologists feel confident in making medical management recommendations; however, cardiologists are more likely to recommend treatment with beta-blockers and exercise limitation for the patient. Compared to cardiac genetic counselors, other genetic counselors (p=0.001) and cardiologists (p=0.014) were more likely to recommend clinical testing for family members even though testing is expected to be uninformative, especially given the absence of any clinical diagnosis in the family. These findings highlight the expertise of different providers in different specialty area and suggest the need for interdisciplinary clinics that include cardiologists, cardiac genetic counselors, nurses, geneticists, psychologists and others to optimize care for challenging cases where VUS results create uncertainty.
INTRODUCTION

Inherited arrhythmias and cardiomyopathies are a group of genetic conditions that alter the natural rhythm of the heart, causing fainting spells or sudden death (Priori et al., 2013). The rapidly increasing numbers of genetic tests in clinical settings have identified many variants of uncertain significance (VUS) in inherited cardiac arrhythmia and cardiomyopathy genes giving rise to uncertainty among both patients and providers about appropriate clinical management. Although the American College of Medical Genetics and Genomics (ACMG) have developed standardized guidelines for variant classification, recent studies show that this process remains a challenge, especially in the field of cardiology (Furqan et al., 2017; Reuter, Grove, Orland, Spoonamore, & Caleshu, 2018; Richards et al., 2015). Interpretation of variants is a complicated process that involves gathering information about the variant in addition to the laboratory reports, including surveying variant databases, performing literature searches and consulting with experts in the field (Reuter et al., 2018).

Uncertainty about a VUS result in inherited arrhythmia and cardiomyopathy genes not only arises from the difficulty of classifying variants, but also from the reduced confidence that the family history is reliable in accurately assessing risks due to incomplete gene penetrance. Risk assessment is particularly important for inherited arrhythmias and cardiomyopathies since the outcomes of failing to treat someone as high risk could result in fatality. Overdiagnosis and overtreatment are additional concerns associated with inherited arrhythmias with possible complications of infections, pneumothoraces and cardiac tamponade caused by surgical management, and the burden of life long therapy with medications and unnecessary restriction from exercise (Gaba et al., 2016; Hofman, Tan, Alders, van Langen, & Wilde, 2010; Schwartz...
et al., 2010). Due to these challenges associated with counseling about VUS results in inherited arrhythmia and inherited cardiomyopathy genes, studies evaluating counseling practices are needed, particularly given that most genetic counselors report the need for more cardiogenetic education due to the recent emergence of this subspecialty (Somers et al., 2014).

Medical management, perceptions and genetic counseling practices related to VUS results have been studied in cancer (C. L. Scherr, Lindor, Malo, Couch, & Vadaparampil, 2015; Courtney L. Scherr, Lindor, Malo, Couch, & Vadaparampil, 2015). These studies show increased anxiety in patients, incorrect recall of the results, physician’s lack of knowledge, unnecessary surgeries and the need for more counseling resources (C. L. Scherr et al., 2015; Welsh et al., 2017). Studies evaluating patients’ perception of an uninformative genetic test result in cardiology showed incorrect recall of results, increased anxiety, reduced uptake of family screening and lower rates of sharing the information with family (Burns, Yeates, Spinks, Semsarian, & Ingles, 2017; Hamang et al., 2012; Hanninen et al., 2015).

The inherent challenges and uncertainties associated with VUS results in inherited arrhythmia and inherited cardiomyopathy genes raises the question of how health care providers discuss these results and implications this may have for patients and their family members. We aim to describe counseling practices and needs across different health professions including pre-test counseling, medical management recommendations, management of uncertainty, evaluation strategies, the risk assessment process and information shared with patients and their families. This study seeks to identify the needs and counseling practices of health care providers as a first step toward revising counseling strategies that can prevent unnecessary treatment, adverse outcomes caused by under-treatment and inappropriate surveillance of at risk family members, and help manage uncertainty and improve family sharing and surveillance.
METHODS

The study was approved by the University of South Florida Institutional Review Board (IRB). This is a descriptive study exploring healthcare providers’ self-reported practices related to Variant of Uncertain Significance (VUS) results in genes associated with inherited arrhythmias and cardiomyopathies.

Recruitment and Data Collection

A call to participate in the study was distributed once via email to genetic counselors using the NSGC listserv and highlighted on the discussion board in the NSGC Cardiovascular Special Interest Group (SIG). Contact was also attempted with 2000 cardiologists using email addresses obtained from public resources and published articles. The recruitment email included a brief description of the study and a link to both the informed consent form as well as the Qualtrics survey.

Participants were eligible if they were able to understand and speak English, capable of consenting, 18 years of age or older and genetic counselors, nurses, or physicians who have seen at least one case referred for risk assessment for inherited cardiac arrhythmia or inherited cardiomyopathy (e.g., Long QT syndrome, Short QT syndrome, Brugada syndrome, Familial Hypertrophic Cardiomyopathy, Familial Dilated Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Familial Atrial Fibrillation (FAF), Catecholaminergic polymorphic Ventricular Tachycardia (CPVT) and Cardiac Conduction Disease (CCD)).

Survey Instrument

The survey questions were specifically developed for the current study by the principal investigator with the input of a cardiovascular genetic counselor, a medical geneticist and a cardiologist with expertise in genetics. The final survey consisted of open- and close-ended
questions comprising of 3 sections to assess practice characteristics, clinical practices before and after genetic testing (including healthcare providers’ confidence in counseling about a VUS, explanation of a VUS to patients, topics covered before and after genetic testing, and medical management recommendations for patients with a VUS and their families using a clinical vignette), and informational sources and preferences of providers. Data was collected over a 10 week period between 11/20/2018 and 01/31/2019.

**Practice Characteristics**

Participants were asked about 1) their profession and specialty areas 2) the number and proportion of patients they have seen that were referred for inherited arrhythmias and/or cardiomyopathies, 3) the number of VUS results in genes associated with inherited arrhythmias and cardiomyopathies they have discussed with patients 4) primary work setting, 5) and the number of providers in their practice providing risk assessment for these conditions.

**Pre- and Post-test Counseling**

Participants were asked to rate their general confidence in various aspects of both pre- and post-test counseling on a 5-point scale ranging from not at all confident (1) to extremely confident (5).

