Follow-up of carriers of *BRCA1* and *BRCA2* variants of unknown significance: Variant reclassification and surgical decisions

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Purpose: Approximately 5–10% of patients who undergo genetic testing of *BRCA1* and *BRCA2* receive a variant of unknown significance (VUS) result. The ambiguous nature of a VUS may increase difficulty in patient understanding and decision making regarding risk reduction and surveillance options, including cancer risk-reducing surgeries. VUS reclassification to benign or deleterious may occur in time; however, clinical decisions may need to be made expeditiously, and some patients may pursue irreversible treatments before VUS reclassification. **Methods:** We reviewed the surgical decisions of 107 women postdisclosure of a *BRCA* VUS result counseled at our institute between 1998 and 2009. **Conclusion:** Among women receiving a *BRCA* VUS result at our center, 11 of 107 (10.3%) pursued cancer risk-reducing mastectomy and 22 of 107 (20.6%) pursued cancer risk-reducing bilateral salpingo-oophorectomy. Reclassification of VUS occurred up to 9 years after testing, and 5 of 22 (22.7%) women followed up for 8 or more years continue to have a VUS result. We discuss considerations for providers of genetic services to discuss with patients who receive a VUS result. ***Genet Med* 2011:13(12):998–1005.**

Key Words: *BRCA, genetic variant, surgical decisions, follow-up, genetic counseling*

Hereditary breast and ovarian cancer associated with mutations in *BRCA1* (OMIM# +113705) or *BRCA2* (OMIM# *600185) account for 5–10% of all breast cancers; carriers of pathogenic mutations in *BRCA1* or *BRCA2* are at 40–73% lifetime risk of breast cancer and 11–41% lifetime risk of ovarian cancer.[1–3] There are available recommendations for when to offer genetic counseling and consider genetic testing of *BRCA1* and *BRCA2,* the genes most commonly associated with hereditary breast and ovarian cancer.[4–6] The proportion of individuals who receive a variant of unknown significance (VUS) result from comprehensive *BRCA1* and *BRCA2* analysis historically varied widely by population with an overall VUS result rate of 7–15%,[7] compared with Hispanic populations with VUS rates of up to 22%[8] and African American populations with VUS rates of up to 46%.[9] However, in more recent years with further testing and VUS reclassification, VUS detection rates in these populations decreased to approximately 5–10%.[10]

Many factors contribute to evaluating the clinical significance of a *BRCA1* or *BRCA2* variant, as addressed in practice guidelines of the National Society of Genetic Counselors[11] (NSGC) (Table 1), and several models have been proposed to characterize these variants.[12,13] However, in practice, it is often not possible to confidently establish the significance of a variant for the purpose of timely clinical decision making. The inherent ambiguity of risk conferred by a VUS result increases the complexity of cancer risk assessment and clinical recommendations. Implications of a VUS, therefore, must be carefully communicated and updates on VUS reclassification should be relayed to the patient. If the VUS is reclassified as deleterious, this provides support for clinical management recommendations, such as breast magnetic resonance imaging screening, beginning surveillance earlier, and cancer risk-reducing surgery.[14,15] If the VUS is reclassified as a benign polymorphism, a patient may still be at increased risk of breast and ovarian cancer for the indications that motivated the initial testing (e.g., family history).

Previous studies have assessed patient comprehension, medical management outcomes, and psychosocial effects of deleterious mutations in *BRCA1* and *BRCA2*, but less data are available in the case of a VUS result. Although the explanation of a VUS result can affect a patient's perception of cancer risk and risk reduction decision making, studies indicate that other variables may also play a role. For example, one woman who pursued risk-reducing bilateral mastectomy after VUS result disclosure cited both the ambiguity of the result and a persistent fear of cancer.[16] Although misunderstanding of a VUS raises concern for false reassurance and less motivation to pursue surveillance options, multiple studies have not supported evidence for this concern.[17–19] One study revealed that women who received a VUS result experienced higher levels of anxiety and depression at 1 and 6 months postdisclosure and higher levels of distress compared with women with no mutation.[20] Other studies revealed that many women who undergo testing hope for a mutation-positive result to explain the etiology of their cancers and can experience frustration in the event of a VUS.[21,22]

