

From the laboratory to the clinic: sharing BRCA VUS reclassification tools with practicing genetics professionals

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Abstract Despite ongoing research efforts to reclassify *BRCA* variant of uncertain significance (VUS), results for strategies to disseminate findings to genetic counselors are lacking. We disseminated results from a study on reclassification of *BRCA* VUS using a mailed reclassification packet including a reclassification guide, patient education aid, and patient letter template for patients/families with *BRCA* VUS. This study reports on genetic counselors' responses to the dissemination materials. Eligible participants ($n = 1015$) were identified using mailing lists from professional genetics organizations. Participants were mailed a *BRCA* VUS reclassification packet and a return postcard to assess responses to the materials. Closed-ended responses were analyzed using descriptive statistics, and thematic analysis was conducted on open-ended responses. In response to the mailing, 128 (13.0%) genetic counselors completed and returned postcards. The majority of respondents ($n = 117$; 91.4%) requested the patient letter template and patient education guides as PDFs ($n = 122$; 95.3%). The majority ($n = 123$; 96.9%) wanted an

updated reclassification guide upon availability. Open-ended responses demonstrate the material was well-received; some specified they would tailor the patient letter to fit their practice and patients' needs. Participants requested additional patient and provider educational materials for use in practice. Materials communicating *BRCA* VUS reclassification updates were liked and were likely to be used in practice. To achieve the benefits of VUS reclassification in clinical practice, ongoing efforts are needed to continuously and effectively disseminate findings to providers and patients.

Keywords Genetic counseling · Genetic testing · Variant of uncertain significance (VUS) · VUS reclassification · Hereditary cancer · Patient education

Introduction

Approximately 5–10% of all breast (Campeau et al. 2008) and 15% of all ovarian (Pal et al. 2005) cancers in women are the result of mutations in inherited cancer susceptibility genes. Genetic testing for such genes among women with a personal or family history of such cancers can guide prevention and treatment decisions (Domchek et al. 2010; Gage et al. 2012; Grann et al. 2011). When undergoing genetic testing for *BRCA*, four results are possible including: (1) positive, a variant that results in increased cancer risk; (2) true negative, the cancer risk is considered to be that of the general population; (3) uninformative negative, no variant is detected but cancer risk may still be higher than the general population; and (4) variant of uncertain significance (VUS) whereby a variant is detected, but cancer risk remains unknown. The ambiguity of VUS results has resulted in negative patient outcomes such as heightened anxiety (O'Neill et al. 2009), depression (O'Neill et al. 2009; Vos et al. 2012), overestimation of risk (Vos et al.

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2012), and undergoing preventative surgeries not clinically supported (Vos et al. 2008).

Using laboratory and epidemiological methods, scientists have increased efforts to reclassify VUS results (Lindor et al. 2012, 2013; Plon et al. 2008; Richards et al. 2015). Resulting from such efforts, the “posterior probability model” assesses clinical actionability of VUS in *BRCA1* or *BRCA2* based on a combination of prior probabilities of causality and likelihoods of causality. This model ultimately allows researchers to reclassify VUS on a five-point scale ranging from 5—definitely pathogenic to 1—not pathogenic (Lindor et al. 2012). Reclassification efforts largely take place at academic medical centers and research institutions, but disseminating outcomes to practicing professionals is critical to ensuring findings impact clinical care of patients.

Genetic counselors play a critical role in relaying information about genetic test results to patients (Scherr et al. 2015a). Therefore, genetic counselors must have access to the most up-to-date tools and information. However, a recent study conducted by our team found that majority of genetic counselors felt information was missing from laboratory reports containing VUS results and reported limited access to resources that might clarify VUS findings (Scherr et al. 2015b). Furthermore, most genetic counselors were confident in their understanding and ability to explain VUS results to patients, but felt less confident in achieving high levels of patient understanding (Scherr et al. 2015a). To facilitate communication regarding VUS reclassification, our team developed, pilot tested and mailed *BRCA* VUS reclassification packets (*BRCA* VUS REPACK) to genetic counselors in the year following the aforementioned study. This paper reports on a brief response postcard that was added to the REPACK materials to elicit feedback from genetic counselors about these materials.