Participants were asked how often they discuss various concepts during pre-test counseling using a 5-point scale ranging from never (1) to always (5). A clinical scenario was developed by the authors to inquire about participants’ practices when their patient receives a VUS result. The clinical vignette described a young adult patient with a VUS in a gene causing Arrhythmogenic Right Ventricular Cardiomyopathy, a genetic condition that can present with both cardiomyopathy and abnormal heart rhythm. The vignette stated that the patient had a history of fainting, but did not meet clinical diagnostic criteria for the condition and the patient’s only concerning family history included sudden death of a 45-year-old first-degree relative. Subsequent questions asked participants to indicate on a 5-point scale how likely or unlikely it is that they would 1) provide certain information to the patient, 2) give various medical
management recommendations, 3) encourage patients with a VUS to share certain information with their family members and 4) utilize specific counseling strategies with the patient described in the clinical scenario. Participants were also asked to rate their confidence in making medical management decisions on a 5-point scale ranging from not at all confident (1) to extremely confident (5).

**Informational Sources and Preferences**

Participants were asked 1) how often they use certain informational sources when they receive a VUS result, and 2) what information they would find helpful in a VUS database.

**Data Analysis**

Participants were grouped into three groups based on their profession and specialty including cardiovascular genetic counselors, other genetic counselors and cardiologists. Frequencies and medians for questions that measured practice characteristics, clinical practices and informational sources were obtained using SPSS.

An average score from 5 questions assessing confidence in counseling was created and medians of the average scores for each group were reported. Results for questions related to topics discussed before ordering a genetic test and to additional informational sources used to evaluate a VUS result were reported by combining the proportion of respondents who would often (score 4) or always (score 5) would discuss the listed topics. Results for questions related to topics discussed during result disclosure were reported by medians. Results for the question related to confidence in making medical management recommendations were reported by combining the proportion of respondents who feel very (score 4) or extremely confident (score 5). Results for questions related to medical management recommendation, information to share with family members and counseling strategies used were reported by combining the proportion of respondents who would likely (score of 4) or extremely likely (score of 5) follow the described clinical practices. Various medical management recommendation questions were then grouped into seven groups representing those who were very likely or extremely likely to: 1) treatment
with Beta-blockers, 2) treat the patient with a VUS with surgical interventions including ICD, cardiac catheter ablation and/or pacemaker, 3) limit exercising 4) conduct further clinical evaluation for the patient including cardiac MRI, exercise stress test, and/or evaluation by Holter monitor, and 5) recommend yearly cardiology follow-up with ECGs, echocardiograms, or cardiology visits; 6) no medical management changes and 7) yearly follow-up with genetics.

Comparisons of confidence and medical management recommendations for both the patients and their family members across groups and post-hoc analyses when a statistically significant differences were found were done by using nonparametric tests and adjusting for multiple comparisons. Comparisons across three groups were made by using Kruskal-Wallis tests and adjusting for multiple comparisons using a Bonferroni correction for each group of questions related to medical management of the patient and recommendations for at risk family members. Post-hoc analysis was done by using Mann-Whitney U tests.

Qualitative analysis of open-ended questions was done by using an inductive approach. Responses were reviewed and coded into themes including uncertainty about the clinical diagnosis, need for further clinical evaluation, need to manage patients based on personal and family history, need for post-mortem testing of deceased relative, cardiac evaluation of at-risk relatives, genetic testing for at risk relatives and not ordering genetic testing for this patient in the first place.
RESULTS

Participants

A total of 120 survey responses were received. Thirty of the respondents were cardiovascular genetic counselors (GCs), 55 of were genetic counselors working in other specialties and 23 were cardiologists. Surveys were excluded from data analysis if the respondent completed less than 50% of questions. A total number of 102 surveys were included in the data analysis; 29 cardiovascular GCs, 50 GCs working in other specialties and 23 cardiologists (Figure 1).

![Sampling and Respondents diagram]

Figure 1. Sampling and Respondents.

Note: 12 participants started the survey; however, they did not fill out their profession. These surveys were excluded.\(^a\)5 Cardiovascular genetic counselors and \(^b\)3 other genetic counselors
didn’t finish the survey but completed more than 50% of questions. These surveys were included in the data analysis.

Practice Characteristics

A vast majority of cardiovascular GCs (93.1%) and cardiologists (78.3%) have seen more than 20 patients to assess risk of inherited arrhythmias or cardiomyopathies, while only 34% of other GCs have seen more than 20 patients (Table 1.) A majority of cardiovascular GCs and cardiologists work in a University Medical Center compared to only 38% of other GCs. Participants work with varying numbers of other healthcare providers ranging from one to over five in the same clinical practice.

Pre-test Counseling

All GCs and the majority of cardiologists (77.3%) discuss the possibility of getting a VUS result before genetic testing is ordered. All cardiovascular GCs, 96% of other GCs and 81% of cardiologists discuss the risks and benefits associated with genetic testing. Most providers also talk about the implication of genetic testing for family members including sharing the results with them (83.3%, 89.6% and 77.3% of other GCs, cardiovascular GCs and cardiologists respectively) and the importance of clinical evaluation of at-risk family members (100%, 91.7% and 85.7% of cardiovascular GCs, other GCs and cardiologists respectively). Less commonly discussed topics before genetic testing include the uncertainty about medical management if the test results are uninformative with only 68.8% of other GCs, 58.6% of cardiovascular GCs and 50% of cardiologists discussing this topic often or always. Discussion about laws protecting against healthcare insurance and employment discrimination based on genetic test results and their limitations before ordering a genetic test is often or always done by 68.9% of cardiovascular GCs, 66.7% or other GCs and 57.1% of cardiologists (Figure 2.).
Table 1. Practice Characteristics