At least one study has investigated associations between patient perceptions of VUS results and life impacts, including risk-reducing surgery outcomes.[23] Subjective interpretation of the meaning of the VUS result was associated with prophylactic surgery outcomes, and participants attributed the decisions to pursue surgery to VUS disclosure instead of personal and family history of cancer. This small study of 24 women implied that despite correct recall that a VUS result was communicated to have an unknown association with cancer; women may subjectively interpret the result as pathogenic and pursue cancer risk-reducing surgery that may not be as beneficial as expected. Interpretation as pathogenic may serve as a coping mechanism to fulfill a need for a reason for cancer occurrence and may provide reasoning to err on the side of caution in determining the course of action for surveillance and prevention.[23]

Although not explicitly addressed in any of the aforementioned studies, the possibility of VUS reclassification may complicate the decision to pursue aggressive prevention treatments immediately because reclassification can occur months to years

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Table 1 National Society of Genetic Counselors (NSGC) recommendations for cancer risk assessment and genetic counseling for hereditary breast and ovarian cancer (HBOC)[11]

Process
Referral for risk assessment and genetic counseling
Intake and history
Obtain accurate personal and family history
Perform psychosocial assessment
Cancer risk assessment
Assess absolute risk of cancer based on family history
Assess probability of identifying heritable genetic mutation
Consider other hereditary syndromes with breast and/or ovarian cancer
Genetic susceptibility testing for HBOC
Identify appropriate candidate for *BRCA1*/*BRCA2* testing using clinical judgment
Obtain informed consent
Interpret *BRCA1* and *BRCA2* genetic test results
Posttest genetic counseling and results disclosure
Medical management specific to variants of uncertain significance (VUS)
Determine whether variant segregates with cancer in family, if possible
Medical management decisions based on strength of personal and family cancer history
Remain updated on VUS reclassification

after disclosure. We describe herein our experience with cancer risk-reducing surgical decisions in patients who have received a *BRCA* VUS result, including those with results later reclassified as deleterious or benign.

METHODS

The University of Washington Medical Center (UWMC) Medical Genetics Clinic is a tertiary care facility that specializes in genetic disorders, including hereditary cancers. The clinic consists of nine medical genetics physicians and four board-certified genetic counselors and serves more than 1900 patients/year. Data are prospectively collected for purposes of quality improvement/assurance, including the number of patients seen for inherited cancer syndromes, genetic tests ordered through UWMC, and test results. Patients who received a *BRCA* VUS result, reclassification of the VUS as pathogenic or benign, and cancer risk-reducing surgery decisions documented in the electronic medical records were reviewed to assess compliance with NSGC practice standards and adequacy of VUS genetic counseling. Those patients with a VUS and an accompanying pathogenic mutation were excluded from further analysis as their decision making was likely influenced by the known deleterious mutation. Men were also excluded. For those individuals with multiple VUS, they were categorized under the result least likely to be interpreted as benign.

Records were reviewed to determine surgical decisions in women identified as *BRCA* VUS carriers. Surgeries were considered risk reducing if they were described as prophylactic or risk reducing in the surgical or clinical records. Surgeries were not considered cancer risk reducing if they were performed for treatment of cancer at that site, at another site (e.g., oophorectomy for estrogen/progesterone-positive breast cancer), or for unrelated benign indications. Each breast was considered as an independent entity, whereas both ovaries were considered as a single entity. For example, a woman whose breast cancer treatment entailed a unilateral mastectomy for breast cancer could have a cancer risk-reducing mastectomy (RRM) on the unaffected side and cancer risk-reducing salpingo-oophorectomy (RRO) to decrease the risk of ovarian cancer, whereas a woman with bilateral mastectomies for bilateral cancer could not have a RRM but could still have a RRO. Women were not recontacted for the purpose of determining whether they pursued risk-reducing surgery at an outside facility and only surgeries reported to a provider within UWMC were captured in this retrospective chart review.