Methods

Participants

Participants ($n = 1015$) were identified through the National Society of Genetic Counselors (NSGC) and the American Board of Genetic Counseling (ABGC) mailing lists. The sample included those who (1) self-identified as practicing cancer genetic counseling, (2) reported patient care as their primary job activity, and (3) had a US mailing address.

Instrumentation

The *BRCA* VUS REPACK was developed based on responses to earlier studies examining genetic counselors’ preferences for information about VUS (Scherr et al. 2015a, b). Prior to dissemination, all materials were reviewed by a convenience

sample of genetic counselors ($n = 10$) from throughout the USA, recruited from the investigator’s professional network. The genetic counselors were sent the materials, asked to review them, and then completed a semistructured interview where feedback was obtained based on comprehension, clarity, and acceptability. Modifications were made to the materials based on an informal synthesis of genetic counselors’ feedback. Feedback about the patient education aid was solicited from the project’s patient advisory panel, which included breast cancer advocates working the SPORE.

The final materials included the following:

- A cover letter—A 1-page letter informing genetic counselors about the materials enclosed in the mailing as they relate to the communication of *BRCA* VUS results with patients and knowing/keeping up with the most current classifications. Materials were created based on results of interviews and a national survey. The letter briefly describes each of the three materials developed.
- Patient letter template—A 1-page template letter to help genetic counselors summarize VUS results for each patient. The template provided space for genetic counselors to insert patient-specific information such as the VUS *gene name*, the technical name of the variant, and interpretation of family history, making each letter customized to the patient (Flesch-Kincaid reading grade level = 7.4).
- Patient education aid—This was an 8-page patient-oriented booklet developed for individuals who had genetic testing and received a VUS result. The booklet explained in layman terms what a VUS is, how it affects the individual, and resources to consider (Flesch-Kincaid reading grade level = 8.0).
- Reclassification guide—A 17-page booklet developed for genetic counselors covers *BRCA1* and *BRCA2* VUS that have been newly reclassified using the International Agency for Research on Cancer (IARC) multifactorial likelihood model. A subgroup of the World Health Organization, the IARC developed a method using multiple lines of evidence to classify the probable pathogenicity of VUS. The guide was intended to be used in addition to laboratory results to help guide clinical recommendations for patients.

While a subsequent survey was planned a year following dissemination of these materials, a brief postcard was developed by the team as an intermediate assessment of study materials. The postcard included with the final *BRCA* VUS REPACK materials asked genetic counselors if they (1) wanted a PDF of the patient letter template (yes or no), (2) planned to modify the patient letter template (responses ranged from “leaving as is” to “heavily modified”), (3) desired a PDF of the patient education aid (yes or no), and (4) wanted an updated version of the

VUS reclassification guide when available (yes or no). For those who responded affirmatively, they were asked about preference for delivery mode (mail, email, or both). In addition, open-ended questions included “If you are modifying [patient letter template], please briefly describe the changes you plan to make” and “Please list any other patient education materials about VUS that you believe would help you in your genetic counseling practice.”

Procedure

A packet containing a copy of the cover letter and *BRCA* VUS REPACK was sent to participants along with a prepaid return postcard. The packet of materials was mailed to participants in August of 2014. Response cards were accepted from August to October 2014. Genetic counselors who returned completed postcards by October 10, 2014 were entered into a drawing to win one of four \$50 bills. A single postcard was also received in March 2015 and was included in this analysis but not included in the drawing.

Data analysis

Using SPSS v. 24, descriptive statistics were calculated for the closed-ended questions. Two members of the research team conducted thematic analysis on the written responses (Braun and Clarke 2006). Study team members reviewed open-ended responses looking for patterns of meaning resulting in the development of an initial codebook. Separate codebooks were developed for each of the two questions. Next, all responses were independently coded using MAXQDA by each team member to assess coding scheme reliability and validity. Krippendorff's alpha of 0.93 was achieved, an acceptable level of agreement (Krippendorff 2012). Finally, study team members extracted coded segments to identify and name overarching themes within and across coded segments.

