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ORIGINAL ARTICLE

Physician interpretation of variants of uncertain significance

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Abstract
A growing number of physicians will interact with genetic test results as testing becomes more commonplace. While variants of uncertain significance can complicate results, it is equally important that physicians understand how to incorporate these results into clinical care. An online survey was created to assess physician self-reported comfort level with genetics and variants of uncertain significance. Physicians were asked to respond to three case examples involving genetic test results. The survey was sent to 488 physicians at Mayo Clinic FL on 8/16/2017. Physicians from all specialties were invited to participate. A total of 92 physicians responded to the survey. Only 13/84 (14.6%) responded to all three case examples with the answer deemed "most correct" by review of literature. Physicians that specialized in cancer were more likely to answer questions appropriately (P = .02). Around half (39/84) of the physicians incorrectly defined a variant of uncertain significance (VUS). Over 75% made a recommendation for genetic testing that was not warranted. Many physicians have never received formal genetics training; however, they will be expected to provide an accurate explanation of the genetic test results and subsequent evidence-based medical management recommendations. These results demonstrate that a substantial proportion of physicians lack a true understanding of the implications a VUS. Utilization of supplemental genetics training programs coupled with increase awareness of genetic services may help to improve patient care.

Keywords Genetics · Cancer surveillance · Variant of uncertain significance

Introduction

With the increase in patients pursuing genetic testing, it is important that physicians understand the basics of how to interpret a genetic test report [1, 2]. Many oncologists, gynecologists, primary care physicians, and other specialists order genetic testing without assistance by a healthcare professional formally trained in genetics [3, 4]. These physicians need to have a strong understanding of how to incorporate genetic test results into patient care, but it is similarly important that physicians not ordering molecular testing have a basic understanding about how to interpret genetic information as they will encounter patients who have completed molecular testing. Some of these patients may have never discussed the results with a healthcare provider previously due to the availability of direct to consumer genetic testing.

One of the factors complicating interpretation of genetic test results is the range of results that are possible. Genetic variants detected can be classified as benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, and pathogenic [5]. A genetic change is termed a VUS when there is not enough relevant data present to determine whether gene function would be disrupted by the alteration [5]. These inconclusive findings are reported frequently with at least one VUS detected over 30% of the time when a 25 gene panel is ordered to assess cancer susceptibility [6]. The likelihood of detecting a VUS is higher in individuals of ethnic backgrounds not as well studied as the European population [7, 8].

As data accumulates, the VUS may eventually be reclassified as benign or pathogenic, but this process takes time. In one study, the median time for VUS reclassification to

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either (likely) benign or (likely) pathogenic was 39 months [9]. Physicians may have to grapple with these inconclusive results for years before receiving clarity. While it is generally suggested that medical management recommendations be based on personal and family history and not a VUS result [7], literature assessing how physicians incorporate a VUS has been mixed [10–12]. Some studies have demonstrated physicians managing patients based on personal and family history and not presence of a VUS [10, 11]. A study of 71 patients with a VUS in *BRCA1/2* showed that the rates of risk-reducing mastectomy (RRM) and risk-reducing oophorectomy (RRO) were comparable between women with a VUS and those with an uninformative negative result [10]. 7% of both populations pursued RRM (P = 1.00), and 5% of the women with a VUS completed RRO vs. 3% of the population with uninformative negatives (P = .42) [10]. Another study of 97 patients with a *BRCA1/2* VUS and a personal history of breast cancer found that 22% completed a contralateral RRM, which was less than the number of women with breast cancer with a negative test result that completed contralateral RRM (25%) [11].

Other research has shown that many surgeons will make the same treatment recommendation for a woman with a *BRCA1/2* VUS as a woman with a known pathogenic *BRCA1/2* variant [12]. The same study reported that half of patients with a *BRCA1/2* VUS and without a significant personal and/or family history of breast cancer underwent a bilateral RRM.

Patients can struggle with interpreting these results as well [13]. Evaluation of patients' perceptions of VUSs has shown that many do not understand the result [13]. One study found that the majority of people interviewed (19/24) thought that the *BRCA1/2* VUS discovered carried at least some predisposition for cancer [13]. This is despite the fact that 16 of the 24 (67%) participants remembered being told that the result was "non-informative" [13].