This study is not designed to assess psychological impact of a VUS result; however, surgery decisions, especially those soon after results disclosure, may reflect patient result interpretation and associated anxiety. This project was ruled exempt from the University of Washington Institutional Review Board approval as it was initiated as a quality assurance measure.

RESULTS

Between 1998 and 2009, approximately 1375 genetic tests for *BRCA1* and *BRCA2* had been ordered through the UWMC Medical Genetics Clinic. Utilization of genetic testing for breast and ovarian cancers has increased over the past 10 years, with five *BRCA1* and *BRCA2* tests ordered by the clinic staff in 1998 and 189 ordered in 2009. A total of 145 individuals were identified as having one or more VUS in *BRCA1* or *BRCA2* (Fig. 1), of which 132 records were sufficiently detailed for analysis. Reasons for referral are summarize in Table 2.

After exclusion of men and women who were tested for a known family variant or who had a known deleterious mutation, 107 female patients with a median age of 45 years (26–84)

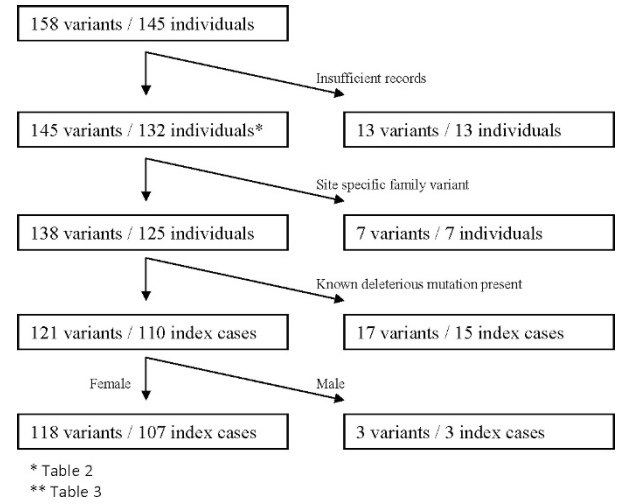

Fig. 1. Details of individuals identified with *BRCA1* or *BRCA2* variants of unknown significance at University of Washington Medical Center, 1998–2009.

Table 2 Reasons for referral in 132 individuals identified with *BRCA1* or *BRCA2* variants of unknown significance

Reason for referral: men	
Personal history breast cancer with family history of breast and/or ovarian cancer	2
Known family VUS	2
Fanconi anemia with family history breast cancer	1
Total	5
Reason for referral: women	
Personal history breast cancer only	8
Personal history breast cancer with family history of breast and/or ovarian cancer	86
Personal history ovarian cancer only	0
Personal history ovarian cancer with family history of breast and/or ovarian cancer	10
Personal history breast AND ovarian cancer only	1
Personal history breast AND ovarian cancer with family history of breast and/or ovarian cancer	3
Family history of breast and/or ovarian cancer with NO personal history of cancer	14
Known family VUS	5
Total	127