Results

Summary of closed-ended responses

Of the mailings sent ($n = 1015$), 31 (3.1%) were returned undeliverable. Of the 984 delivered, we received 128 (13.0%) completed postcards. Although no questions were asked on the postcard about participants, the characteristics based on the sample obtained in our previous study (Scherr et al. 2015a), and the general demographics of genetic counselors nationally (NSGC 2016), we believe this current sample is likely to be predominately female, White, and non-Hispanic, averaging 37 years of age.

The majority wanted to receive a PDF of the VUS patient letter template ($n = 117$; 91.4%) and VUS patient education

aid ($n = 122$; 95.3%). Of those who wished to receive the VUS patient letter template ($n = 117$), responses varied as to how they planned to use it. Though instructed to select one response reflecting the extent to which modifications would be made to materials prior to use, some genetic counselors ($n = 12$; 9.7%) selected multiple responses (thus the total % of responses for this category is > 100%). A minority indicated they planned to use the letter as is, by itself ($n = 17$; 13.7%); as is, with a letter currently used in their practice ($n = 46$; 37.1%); slightly modified ($n = 56$; 45.2%); and/or heavily modified ($n = 5$; 4.0%). The majority of participants ($n = 123$; 96.9%) wanted to receive an updated version of the VUS reclassification guide upon availability either mailed ($n = 11$; 8.7%), emailed ($n = 104$; 81.9%), or both mailed and emailed ($n = 8$; 6.3%) to them (Table 1).

Summary of open-ended responses

Of the respondents, 56 (43.8%) wrote in changes they planned to make to the VUS patient letter template, and 29 (22.7%) listed other patient education materials they felt would be helpful to have in practice. For each open-ended response, separate themes emerged (Table 2).

Discussion

This study focused on genetic counselors' responses to provider- and patient-focused resources to support genetic counseling in the context of a *BRCA* VUS result. The majority of cancer genetic counselors who responded to our mailing indicated that they wanted to receive PDFs of the patient letter template and patient education aid for their use in practice. In addition, these same genetic counselors indicated they wanted to receive updated reclassification guides upon availability. These results reinforce findings from our previous work (Scherr et al. 2015a, b) as well as that of others (Petrucci et al. 2002; Richter et al. 2013) indicating genetic counselors have a need for additional information to aid in genetic counseling practice, particularly when faced with complex or uncertain genetic test results. In previous studies, genetic counselors felt confident communicating VUS results to patients, but less confident in their own ability to elicit high levels of patient understanding about VUS and clinical management options (Petrucci et al. 2002; Scherr et al. 2015a), which may be the reason they desired patient educational materials in this study.

With regard to the provider-focused reclassification guide, the majority of genetic counselors who completed our response postcard wanted an updated version when it became available. A previous study found genetic counselors wanted consistent and standardized formats across laboratories

Table 1 Postcard quantitative summary of closed-ended responses ($n = 128$)

Question	Response options	n (%)
Would you like to receive an electronic version of the VUS patient letter?	Yes	117 (91.4)
	No	11 (8.6)
How do you plan to use the electronic version of the patient letter? ^a	As is, by itself	17 (13.7)
	As is, with a letter currently used in our practice	46 (37.1)
	Slightly modified	56 (45.2)
	Heavily modified	5 (4.0)
Would you like to receive an electronic version of the VUS patient education guide	Yes	122 (95.3)
	No	6 (4.7)
Would you like to receive an updated version of the VUS reclassification guide when it becomes available? ^b	Yes, mailed to me	11 (8.7)
	Yes, emailed to me	104 (81.9)
	Yes, both mailed and emailed to me	8 (6.3)
	No	4 (3.1)