Physician knowledge regarding genetic test result interpretation has been tested previously [14, 15]. In 2015, 155 breast cancer specialists in the UK were tested regarding their understanding of variants of uncertain significance [14]. Nearly three-quarters reported feeling unsure about the clinical interpretation of a VUS. The majority (94%) could correctly interpret and communicate the implication of a *BRCA1/2* VUS in a patient with a positive family history. Relaying this information became more difficult when the family history was negative, and the success rate dropped to 61%. A study in 2013 in the US measured the understanding of 22 family physicians that had referred a patient for genetic testing [15]. All physicians made the inappropriate recommendation to test unaffected relatives of a proband carrying a *BRCA1/2* VUS [15].

The purpose of this study was to further investigate how physicians across medical-specialties interpret a VUS. Understanding from an array of specialists has previously not been studied and compared. Genetic testing has become more commonplace since these two studies were completed, and it is unclear whether overall physician comprehension of VUSs has increased. It was hypothesized that the majority of providers would make a recommendation inconsistent with guidelines surrounding variants of uncertain significance. It was also hypothesized that healthcare professionals specializing in cancer prevention and/or treatment would perform better than other specialists due to greater interaction in their practices with hereditary syndromes.

Materials and methods

A nine question survey was created to assess physician understanding about variants of uncertain significance. The survey invitation was sent electronically to all physicians at Mayo Clinic Florida on 8/16/2017 (488 total), and the last survey response was collected on 9/21/2017. Survey responses were anonymous, and participants had the option to skip any question that they preferred not to answer. Demographic information was collected, including age and specialty. We also asked each physician to perform self-assessment of their own comfort level with genetics and variants of uncertain significance.

The survey concluded with three case examples with multiple choice options representing how the physician could proceed (Table 2). Based on a review of the literature, one answer from each case example was deemed "most correct". For case 1, neither RRO nor ovarian cancer surveillance should typically be recommended to an unaffected individual with a *BRCA1 VUS* and no family history of ovarian cancer [7, 16]. In case 2, generally no genetic testing should be offered to the unaffected sibling of a proband with a *BRCA1* VUS [17]. Finally, the correct definition was not presented for a VUS in case example 3; the correct answer was "none" [5, 16].

Fisher's exact test was used to compare how different specialists responded to questions. Unpaired *t* test was used to compare quiz accuracy amongst groups. One-way analysis of variance (ANOVA) was used to compare case example answers amongst different age groups. A P value of 0.05 was viewed as statistically significant.

Results

A total of 92 physicians at Mayo Clinic FL responded to the survey, which corresponded with an 18.8% (92/488) response rate. A wide array of specialists responded to the survey (Table 1). 8 (9%) respondents were less than 34 years

Table 1 Physician specialties

Specialty	N (%)	N that responded to all questions
Family/internal medicine	24 (26.1%)	23[c]
Oncology[a]	21 (22.8%)	19[d]
Neurology	8 (8.7%)	7[d]
Gastroenterology	8 (8.7%)	7[d]
Anesthesiology	4 (4.3%)	4
Emergency medicine	3 (3.3%)	3
Dermatology	3 (3.3%)	2[d]
Cardiology	2 (2.2%)	1[d]
Radiology	2 (2.2%)	1[c]
Orthopedic surgery	2 (2.2%)	2
Pulmonary	2 (2.2%)	2
Other[b]	13 (14.1%)	11[d]
Total	92	82

[a]Aside from oncologists, this included surgeons, internists, and radiologists specializing in cancer surveillance and management

[b]The remaining specialties were reported a single time

[c]Respondent skipped a question regarding comfort with genetics and/or variants of uncertain significance

[d]Repondent(s) skipped at least one question in the case examples

old, 26 (29%) were 35–44, 26 were 45–54, 20 (22%) were 55–64, and 11 (12%) were older than age 64.

When asked, "How comfortable do you feel discussing genetics in your practice?" 23 (25%) reported feeling uncomfortable, 22 (24%) somewhat uncomfortable, 31 (34%) somewhat comfortable, and 14 (15%) comfortable. One physician answered uncomfortable and shared that "[there is] so much new knowledge that I'm not familiar enough with to confidently launch into a genetic discussion with my patients." Another responded somewhat uncomfortable and added, "I prefer for my patients to seek a genetic counselor for more detailed discussion regarding benefits and risks to genetic testing." A physician that reported feeling somewhat comfortable added that he/she has "to review specific phenotypes/genotypes before discussing with a patient, but after review and/or discussion with a clinical geneticist, [he/she] could counsel a patient on these issues". A fourth that stated feeling comfortable with the discussion cited lack of time and lack of proper visual aids as challenges.