received a *BRCA* VUS test result. Ancestries as reported by the patients are as follows: 68.2% white, 8.4% Ashkenazi (at least one grandparent), Asian 7.5%, African descent 5.6%, native American 2.8%, African and Native American descent 0.9%, and unspecified 6.5%. Sixty-one women (57%) were counseled solely by genetic counselors, 42 (39.3%) were counseled by a medical geneticist and genetic counselor, and four (3.7%) were counseled solely by a medical geneticist. Cancer risk assessment and candidacy for genetic testing were typically based on clinical judgment, which permitted consideration of incomplete or complex family information, and family history of other associated cancers, such as melanoma or pancreatic cancer. Documentation of use of tools such as BRCAPro and Myriad prevalence tables was inconsistent and insufficient for meaningful analysis. Only nine women with VUS results reported no family history of breast and/or ovarian cancer. Eight of these women were referred for premenopausal breast cancer and one for ovarian and postmenopausal breast cancer. There was no follow-up for two women, including the one with ovarian cancer. One woman with breast cancer treated with lumpectomy and no reported family history went on to have bilateral RRM. Another woman with a result of "suspected deleterious" had a unilateral mastectomy for breast cancer treatment and went on to have risk-reducing bilateral salpingo-oophorectomy. The total number of women with no family history of cancer is insufficient to compare the likelihood of pursuing risk-reducing surgeries for women with and without family history of breast and/or ovarian cancer. The 13 unaffected women with a VUS result who were referred solely due to family history typically had a first-degree relative with ovarian cancer or premenopausal breast cancer who was unavailable or uninterested in testing or multiple generations of postmenopausal breast cancers with or without ovarian cancer.

The types of results disclosed included six (5.6%) initially classified as "suspect deleterious" and six (5.6%) initially classified as "favor polymorphism." Forty-eight (44.9%) patients later received amended reports due to variant reclassification; among the amended reports, three (6.3%) VUS were reclassified as deleterious, three (6.3%) as "suspect deleterious," three (6.3%) as "favor polymorphism," and 39 (81.3%) as benign (Table 3). This classification reflects the test interpretation or amended reports issued by Myriad Genetics Laboratories.[24] Years to reclassification ranged from 0 to 9; 5 of 22 (22.7%) female index cases followed for 8 or more years still had a result classified as a VUS (Fig. 2, A and B). As of June 1, 2010, 47 female patients (44% of the VUS population) tested at the UWMC Medical Genetics Clinic still had a result classified as a VUS; the median period of follow was 4 years (6 months to 11 years).

Where available, pre- and posttest genetic counseling records documented the genetic counselor and/or geneticist gathered and provided information in accordance with the NSGC recommendations. On VUS result disclosure, the genetic counselors consistently relayed additional data provided by Myriad, including the number of times the result had been detected in index families in the Myriad Genetics database, the cosegregation with cancer in families, and the co-occurrence with deleterious mutations.

Women receiving a VUS result were advised to recontact the Medical Genetics clinic in 1–3 years for an update of the variant status and availability of additional testing; however, they were not seen routinely except as clinically indicated, such as when new personal, family, or variant information became available. Women for whom follow-up information is available typically received ongoing care at our affiliated multidisciplinary cancer care center; accordingly, follow-up intervals and duration were highly variable and dependent on the woman's health status. The pre- and posttest cancer diagnoses and surgical decisions of patients who received a *BRCA* VUS result are presented in Table 3. Post-VUS disclosure, 14 RRMs were performed in 11 women (7.5% unilateral and 2.8% bilateral); four were unilateral and performed at the time of contralateral therapeutic mastectomy, four were unilateral in a woman with a history of contralateral therapeutic mastectomy, two were bilateral in a woman who previously had unilateral breast conserving therapy (BCT), and four were bilateral in women with no personal history of cancer but who were assessed to be at high risk based on family history of breast cancer. At the time of this study, 7 of the 11 women who underwent RRM had results that remained classified as a VUS, 2 of 11 women had results that remained classified as a "suspect deleterious," one woman had a result reclassified as deleterious, and one woman had a result reclassified as benign. Post-VUS disclosure, RROs were performed in 22 women (20.5%); 20 occurred in women with a personal history of breast cancer and two occurred in women with a family history of breast and/or ovarian cancer. Of the women pursuing postdisclosure RRO, 17 were treated by the same surgeon affiliated with UWMC, three by unidentified unaffiliated surgeons, and two by a separate affiliated surgeon. At the time of this study, 18 of 22 (81.8%) women pursing RRO post-VUS disclosure retained their originally classified results (15 VUS, three "suspect deleterious"); two (9.1%) women had a result reclassified as benign, one (4.5%) woman had a result reclassified as "suspect deleterious," and one (4.5%) woman had a result reclassified as deleterious.