^a Responses were not mutually exclusive

^b Some responses were left blank

reporting genetic test results (Eccles et al. 2015a, b). However, numerous studies show conflicting interpretations of genetic findings among testing laboratories (Vail et al. 2015). Among all participants in one particular study, 11% were found to have a variant with conflicting interpretations ranging from pathogenic to VUS—discrepancies of concern that could alter medical management decisions (Balmaña et al. 2016). Publicly available databases, like ClinVar, allow clinical laboratories to submit identified variants; however, submission is voluntary and not all laboratories freely share this data. The lack of shared data is a contributing factor to the discordance between laboratories (Pepin et al. 2015). The fact that the information included on the reclassification list came from an academic institution and was based on published functional studies may increase perceptions of credibility. Additionally, the reclassification list provides another resource for genetic counselors to look at when searching for additional information on a VUS received from *BRCA* testing (Scherr et al. 2015b).

Written communication targeted toward patients is a critical component of genetic counseling practice. Patient letters provide a summary of what was discussed during the patient's session including any additional information (e.g., laboratory results) that becomes available after the session (Baker et al. 2002). For example, summary letters are often used to review both pre- and posttest counseling sessions, and have been shown to improve patient comprehension and information retention (Sandberg et al. 2012; Treacy et al. 2008; White et al. 2004). Our patient letter template was well received by genetic counselors, although several modifications were suggested, most related to customizing the letter for the patient or the practice which is consistent with the intended use of a template.

Due to previous concerns revealed by patients, genetic counselors suggested incorporating information for family

members in the patient letter template. Genetics professionals encourage and support the dissemination of information within families (Mendes et al. 2016); however, a study found 41% of genetic health professionals never write letters aimed for at-risk family members (Forrest et al. 2010). Helping patients communicate accurate risk information to their relatives is critical to reaching the full potential of genetic health care (Mendes et al. 2016).

Although genetic counselors were provided a VUS patient education aid and patient letter template developed by our team, genetic counselors were asked to identify any other patient education materials they felt would be helpful for use in practice. In addition to materials for the patient's family, genetic counselors requested modified versions of the patient education aid and patient letter template, particularly shorter versions and a lower reading level. In the USA, close to 50% of the general population reads below a ninth grade reading level (Kindig et al. 2004); thus, addressing this issue is vital. In a case-control study assessing the effectiveness of a long (4–5 pages) narrative formatted summary letter versus a short (1.5 pages) concise letter, both the short letter and counseling session were rated higher by parents and were associated with a more positive emotional reaction (Roggenbuck et al. 2015). Our patient letter template was 1-page long and our findings reflect that of previous research. In addition, open-ended responses indicate genetic counselors wanted to reword or revise certain components of the template letter. Such suggestions like "I also plan to define the word 'mutation'" support changes to increase reader comprehension. Previous studies found low health and genomic literacy among the general population (Kutner et al. 2006; Mesters et al. 2005; Molster et al. 2008) and over 75% of genetic terms were not defined in patient letters

Table 2 Postcard qualitative summary of open-ended responses ($n = 56$)

Theme	Subtheme	Quotes
Q1. Modifications to the patient letter template		
Rewording the patient letter template		“Prefer my own wording in some places.”
Tailoring the patient letter template to their practice	Modifications undertaken to tailor patient letter template to their practice	“Adding logo and contact information”
	Incorporating parts of patient letter template into existing letter already used in practice	“Will take some sentences/sections to include in our own VUS letter to patient.”
Tailoring the patient letter template to the patient	Adding information about length of time patients should take to recontact the practice for updates	“Have patient call us in 2 years.”
	Tailoring patient letter template to the specific needs of their patient	“Tailor for each patient with management recommendations.”
	Including information geared toward family members of the patient	“Might make slight changes to include information regarding family studies programs offered by some labs.”
Q2. Additional VUS patient education materials to use in practice		
Additional patient information	Desire for additional patient-oriented information or materials	“Explaining a VUS during the initial GC consultation.”
	Visual aids	“Visual aid: normal sequence vs mutation.”
	Shortened or brief versions of the patient educational materials	“I would like if the booklet was just a little shorter!”
Additional genetic counselor/provider materials	Additional materials for other genetic counselors or providers	“Letter for referring physician.”
	Access to online resources or databases	“List websites to check variant status.”