Nearly 60% (54/91) reported that they would not feel comfortable explaining a VUS to their patient. Neurologists were significantly more likely to share that they were comfortable with discussing a VUS result (88 vs. 36%, P = .007). Only 13/84 (16%) physicians responded with all three answers that had been deemed "most correct" in the case examples, with a mean score of 1.25/3 (SD = 1.0). Self-reported comfort with explaining a VUS to a patient correlated with quiz accuracy (P = .01), but 25 respondents reported comfort but did not answer according to general recommendations. While physicians specializing in cancer were not statistically more likely to report comfort with communicating a VUS to a patient, they were more likely to answer questions with the most appropriate answer (58 vs. 37%, P = .02). Only one physician recommended RRO to a woman with a *BRCA1* VUS and no family history of ovarian cancer, but the recommendation for ovarian surveillance vs. no action was nearly split 50:50 (Table 2). The majority of respondents (76%) recommended some type of genetic testing for the unaffected relative of a proband with a VUS (Table 2). Around half (39/84) incorrectly defined a VUS in case example 3 (Table 2). In this sample, age did not appear to affect how physicians responded to the case examples.

Discussion

Unnecessary treatment and surgery, avoidable anxiety and/or false reassurance could all result from misinterpretation of a VUS [18]. Misunderstanding could also lead to inappropriate genetic testing [18]. The survey responses suggest a limited understanding about VUSs and of the implications on management.

Many of the physicians in our survey responded that they would tell their patient a VUS in *BRCA1* was responsible or likely responsible for their early onset breast cancer. Variants of uncertain significance are a common finding when performing next-generation sequencing. VUSs are common in both *BRCA1* and *BRCA2* as these are large genes, which lead to more benign variation [7]. The majority of *BRCA1/2* VUSs are not thought to cause hereditary breast and ovarian cancer syndrome [7]. If a patient has a VUS and a highly suspicious family history, there are potential options to aid reclassification. Clinicians can reach out to the reporting laboratory and discuss whether pursuing segregation analysis will provide enough data to reclassify the VUS [19]. Other methods like protein modeling and/or functional data can be considered.

Frequently, there will not be enough data present to reclassify the VUS for years. Physicians will have to make management recommendations with the knowledge of this inconclusive result in the background. In this sample, only one physician recommended prophylactic surgery for a cancer not seen in the family history. With no family history of ovarian cancer and a *BRCA1* VUS, there is not enough evidence present to support RRO in most scenarios.

Many others did not recommend surgery, but did recommend surveillance for this cancer. The presence of a VUS can put physicians offering management recommendations in a difficult spot, and some may consider a non-invasive approach such as high-risk surveillance a suitable alternative to prophylactic surgery. This approach, however, may lead

Table 2 Physician responses to case examples

Case example	N (%)	N (%)	N (%)	N (%)
Case 1: Your patient has no personal history of cancer. Her sister had breast cancer at age 52, but there is no family history of ovarian cancer. Your patient is found to have a variant of uncertain significance in the BRCA1 gene. What management recommendation do you make to your patient?	Recommend that patient considers a prophylactic oophorectomy to greatly reduce risk for ovarian cancer 1 (1.2%)	Recommend that patient proceeds with ovarian cancer surveillance (i.e. CA-125 and transvaginal ultrasound) 41 (50.0%)	Recommend that patient do neither prophylactic surgery nor surveillance at this time 40 (48.8%)	
Case 2: Your patient has no personal history of cancer. Her sister was diagnosed with breast cancer at age 45. Her sister completed comprehensive genetic testing and was found to carry a variant of uncertain significance in the BRCA1 gene. Which of the following recommendations do you make to your patient?	Recommend that she proceed with comprehensive genetic testing for hereditary cancer syndromes 20 (23.8%)	Recommend that she proceed with targeted genetic testing for the BRCA1 variant of uncertain significance 44 (52.4%)	Recommend that she not proceed with genetic testing for the BRCA1 variant of uncertain significance at this time 20 (23.8%)	
Case 3: Your patient was diagnosed with breast cancer at age 45. She was found to carry a variant of uncertain significance in the BRCA1 gene. How do you explain her result?	This BRCA1 variant is responsible for your personal history of breast cancer 2 (2.4%)	This BRCA1 variant is very likely responsible for your personal history of breast cancer 27 (32.1%)	This BRCA1 variant is not responsible for your personal history of breast cancer 10 (11.9%)	None of the above 45 (53.6%)