Motivations for risk-reducing surgery post-VUS disclosure cannot be fully ascertained from this retrospective chart review. Two women with no personal cancer history pursued bilateral

Table 3 Surgical decisions of women initially identified as carriers of *BRCA* variants of unknown significance

	Current status of original VUS (women only, $N = 107$[a])					
	Benign, $N = 39$ (36.4%)	Favor polymorphism, $N = 9$ (8.4%)	VUS, $N = 47$ (43.9%)	Suspected pathogenic, $N = 9$ (8.4%)	Pathogenic, $N = 3$ (2.8%)	Total, $N = 107$ (214 breasts)
Pretest cancer diagnosis						
Breast[b]	37	3	44	8	3	95
Ovarian	3	3	2	0	1	9
Both	0	0	1	0	0	1
None	4	3	7	1	0	15
Pretest surgery						
TxM	18	2	24	2	2	48
BCT	14	1	17	5	0	37
TxO	3	3	2	0	1	9
RRM	5	0	6	0	0	11
RRO	0	1	0	0	0	1
Ben O	4	0	5	2	0	11
O BrCa	2	0	0	0	0	2
Posttest new cancer diagnosis						
Breast[b]	2	0	1	0	1	4
Ovarian	0	0	0	0	0	0
Both	0	0	0	0	0	0
None	28	8	30	6	2	74
No F/U	9	1	16	3	0	29
Posttest surgery						
TxM	2	0	3	1	2	8
BCT	1	0	0	0	0	1
TxO	0	0	0	0	0	0
RRM	2	0	9	2	1	14
RRO	2	0	15	4	1	22
No F/U	9	1	16	3	0	29
Ben O	1	0	1	0	0	2
O BrCa	2	0	0	0	0	2

[a]Women with multiple VUS are categorized under the result least likely to be interpreted as benign.
[b]Each breast counted as separate unit and both ovaries counted as single unit.
Ben O, benign oophorectomy; BCT, breast conserving therapy (lumpectomy); No F/U, no records available after results disclosure; O BrCa, oophorectomy for treatment of breast cancer; RRM, risk-reducing mastectomy; RRO, risk-reducing oophorectomy; TxM, therapeutic mastectomy; TxO, therapeutic oophorectomy; VUS, variant of unknown significance.

RRM after *BRCA* VUS disclosure with the primary documented factor being strong family history of breast cancer. Factors documented in the other woman pursuing bilateral RRM after *BRCA* VUS disclosure included personal history of breast cancer successfully treated with lumpectomy and VUS results. Multiple factors in RRO surgical decision making were considered in 18 of 22 (81.8%) cases; of those, factors documented included uncertainty of genetic testing (61.1%), family history of breast and/or ovarian cancer (94.4%), and personal history including menopausal status and cancer history (83.3%). Two cases (9.1%) cited the VUS as the sole purpose for pursuing RRO; both were initially classified as "suspected deleterious" and both women had a history of breast cancer. Two cases (9.1%) were performed by unaffiliated surgeons, and records were not available for review.

Use of chemoprevention, such as tamoxifen, as an alternative or supplemental breast cancer risk-reducing option was not consistently documented.