(Brown et al. 2016). The goal of our next version is to develop materials for two different health literacy groups, thus improving the readability of our patient letters to increase access to and comprehension of genetic information.

Supported by previous research (Richter et al. 2013), genetic counselors also identified the need for VUS materials for genetic counselors or other medical providers to assist in communication with patients; this included the need for visual aids to use during counseling sessions. This provides further support for genetic counselors’ needs for a variety of supplemental information to be used when addressing VUS results and reclassification.

Study limitations

Findings should be considered in light of study limitations. Genetic counselors self-selected to complete the response postcard resulting in a low response rate (13%); therefore, responses may differ from those who chose not to participate, limiting generalizability. Our primary focus of this portion of the project was to distribute the materials rather than elicit feedback. The limited space on the postcard was used only to obtain preliminary feedback on our materials; no demographics of any kind were asked. Although we have no data to verify this, we assumed that the demographics for this population would be similar to that of our first and second surveys which also surveyed genetic counselors from the mailing lists

of ABGC and NSGC (Scherr et al. 2015a, b). A passive data collection process was used with an incentive of four \$50 raffles, and no additional reminders were provided to genetic counselors to complete and return the postcards. This was seen as an effective and low-cost way to disseminate the materials; however, it resulted in a small sample size and limited collected feedback. A meta-analysis examining response rates of health professionals (Cho et al. 2013) found that the highest estimated response rates of mailed surveys (versus online and mixed mode) were among those that offered monetary incentives (versus no incentive and non-monetary) and had two follow-ups (versus none, 1, and more than 3). Such findings shed light onto our low response rate and explain why our previous survey (Scherr et al. 2015a), sampling a similar pool of genetic counselors about their current practices and confidence, obtained a higher response rate at 46% through use of a multiphase mailing approach (Dillman 2000) that utilized both mailed and online surveys. A recent study conducted by McMaster et al. (2017) demonstrated that a web-push methodology (i.e., contacting people via mail and requesting completion of an Internet survey while withholding a paper option until later in the contact process) was both more effective and less costly than a paper-only approach (McMaster et al. 2017). However, the databases provided by professional organizations often do not include email addresses for the entire membership, limiting the ability to use email-based approaches to enhance recruitment rates.

To increase participation in future studies where a higher response rate is critical, we should be mindful of mode, incentive, and number of follow-ups. Regarding genetic counselors planned use of the VUS patient letter template, counselors were meant to select one of four responses; however, some ($n = 12$; 9.7%) selected multiple responses, thus limiting our use of the results for that particular question. Lastly, this study only looked at genetic counselor responses to the materials. In the future, these materials should also be reviewed by patients.

Conclusion

In summary, these initial findings reinforce previous conclusions that genetic counselors would like supplemental materials for themselves and patients to aid in their counseling practice when disclosing VUS results. The next phase of this study will involve surveying genetic counselors in the year following dissemination of the materials to further explore whether they referred to our materials in practice and the extent to which they found them useful. Those findings will be used to further refine our *BRCA* VUS REPACK for genetic counselors.

The role genetic counselors play in relaying the ambiguity associated with VUS results to patients is vital. The increased use of genetic testing increases the likelihood and number of VUS results (Cragun et al. 2014; Kurian et al. 2014; Maxwell et al. 2014; Tung et al. 2015); therefore, it is critical that genetic counselors are equipped with the necessary tools and information to effectively communicate with their patients. Materials such as the ones developed in this study will not only be beneficial for *BRCA* VUS results, but they will serve as a foundation for the development of materials for other genetic VUS. We also hope to extend our research to explore patient outcomes related to the use of these materials in the future.

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Compliance with ethical standards

Conflict of interest Authors Augusto, Lake, Scherr, Lindor, and Couch declare that they have no conflict of interest. Author Vadaparampil has a research grant from Myriad Genetics Laboratories.

Human studies and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Prior to conducting this study, approval was obtained from the University of South Florida and Mayo Clinic IRBs.

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