<table>
<thead>
<tr>
<th>Practice Characteristics</th>
<th>Cardiovascular Genetic Counselors (n=29)</th>
<th>Other Genetic Counselors (^a) (n=50)</th>
<th>Cardiologists (^b) (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients seen for inherited arrhythmias and cardiomyopathies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>-</td>
<td>17 (34%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>6-10</td>
<td>-</td>
<td>9 (18%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>11-20</td>
<td>2 (6.9%)</td>
<td>7 (14%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>27 (93.1%)</td>
<td>17 (34%)</td>
<td>18 (78.3%)</td>
</tr>
<tr>
<td>Primary work setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University Medical Center</td>
<td>20 (69%)</td>
<td>19 (38%)</td>
<td>22 (93.7%)</td>
</tr>
<tr>
<td>Private Medical Facility</td>
<td>-</td>
<td>14 (28%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Public Medical Facility</td>
<td>8 (27.6%)</td>
<td>11 (22%)</td>
<td>-</td>
</tr>
<tr>
<td>Health Maintenance</td>
<td>-</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.4%)</td>
<td>5 (10%)</td>
<td>-</td>
</tr>
<tr>
<td>Total number of healthcare providers in practice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (17.2%)</td>
<td>10 (20%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (13.8%)</td>
<td>11 (22%)</td>
<td>4 (17.4%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (20.7%)</td>
<td>10 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>3 (10.3%)</td>
<td>5 (10%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>11 (37.9%)</td>
<td>14 (28%)</td>
<td>12 (52.2%)</td>
</tr>
<tr>
<td>Percentage of patients seen for inherited arrhythmias and cardiomyopathies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>2 (6.9%)</td>
<td>37 (74%)</td>
<td>17 (73.9%)</td>
</tr>
<tr>
<td>10-24%</td>
<td>-</td>
<td>8 (16%)</td>
<td>-</td>
</tr>
<tr>
<td>25-50%</td>
<td>4 (13.8%)</td>
<td>3 (6%)</td>
<td>3 (13.1%)</td>
</tr>
<tr>
<td>51-75%</td>
<td>3 (10.3%)</td>
<td>1 (2%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>20 (69%)</td>
<td>1 (2%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Number of patients seen with a VUS result in inherited arrhythmia and cardiomyopathy genes in the past year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>19 (38%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>1-10</td>
<td>3 (10.3%)</td>
<td>22 (44%)</td>
<td>12 (52.2%)</td>
</tr>
<tr>
<td>11-20</td>
<td>5 (17.2%)</td>
<td>6 (12%)</td>
<td>4 (17.4%)</td>
</tr>
<tr>
<td>21-30</td>
<td>7 (24.1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;30</td>
<td>14 (48.3%)</td>
<td>3 (6%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Genetic Counseling Board certification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Board Certified</td>
<td>26 (90%)</td>
<td>45 (90%)</td>
<td>-</td>
</tr>
<tr>
<td>Board Eligible</td>
<td>3 (10%)</td>
<td>5 (10%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: \(^a\) specialty areas of these counselors include: cancer (24%), prenatal (16%), pediatrics (30%), adult (18%), and other: neurology, nephrology, metabolic, newborn screening, research,
ophthalmology and endocrinology (12%). Specialty areas of these cardiologists include: electrophysiologist (26%), adult cardiologist (65%), and heart failure cardiologist (9%).

Figure 2. Percent who would often or always discuss various topics prior to genetic testing.

**Post-test Counseling**

When asked which response best captures what providers would say about the VUS result to the patient in the scenario, most selected the option ‘At this point, we don’t have enough information on this variant to determine for certain if the gene change is causing your family history of sudden death and your symptoms.’ A total of 8.8% of all providers (6.1%, 7.1% and 28.6% of GCs, cardiovascular GCs and cardiologists respectively) would describe these results as likely pathogenic as evidenced by selecting the following response ‘At this point, we just don’t have enough information on this variant to determine if it causing your symptoms and your family history, but I think it probably is’. Finally, 14.7% of all providers would be more
reassuring about these results and downplay the finding by explaining that ‘Most VUS results end up being found to be normal variation that is not associated with disease risk, but we just don’t have enough information to determine if this variant is or is not responsible for your family and personal history.’ (Figure 3.) Five respondents explained in comments that they would prefer to do more clinical evaluation before they would explain the results to the patient. These responses were excluded from the analysis and valid percentages are reported.

Figure 3. How VUS results were explained to the patient.

The likelihood of discussing various topics during result disclosure varied widely across groups. All three groups were very or extremely likely to discuss what it would mean for the patient if the VUS was reclassified. Genetic counselors are not likely to discuss risks associated with treatment or lack of treatment or the information considered in variant classification, while cardiologists are more likely to discuss these topics. All providers are moderately to very likely
to provide written information to the patient about VUS results and the cardiovascular condition (Figure 4). Additional written comments from cardiovascular and other GCs emphasized the importance of highlighting that based on the personal, family and genetic testing history, this patient does not meet clinical diagnostic criteria for an inherited cardiovascular conditions; however, she is at an increased risk based on her family and personal history alone as illustrated in the following quote: “...her personal and family history may predispose her to sudden cardiac death even though she does not meet criteria for a known clinical condition associated with sudden cardiac death”. A couple of respondents indicated that for the individual described in their hypothetical clinical scenario, they would not have ordered panel genetic testing to an unaffected individual.

![Figure 4](image)

**Figure 4.** Median likelihood of discussing various topics when disclosing VUS results. 

*Note: Each individual’s Likert-type responses to several questions within each topical category were averaged and then medians for the three groups were calculated.*
Confidence

There was a statistically significant difference across the three groups in level of confidence in counseling about a VUS result (p<0.001) with both cardiovascular and other genetic counselors reporting a higher level of confidence than cardiologists (p=0.001) in counseling about VUS results (Figure 5.)

![Bar chart showing median levels of confidence in counseling about a VUS result.

Note: Each individual’s scores on 5 Likert-type questions were averaged and then medians for the three groups were calculated.* A statistically significant difference was found between the three groups (p<0.001). Post-hoc analyses showed cardiologists differed significantly from cardiac genetic counselors (p<0.001) and other genetic counselors (p=0.001)

Confidence in making medical management recommendations was also statistically significantly different across the three groups (p=0.002). Other GCs compared to cardiovascular...
genetic counselors (p=0.001) and cardiologists (p=0.01) reported less confidence in making medical management recommendations if they were asked to (Figure 6.)

![Figure 6. Proportions who are very or extremely confident in making medical management recommendations for the patient with a VUS.](image)

*Note:* Kruskall-Wallis test showed a statistically significant difference between groups (p=0.002). Post-hoc analyses by Mann-Whitney U tests found other genetic counselors differed significantly from cardiac genetic counselors (p=0.001) and cardiologists (p=0.01).