to increased medical costs, negative psychological consequences from false positives, and risk for unnecessary procedures to evaluate indeterminate incidental findings [20, 21]. Generally, the recommendation for management should be based on the patient's individual risk assessment from their personal and family history. Certainly, there are exceptions to this recommendation. It is important that healthcare professionals think critically about the benefits, limitations, and risks of different management options and explain these clearly to patients.

Many physicians also recommended testing for an unaffected relative of a proband with a VUS. If the VUS is discovered in an unaffected patient, the ordering provider is then forced to make the same difficult management recommendations. This patient is then at risk to receive unnecessary care. The potentially more dangerous outcome is the risk of a false sense of security if the VUS is not present. The patient may then believe that they are not at increased risk to develop the cancer previously seen in the family. This result would not be considered a true negative as no known pathogenic variant has been identified. In this scenario, it is again recommended that management be based on personal and family history and further testing not be completed unless the VUS is reclassified as likely pathogenic or pathogenic [19]. Comprehensive testing would also generally not be recommended for an unaffected relative of an affected proband who had uninformative comprehensive testing completed already since the affected proband would have the highest pretest probability of carrying a pathogenic variant. Most of the time, this would be a misuse of healthcare dollars.

Interestingly, many physicians reported comfort with medical genetics and/or discussing a VUS with a patient, but answered contrary to general guidelines regarding VUSs. There could be multiple explanations for this, but the observation may be partly due to the Dunning–Kruger effect, but further research would be required to confirm [22]. It has been suggested that some physicians may be susceptible to this bias of overestimating their knowledge level [23]. Genetic testing has been integrated so rapidly into clinical care that likely many physicians have not been able to stay abreast of advances in addition to all of their normal responsibilities. Medical geneticists and genetic counselors can serve as a resource for physicians trying to interpret variants of uncertain significance. Many patients that receive testing for a hereditary cancer syndrome do not meet with a genetic counselor before or after testing [12] despite the recommendation by the National Comprehensive Cancer Network that a healthcare professional trained in genetics complete pre- and post-test counseling [24]. If a genetic professional cannot participate in a patient's care, it is the responsibility of the ordering provider to complete adequate genetic counseling. This pre-test discussion should include the possibility of discovering a VUS [24, 25]. Many patients report not being aware of the potential for an inconclusive test result from genetic testing [26]. Additional pre and posttest counseling recommendations can be found through the National Comprehensive Cancer Network.

Limitations

The response rate to our survey was low, and some physicians chose not to answer all three case example questions. It is possible that physicians with a stronger interest in genetics may have been more likely to answer survey questions, which would make our results not representative of physicians as a whole. Also, while questions were designed to be answerable without much prior knowledge on *BRCA1*, physicians that have not encountered patients with variants in this gene may have felt less comfortable with the questions. Similarly cancer specialists may have answered more appropriately due to more familiarity with the *BRCA1* gene specifically. More comparison of specialties would be interesting to complete, but was not possible with the smaller sample sizes. This should be studied in a large population.

Conclusion

While genetic testing is becoming more commonplace, it is still not widely used by many specialties [2]. Over half of the physicians stated that they did not feel comfortable disclosing a VUS to a patient, and half did not report at least being somewhat comfortable with discussing genetics in their practice. "Lack of training" has been commonly cited as a barrier to physician use of personalized medicine [27]. While comfort is likely to increase with clinical exposure, it is also important to actively increase physician knowledge of genetics. Many genetic education programs are available for physicians not formally trained in genetics [28]. The importance of utilizing this training should be encouraged to physicians in all specialties. Increasing investments into training genetics professionals should also be considered. Many physicians likely would like to include a geneticist or genetic counselor into their patient's care, but do not have access to one [29]. Multiple positions for geneticists and genetic counselors are unable to be filled which decreases access [30, 31].

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest, financial or otherwise.

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