**Medical Management Recommendations**

Forty-four percent of cardiologists, 6.7% of cardiovascular GCs and 33.3% of other GCs would be very or extremely likely to recommend some treatment with Beta-blockers. None of the genetic counselors and only a small percentage of cardiologists (11.1%) would recommend treatment with surgical intervention including ICD, cardiac catheter ablation and/or pacemaker. While none of the cardiovascular GCs would recommend limiting exercise as treatment, almost
half of cardiologists (43.8%) and 28.6% of other GCs would. The three groups have a statistically significant difference (p=0.001) with cardiovascular GCs less likely to recommend exercise limitations than other GCs (p=0.006) and cardiologists (p=0.001). Most providers in all three groups (91.3% of cardiovascular GCs, 94.7% of cardiologists and 71.4% of other GCs) would likely to recommend further cardiac evaluation in the form of cardiac MRI, exercise stress test, and/or evaluation by Holter monitor. Cardiovascular GCs (73.9%), other GCs (71.4%) and cardiologists (78.9%) were also likely to recommend yearly follow-up visits with a cardiologist including yearly ECGs, echocardiograms, and/or cardiology visits to evaluate the disease state. A majority of respondents selected that there should be some medical management changes made with only 25% of cardiovascular GCs, 8.7% of other GCs and 16.7% of cardiologists believing that no medical management changes should be made. Although 50% of cardiovascular GCs and 57.8% of other GCs would recommend yearly follow up with genetics, only 16.7% of cardiologists reported that they would likely recommend genetics follow-up as part of medical management.

Open-ended comments from respondents supported these findings, highlighting the perceived importance of further evaluation and cardiac and genetics follow-up. Multiple respondents indicated that post-mortem genetic testing and/or autopsy report on the deceased relative would be part of their clinical investigation: ‘Additionally, would clarify if sample available for post-mortem genetic testing of family member as well as additional records regarding autopsy of this individual.’ Comments emphasized the importance of treating a patient with a VUS based on personal and family history without considering the VUS result when making a plan for medical management: ‘Would recommend routine echo/ECG based on her family history of SCD in 1st degree relative alone. VUS not necessarily prompting those evaluations.’
Figure 7. Proportions who would likely or very likely make the following medical recommendations for the patient with a VUS.

Note: *Kruskall-Wallis test showed a statistically significant difference among groups (p=0.001).

Post-hoc analyses by Mann-Whitney U tests found that cardiovascular genetic counselors differed significantly from other genetic counselors and cardiologists (p=0.006 and p=0.001 respectively). Proportions who would likely or very likely do one or more of the following: a) surgical treatment options (ICD, cardiac catheter ablation and/or pacemaker); b) further evaluations (cardiac MRI, exercise stress test, and/or evaluation by Holter monitor); c) yearly follow-up (ECGs, echocardiograms, and/or cardiology visits).

Family Sharing

There is variability across providers about what topics they would recommend patients share with their family members. Most respondents would recommend sharing the genetic test report with family members (41.7%, 61.2%, 55.6% of cardiovascular GCs, other GCs and cardiologists respectively), discussing the risk of having an inherited genetic condition (50%,
57.1%, 77.8% of cardiovascular GCs, other GCs and cardiologists respectively) and discussing the option of genetic counseling (45.8%, 58.3% and 64.7% of cardiovascular GCs, other GCs and cardiologists respectively). Cardiac evaluation of at-risk family members was recommended by most cardiovascular GCs (95.7%) and cardiologists (83.3%); however, most of the other GCs did not find it important with only 32.7% of them recommending clinical evaluation of at-risk family members. Cardiologists (58.8%) and other GCs (58.3%) are significantly more likely to recommend genetic testing for at-risk family members (p=0.014 and p=0.001 respectively) compared to cardiovascular GCs (6.9%).

Figure 8. Proportions who would likely or very likely recommend the patient with a VUS share the following with family members.
Counseling Strategies

The most frequently used counseling strategies for a patient with an uncertain or inconclusive result in all three groups were checking for patient understanding (100%, 100%, 83.3% of cardiovascular GCs, other GCs and cardiologists respectively) and exploring patient concerns (100%, 95.9%, 83.3% of cardiovascular GCs, other GCs and cardiologists respectively). Most providers would discuss different sources of uncertainty (87.5% of cardiovascular GCs, 87.7% of other GCs and 72.2% of cardiologists) and the uncertainty related to the variability and severity of inherited cardiac conditions (88% of cardiovascular GCs, 77.1% of other GCs and 83.3% of cardiologists). Less frequently used counseling approaches across all three providers are helping patients identify ways that they can feel in control of their lives (44%, 55.1%, 55.6% of cardiovascular GCs, other GCs and cardiologists respectively) and helping patients create a plan to deal with uncertainty (44%, 62.5%, 61.1% of cardiovascular GCs, other GCs and cardiologists respectively). Finally, 20.9% of cardiovascular GCs, 36.8% of other GCs and 44.4% of cardiologists would refer their patient for additional, long term counseling if they felt it was indicated (Figure 9.)

Figure 9. Proportions who would be very or extremely likely to use the following counseling strategies.
Informational Needs

The least frequently utilized resource to gather more information about a VUS in all three groups was contacting researchers (4.2% of cardiovascular GCs, 18.4% of other GCs and 41.2% of cardiologists). Most providers would use the supplemental information included in the laboratory report (79.2%, 87.2%, 58.9% of cardiovascular GCs, other GCs and cardiologists respectively), search the scientific literature (83.4%, 81.3%, 70.6% of cardiovascular GCs, other GCs and cardiologists respectively), review databases (95.8%, 85.7%, 47.1% of cardiovascular GCs, other GCs and cardiologists respectively), and discuss the results with colleagues (83.4%, 77.5%, 70.6% of cardiovascular GCs, other GCs and cardiologists respectively) to gain more insight into the clinical meaning of a VUS. Cardiologists less frequently contact the laboratory about their variant classification program (25.1%) than cardiovascular (50%) or other GCs (69.4%) (Figure 10).

Figure 10. Proportion who would often or always use the following resources to learn more about a VUS.
Most genetic counselors would find it helpful if the following information was available in variant databases: allele frequencies, computer modeling of functional effect on protein function, references to scientific publications, results of segregation studies, location of the variant, type of mutation, whether the variant has been reported before and whether the variant was found in patients with symptoms. Cardiologists were less likely to find the above-mentioned information helpful (Figure 11).

Figure 11. Proportions who would find the following database information helpful.
DISCUSSION

Genetic testing is becoming more common and are ordered by a variety of healthcare providers. This study aimed to evaluate the clinical practices of both providers who have specialized genetic training and those who don’t in a cardiovascular setting in order to obtain a broad description of the clinical practices related to VUS results. To our knowledge, this is the first study assessing clinical practices related to VUS results in genes associated with inherited arrhythmias and cardiomyopathies. Based on our findings, the possibility of getting a VUS result is frequently discussed prior to testing; however, the possibility that an uninformative test result may increase rather than reduce uncertainty associated with inherited cardiovascular conditions is discussed less frequently. The negative impact of VUS results on patients’ risk perceptions, distress related to the condition, sustained levels of anxiety and depression have been established in the cancer setting (Culver et al., 2013; O’Neill et al., 2009; Vos et al., 2008; Welsh et al., 2017). In the cardiovascular setting, studies show dissatisfaction, reduced familial screening and incorrect recall of results in VUS result recipients (Burns et al., 2017; Lawal et al., 2018). Additionally, uncertainty and ambiguity can result in distress manifesting in both behavioral (for example avoidance) and cognitive symptoms (for example cardiac event related fear) among cardiovascular patients (Rhodes et al., 2017). Ingles and Semsarian (2014a) describe the importance of discussing the inherent uncertainty associated with genetic testing for inherited cardiovascular conditions during pre-test counseling (Ingles & Semsarian, 2014a). The authors describe the need to convey the probabilistic nature of genetic testing, the chances of receiving an uninformative test result, implications of a VUS result to family members and the possibility of reclassification (Ingles & Semsarian, 2014a). More frequent and detailed discussion of implications of VUS results before genetic testing may help patients make a more
informed decision. Furthermore, it is important to address the level of perceived uncertainty because perceptions of uncertainty after genetic testing can affect individuals’ decisions to learn, interpret, and act on recommendations (Biesecker et al., 2014). This study found that in the described clinical scenario, without additional information available, most providers would describe a VUS result as truly uncertain during result disclosure; however, a small subset of providers incorrectly described the VUS as likely pathogenic raising concerns about introducing unnecessary worry, anxiety and distress to patients and subsequently increasing negative psychological outcomes.

Almost half of cardiologists in this study would recommend some type of treatment including therapy with medication, exercise limitation and less frequently ICDs to the individual described in the hypothetical scenario who received a VUS result and lacked a clinical diagnosis of an inherited cardiovascular condition. Decisions about treatment in a genetically and clinically uncertain scenario described are complicated by the risks of over- and under-treatment and the risk of possibly fatal outcome of first presenting symptom. Additionally, over-treatment and over-diagnosis has reportedly been an issue for inherited arrhythmias and cardiomyopathies potentially resulting in adverse physical and psychological patient outcomes (Furqan et al., 2017; Gaba et al., 2016; Schwartz et al., 2010). While ACMG guidelines do not recommend medical management changes solely based on a VUS result, these guidelines are not specific to inherited cardiovascular conditions and cardiologists may have more experience with weighing the risks and benefits of treatment in an uncertain case (Green et al., 2013). Our study also supported this assumption by showing that cardiologists were more likely to discuss the risks and benefits associated with treatment and the lack of it and feel more confident in making medical management recommendations compared to other genetic counselors. On the other hand, both cardiovascular genetic counselors and other GCs reported a higher level of confidence in counseling about VUS results in general compared to cardiologists and were likely to recommend regular follow-up with genetics. Regular follow-up with genetics is important in
providing information to patients about variant reclassification and updating medical and family history. As additional information is gathered over time, the uncertainty associated with these cases can be resolved. Several articles have argued that genetic counselors may be in the perfect position to help cardiologists understand the implications of complex genetic information to care for patients and their family members (Ackerman et al., 2011; Caleshu, Day, Rehm, & Baxter, 2010; Dunn, Caleshu, Cirino, Ho, & Ashley, 2013; Ingles, Yeates, & Semsarian, 2011). Additionally, genetic counselors are trained in delivering complex information in a sensitive manner which may improve negative psychological outcomes (Ingles et al., 2011). These findings highlight the unique expertise of different providers and the importance of communication between different specialties.

Another key finding that has important implications is that over half of cardiologists and genetic counselors would recommend clinical genetic testing for the familial VUS for family members even though testing is expected to be uninformative in the described scenario, where segregation study is not possible due to the lack of symptomatic relatives. This finding is concerning because testing family members for a VUS in this case would have no clinical utility and could lead to harm if unaffected individuals are treated based on the presence of a VUS and those without the VUS are released from cardiac surveillance (Arscott et al., 2016; Ingles & Semsarian, 2014b). Furthermore, predictive genetic testing for a VUS results in wasting healthcare dollars and may introduce unreasonable reassurance or unnecessary worry in family members.

**Practice Implications**

Inclusion of genetic counselors in the care of patients who are at risk for inherited cardiovascular conditions has been recommended in clinical practice guidelines and consensus statements (Ackerman et al., 2011; Gersh et al., 2011; Hershberger et al., 2018). Genetic counselors have unique training in pedigree analysis, identifying the most appropriate individual to test and most appropriate test to order resulting in the reduction of unnecessary healthcare
costs (Arscott et al., 2016). Multiple studies highlighted the benefits of an interdisciplinary care team for inherited cardiovascular conditions with the involvement of genetic counselors, cardiologists, geneticists, nurses, psychologists, and others (Erskine et al., 2013; Ingles et al., 2011). Studies show that hypertrophic cardiomyopathy patients who attend specialized cardiovascular genetics clinics have low distress, good adjustment, appropriate risk perception and compliance with medical recommendations related to understanding the condition, time spent with the patients and having a good clinical relationship with healthcare providers, highlighting the value of an interdisciplinary care team (Ingles, Lind, Phongsavan, & Semsarian, 2008).

**Study Limitations**

Our study was limited by our ability to calculate response rate because we don’t have information on how many genetic counselors received the survey through the listerv and how many cardiologists opened the invitation email. The results are limited by the small sample size and the self-selecting nature of the study population. We anticipate this may bias the results to be more representative of providers who have more interest in the topic, who specialize in cardiogenetics and have significantly more experience than other providers. Another limitation is that the survey instrument was developed specifically for this study and it has not been validated before. Given that the survey was already quite long we had to reduce the number of questions and there are aspects of clinical practices related to VUS results that were not explored. Future studies could explore these clinical practices by interviewing providers.

Finally, data were self-reported and may not reflect actual practice. We aimed to be as detailed and specific as possible by giving a clinical scenario related to VUS results to help provide a concrete point of reference. However, it is possible that clinical practices related to a VUS result would change if certain aspects of the scenario were altered, such as the condition, family history or personal symptoms. Future studies could evaluate how these different factors might change clinical practices.
Research Recommendations

Our study was limited by the small sample size and possible self-selection bias limiting the generalizability of this study. Additionally, qualitative studies or review of actual patient visits may provide a more detailed and accurate insight into genetic testing and counseling practices. Finally, a better understanding of how patients perceive VUS results and what they need to be able to manage the inherent uncertainty associated with them can help develop counseling strategies for managing uncertainty and ultimately improve patient outcomes (Lawal et al., 2018).
REFERENCES


https://doi.org/10.1007/s10897-016-0017-z


https://doi.org/10.1161/CIRCULATIONAHA.110.950147


APPENDICES
Appendix A: Informed Consent to Participate in Research

Information to Consider Before Taking Part in this Research Study

Pro # 00036645

Researchers at the University of South Florida (USF) study many topics. To do this, we need the help of people who agree to take part in a research study. This form tells you about this research study. We are asking you to take part in a research study that is called: Clinical practices related to variant of uncertain significance (VUS) results in cardiac arrhythmia and inherited cardiomyopathy genes. The person who is in charge of this research study is Reka Muller. This person is called the Principal Investigator.

Purpose of the Study
The purpose of this study is to explore informational needs and communication practices of healthcare providers who conduct genetic testing for inherited arrhythmias and inherited cardiomyopathies. Our focus is on current communication practices and informational sources and needs about variant of uncertain significance (VUS) results. Our long term goal is to help health care professionals provide the best possible care when counseling about VUS results related to cardiac arrhythmias and inherited cardiomyopathies. By evaluating providers’ needs and practices in communicating about VUSs, we can develop better resources.

Why are you being asked to take part?
We are asking you to take part in this research study because you are a provider who sees patients regarding inherited arrhythmias and/or inherited cardiomyopathies.

Study Procedures
If you take part in this study, you will be asked to fill out an online survey. The survey will ask about your practice characteristics, counseling practices before a genetic test is ordered, your informational sources and needs about a VUS result and your communication practices related these results. Your responses will be anonymous and will not be linked to your identity. This is a one-time survey that will take approximately 10-15 minutes to complete.

Alternatives / Voluntary Participation / Withdrawal
You have the alternative to choose not to participate in this research study. You should only take part in this study if you want to volunteer; you are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study. Your decision to participate or not to participate will not affect your job status, employment record, employee evaluations, or advancement opportunities.

Benefits and Risks
We are unsure if you will receive any benefits by taking part in this research study. This research is considered to be minimal risk.

Compensation
We will not pay you for the time you volunteer while being in this study.
Privacy and Confidentiality
We will do our best to keep your records private and confidential. We are not collecting any personally identifying information, but we cannot guarantee absolute confidentiality. It is possible, although unlikely, that unauthorized individuals could gain access to your responses because you are responding online.

Certain people may need to see your study records. The only people who will be allowed to see these records are: Reka Muller (PI), Dr. Deborah Cragun (Faculty Advisor), others on Reka’s thesis committee, The University of South Florida Institutional Review Board (IRB). It is possible, although unlikely, that unauthorized individuals could gain access to your responses. Confidentiality will be maintained to the degree permitted by the technology used. No guarantees can be made regarding the interception of data sent via the Internet. However, your participation in this online survey involves risks similar to a person’s everyday use of the Internet. If you complete and submit an anonymous survey and later request your data be withdrawn, this may not be possible as the researcher will be unable to extract anonymous data from the database.

We may publish what we learn from this study. We will not publish anything that would let people know who you are.

There will be no identifiable personal information collected in this study. The data collected for this research will be kept as long as it is needed to conduct this research. Once your participation in the research is over, your information will be stored in accordance with applicable policies and regulations.

If you have concerns about the use or storage of your personal information, you have a right to lodge a complaint with the data supervisory authority in your country.

Contact Information
If you have any questions about your rights as a research participant, please contact the USF IRB at (813) 974-5638 or contact by email at RSCH-IRB@usf.edu. If you have questions regarding the research, please contact the Principal Investigator at rekamuller@health.usf.edu. You can print a copy of this consent form for your records.

I freely give my consent to take part in this study. I understand that by proceeding with this survey that I am agreeing to take part in research and I am 18 years of age or older.
Appendix B: Institutional Review Board Approval Letter

Reka Muller,
Global Health
6016 Laketree lane apt A
Tampa, FL 33617

RE: Exempt Certification
IRB#: Pro00036645
Title: Clinical practices related to variant of uncertain significance (VUS) results in cardiac arrhythmia and inherited cardiomyopathy genes

Dear Ms. Muller:

On 11/1/2018, the Institutional Review Board (IRB) determined that your research meets criteria for exemption from the federal regulations as outlined by 45CFR46.101(b):

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

As the principal investigator for this study, it is your responsibility to ensure that this research is conducted as outlined in your application and consistent with the ethical principles outlined in the Belmont Report and with USF HRPP policies and procedures.

Please note, as per USF HRPP Policy, once the Exempt determination is made, the application is closed in ARC. Any proposed or anticipated changes to the study design that was previously declared exempt from IRB review must be submitted to the IRB as a new study prior to initiation of the change. However, administrative changes, including changes in research personnel, do not warrant an amendment or new application.

Given the determination of exemption, this application is being closed in ARC. This does not limit your ability to conduct your research project.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

Kristen Salomon, Ph.D., Chairperson
USF Institutional Review Board
Appendix C: Cardiogenetics and Variant of Uncertain Significance Questionnaire

The following questions ask for information about your clinical experiences related to Inherited Arrhythmia and Cardiomyopathy risk assessment and testing.

1. Approximately how many patients have you talked to about risks for inherited arrhythmias and/or inherited cardiomyopathies?
   - 0
   - 1-5
   - 6-10
   - 11-20
   - >20

(Thank you for your participation! We are interested in learning more about providers who have experience talking to at least one patient about inherited arrhythmias.)

2. Which of the following best describes your primary work setting?
   - University Medical Center
   - Private Hospital/Medical Facility
   - Public Hospital/Medical Facility
   - Diagnostic Laboratory
   - Physician's Private Practice
   - Health Maintenance Organization
   - University/Non-Medical Center
   - Other (please specify):

3. Including yourself, how many individuals provide risk assessment for inherited arrhythmias and/or inherited cardiomyopathies in your practice setting?
   - 1
   - 2
   - 3
   - 4
   - 5 or more

4. What is your profession?
   - Cardiac Electrophysiologist
   - Adult cardiologist
   - Pediatric cardiologist
   - Medical/Clinical Geneticist
   - Primary Care Physician
   - Genetic Counselor
   - Nurse Practitioner
   - Other (please specify):

Automatic branching genetic counselor and geneticist, will be asked questions 5-7.

5. Are you board certified in genetic counseling or medical genetics?
   - Yes
No, exam taken and awaiting results
No, but I am board eligible in genetics
No, I am not board eligible in genetics

6. Please select your primary specialty area (Please check only one option):
   Cancer
   Prenatal
   Pediatric
   Adult
   Cardiovascular
   Other (please specify):

7. Please select any additional practice area(s), if applicable (select ALL that apply):
   None
   Cancer
   Prenatal
   Pediatric
   Adult
   Cardiovascular
   Other (please specify):

8. Approximately what percentage of patients seen in your clinic are referred for risk assessment for inherited arrhythmias and/or inherited cardiomyopathies?
   <10%
   10-24%
   25-50%
   51-75%
   >75%

9. In the last year, about how many patients have you seen with a variant of uncertain significance (VUS) in inherited arrhythmia or cardiomyopathy genes? (Do not include "pathogenic", "likely pathogenic, "likely benign" or "no mutation detected" results)
   0
   1-5
   6-10
   11-20
   21-30
   31-40
   >40

10. At your institution, who would help patients at increased risk for inherited arrhythmias or inherited cardiomyopathies make medical management decisions? (select all that apply)
    Cardiologist
    Medical/Clinical Geneticist
    Primary Care Physician
    Genetic Counselor
    Nurse Practitioner
    Other (please specify):
11. At your institution, who typically discusses options about genetic testing for family members for inherited arrhythmia or cardiomyopathy genes? (select all that apply)
Cardiologist
Medical/Clinical Geneticist
Primary Care Physician
Genetic Counselor
Nurse Practitioner
Other (please specify):

12. Please indicate on a scale of 1-5 (1= not at all confident, 5=extremely confident) how confident you feel that you are able to do the following for a patient with a VUS in an arrhythmia or cardiomyopathy gene? If this is not applicable to your clinical responsibilities please select that option.

<table>
<thead>
<tr>
<th>Not applicable to my clinical role</th>
<th>Not at all confident (1)</th>
<th>Somewhat confident (2)</th>
<th>Moderately confident (3)</th>
<th>Very confident (4)</th>
<th>Extremely confident (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate supporting evidence for the classification of the VUS</td>
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<tr>
<td>Explain what a VUS result is to a patient</td>
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<tr>
<td>Explain whether a VUS result would change the patient’s risks</td>
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<td>Provide psychosocial support to patients with a VUS</td>
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<td>When appropriate, assist patients in communicating a VUS result to family members</td>
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</table>

13. On a scale of 1-5 (1=Never, 5=Always) how often do you discuss the following with patients about genetic testing before the testing is ordered for inherited arrhythmias and/or inherited cardiomyopathies?
<table>
<thead>
<tr>
<th></th>
<th>Never (1)</th>
<th>Rarely (2)</th>
<th>Sometimes (3)</th>
<th>Often (4)</th>
<th>Always (5)</th>
<th>I don’t know</th>
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<tbody>
<tr>
<td>Possibility of a variant of uncertain significance (VUS) result</td>
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<td>Number of genes included on a panel test</td>
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<tr>
<td>Different types of genes included on a panel test</td>
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<td>Possibility of not getting a definitive yes or no answer from genetic testing</td>
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<td>How different test results may or may not change treatment options</td>
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<tr>
<td>Uncertainty in gene variant classification across laboratories</td>
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<td>Uncertainty about medical management recommendations based on an uninformative test result</td>
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<td>Uncertainty about prognosis if a pathogenic variant is identified in a gene with reduced penetrance</td>
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<td>Sharing test result information with family members</td>
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<td>The importance of at risk family members being evaluated</td>
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<td>Patient’s own reasons for wanting or not wanting testing</td>
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<td>Risks and benefits associated with testing</td>
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<td>Possibility of lifestyle changes based on the test result</td>
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<td>Anticipated or possible reactions of the patient to a VUS result</td>
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<td>Issues about disability and long-term care insurance</td>
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<td>The extent to which laws protect against discrimination by health insurers and employers</td>
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The following questions refer to the following scenario:

You are seeing a patient with a VUS result in PKP2, one of the genes associated with Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). ARVC is characterized by fibrofatty replacement of the myocardium that can cause cardiomyopathy, arrhythmia, heart failure and sudden death. She is 25 years old with a personal history of fainting during exercise on a few occasions and a normal ECG. Her echocardiogram appeared normal. She does not meet clinical diagnostic criteria for ARVC. She has a family history of sudden cardiac death at age 45 in one first degree relative and no other concerning family history.

14. Assuming you have no information that would lead you to believe this VUS is more likely benign or more likely pathogenic, which statement most closely matches what you would say to the patient about her risk based on this test result? (select one)
   - I am very concerned that this variant is the cause of the sudden death in your family and your fainting episodes.
   - At this point, we just don’t have enough information on this variant to determine if it causing your symptoms and your family history, but I think it probably is.
   - At this point, we don’t have enough information on this variant to determine for certain if the gene change is causing your family history of sudden death and your symptoms.
   - Most VUS results end up being found to be normal variation that is not associated with disease risk, but we just don’t have enough information to determine if this variant is or is not responsible for your family and personal history.
   - Other (please specify):

15. How likely is it that you would provide the following information to this patient after learning the patient’s test result?

<table>
<thead>
<tr>
<th>What it would mean if the VUS is later reclassified as pathogenic</th>
<th>Not at all likely (1)</th>
<th>Somewhat likely (2)</th>
<th>Moderately likely (3)</th>
<th>Very likely (4)</th>
<th>Extremely likely (5)</th>
<th>I don’t know</th>
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<tbody>
<tr>
<td>What it would mean if the VUS is later reclassified as benign</td>
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<td>Risk of sudden death (in case the VUS is later</td>
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<td>VUS Information</td>
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<td>-------------------------------------------------------------------------------</td>
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<td>classified as pathogenic)</td>
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<td>Risks of undergoing treatments (in case the VUS is later classified as benign)</td>
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<td>Risks of various treatment options for ARVC</td>
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<td>Penetrance associated with the PKP2 gene</td>
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<td>Allele frequency of the variant</td>
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<td>Whether the variant has been found in patients with symptoms</td>
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<td>Information on how the gene change may or may not impact the protein (if available)</td>
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<td>Whether the change occurred in a site that is highly conserved across species</td>
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<tr>
<td>General written information about VUS results</td>
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<tr>
<td>General written</td>
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</tbody>
</table>
16. How confident would you be in providing your input about medical evaluation and management recommendations for this patient if you were asked to?

<table>
<thead>
<tr>
<th>Not part of my clinical role</th>
<th>Not at all confident</th>
<th>Somewhat confident</th>
<th>Moderately confident</th>
<th>Very confident</th>
<th>Extremely confident</th>
</tr>
</thead>
</table>

17. Regardless of who makes the medical management decisions, how likely is it in your clinic that a patient with this history from the scenario would be given the following medical evaluation and management recommendations or options?

<table>
<thead>
<tr>
<th>Beta blockers</th>
<th>Not at all likely (1)</th>
<th>Somewhat likely (2)</th>
<th>Moderately likely (3)</th>
<th>Very likely (4)</th>
<th>Extremely likely (5)</th>
<th>I don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantable cardioverter-defibrillator (ICD)</td>
<td></td>
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<tr>
<td>Cardiac catheter ablation</td>
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<tr>
<td>Pacemaker</td>
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<tr>
<td>Evaluation by Holter monitor</td>
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<tr>
<td>Cardiac MRI</td>
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<tr>
<td>Exercise stress test</td>
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<tr>
<td>Yearly ECGs</td>
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<tr>
<td>Yearly echocardiograms</td>
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<tr>
<td>Yearly follow up with a cardiologist</td>
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<tr>
<td>Clinical genetic testing for family members</td>
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<tr>
<td>Research genetic testing for family members</td>
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<tr>
<td>Cardiac evaluation of other at-risk family members</td>
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<tr>
<td>Limiting exercise Dietary or weight management recommendations</td>
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<tr>
<td>No medical management changes</td>
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<tr>
<td>Yearly follow up with genetics to determine if the variant has been reclassified</td>
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<tr>
<td>Other (please specify):</td>
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</tbody>
</table>

18. How likely is it that you would use any of the following strategies with a patient like this who has a VUS result?

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Not at all likely (1)</th>
<th>Somewhat likely (2)</th>
<th>Moderately likely (3)</th>
<th>Very likely (4)</th>
<th>Extremely likely (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check for patient understanding</td>
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<tr>
<td>Identify sources of uncertainty</td>
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<tr>
<td>Discuss how the VUS may not help in making treatment decisions</td>
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<tr>
<td>Discuss the uncertainty about the most appropriate medical management</td>
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<tr>
<td>Discuss the uncertainty that can come from variability in the severity of inherited cardiac conditions</td>
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<tr>
<td>Discuss the uncertainty about how well medical management will work to prevent symptoms (for example fainting or sudden death)</td>
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<tr>
<td>Explore patient concerns</td>
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<tr>
<td>Help patients create a plan for dealing with the uncertainty</td>
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<tr>
<td>Help patients identify ways they can feel more in control of</td>
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</tbody>
</table>
their life despite the uncertainty

Referral for additional longer term counseling (social worker/psychologist)

Other (please specify):

| 19. How likely is it that you would encourage the patient to share the following information with her family? |
|---|---|---|---|---|
| Possibility of having ARVC based on family history | Not at all likely (1) | Somewhat likely (2) | Moderately likely (3) | Very likely (4) | Extremely likely (5) |
| Her own genetic test report |  |  |  |  |  |
| Risk of sudden death (in case the VUS is later classified as pathogenic) |  |  |  |  |  |
| Risks of undergoing treatments (in case the VUS is later classified as benign) |  |  |  |  |  |
| Inheritance pattern of ARVC |  |  |  |  |  |
| Possible symptoms of AVRC |  |  |  |  |  |
| Penetrance associated with the PKP2 gene |  |  |  |  |  |
| Recommendation that certain family members consider genetic counseling |  |  |  |  |  |
| Recommendation for clinical genetic testing of other family members to see who else has the variant |  |  |  |  |  |
Recommendation of cardiac evaluation for at risk family members:

Other (please specify):

20. Would the medical management recommendations and the information the patient is encouraged to share with her family change if the variant appeared like it could be **pathogenic** based on additional information you gathered or additional information provided by the lab?

   No
   I don’t know
   Yes, please explain:

   Please use this space to describe how recommendations or information the patient is encouraged to share with family might change __________

21. Would the medical management recommendations and the information the patient is encouraged to share with her family would change if the variant appeared like it may be **benign** based on additional information you gathered or additional information provided by the lab?

   No
   I don’t know
   Yes, please explain:

**Information Sources and Preference**

22. Please indicate how often do think you would use the following resources when/if you have a patient with a VUS result in an inherited arrhythmia or inherited cardiomyopathy gene.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
<th>I don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemental information included with test results from the laboratory</td>
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<tr>
<td>Contact laboratory about variant classification program</td>
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<tr>
<td>Contact researcher working in this area of genetics</td>
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<td>Search the scientific literature for publications</td>
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<tr>
<td>Search variant databases</td>
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<tr>
<td>Discuss with colleague</td>
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<tr>
<td>Other (please specify):</td>
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</table>

45
23. What would you find helpful in a variant database? (select all that apply)
   - Allele frequency
   - Computer modeling prediction of functional effect on protein
   - References to scientific publications
   - Results of segregation studies
   - Location of the variant (whether the variant is at a conserved region of the gene)
   - Type of mutation (missense, nonsense, frameshift)
   - Whether or not the variant was reported before
   - Whether the variant has been found in patients with symptoms (including the list of symptoms)
   - Other (please specify):

24. How likely is it that you would use the following communication methods to help your patient share information of results (pathogenic, likely pathogenic, VUS, likely benign, benign) with their families?

<table>
<thead>
<tr>
<th>Method</th>
<th>Not at all likely (1)</th>
<th>Somewhat likely (2)</th>
<th>Moderately likely (3)</th>
<th>Very likely (4)</th>
<th>Extremely likely (5)</th>
<th>I don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifying individuals with whom they may want to share the information</td>
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<tr>
<td>Providing a patient letter to share with family members</td>
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<tr>
<td>Role playing with patient about how to share information with family members</td>
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<tr>
<td>Motivational interviewing</td>
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<tr>
<td>Identifying barriers to sharing information and possible ways to overcome them</td>
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</tbody>
</table>
### Addressing guilt/anxiety about the test result

<table>
<thead>
<tr>
<th>Option</th>
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</thead>
<tbody>
<tr>
<td>Offer your contact information to share with family members</td>
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<tr>
<td>Offer group genetic counseling for the family</td>
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<tr>
<td>Other (please specify):</td>
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</table>

25. What additional information would you like to have available on Inherited Arrhythmia or inherited cardiomyopathy VUS results to help you or your patients?

26. If you have any additional comments you would like to share with our research team, please feel free to share them here.