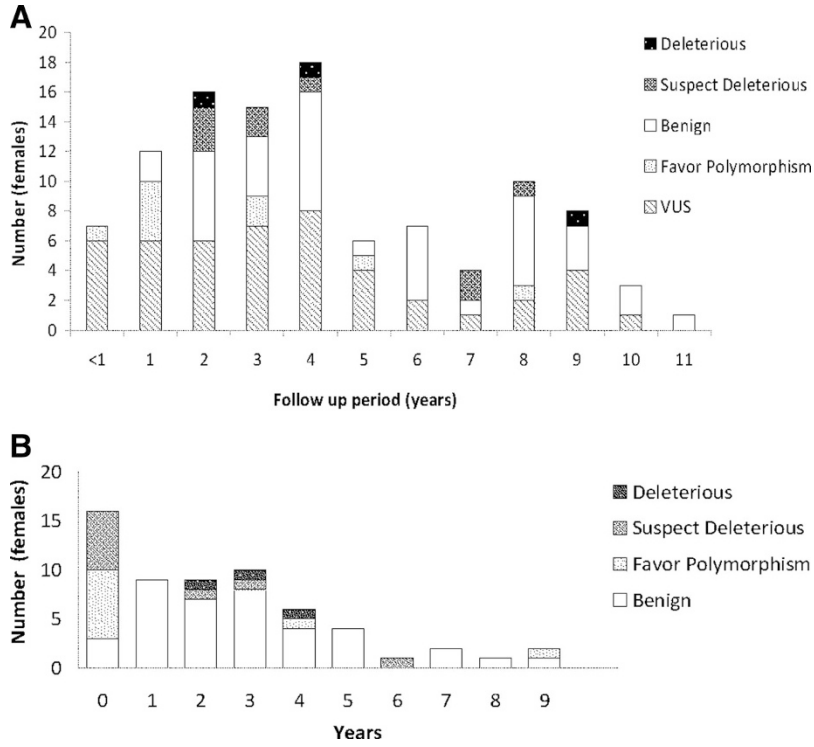

Fig. 2. A, Current classification of initial VUS result. Length of available follow-up depends on year the woman was tested and her health status and cessation of ongoing care within our institute. Total bar height represents total number of women with follow-up for a given time period, and subgroups indicate current classification of initial VUS result. B, Time from identification of initial VUS result to reclassification. Time to reclassification of initial VUS result varied. Total bar height represents total number of VUS results reclassified at the designated time period, and subgroups indicate how VUS was reclassified.

DISCUSSION

In women referred for genetic counseling due to concern for being at increased risk of breast and/or ovarian cancer, identifying a VUS in *BRCA1* or *BRCA2* increases the complexity of genetic counseling and medical decision making. Irreversible treatment decisions may be made without knowing whether or when the VUS will be reclassified. Certainly, several other factors may impact a patient's clinical decision-making process.[25,26] In women considered at high risk for breast and/or ovarian cancer, personal and family experience of cancer is likely to influence surgical decisions, as observed in our experience and elsewhere.[27,28] Also, the available data, such as characteristics of the genetic alteration, results of functional assays, or observed cosegregation of VUS with disease, may give clues as to the direction the variant may be reclassified, and communication of this data may influence a patient's perception of a VUS. Other important factors, such as marital/partner status, ethnicity, parity, employment status, education, and insurance status may influence a patient's decision to undergo certain surveillance or risk-reducing procedures, although the first three factors were not observed to correlate with surgical decisions in a previous study.[27] We did not evaluate these data for our study population due to inconsistent documentation.

Previous studies of women with pathogenic *BRCA* mutations are widely variable, showing 0–54% pursue RRM[27,29–36] and 12–74% pursue RRO[27,29–37] (Table 4). Comparatively, women tested for but not found to have *BRCA* pathogenic mutations pursued RRM and RRO, at estimated rates of 2–24% and 2–23%, respectively.[27,32,38,39] In our study population of women receiving *BRCA* VUS results, 11 of 107 women (10.3%) pursued uni- or bilateral RRM and 22 of 107 women (20.6%) pursued RRO. This observed uptake rate overlaps those reported for women both with and without clearly pathogenic mutations. Surgical decision making in our population was highly contextual, and in only two cases, the VUS was the sole attributed reason for surgery (RRO); both cases were classified as "suspected deleterious" in women with a history of breast cancer. Two women with VUS later classified as benign pursued RRO, raising concern that surgery may have been performed in women not at increased risk of ovarian cancer. Although the risks of postmenopausal oophorectomy are largely limited to procedural risks, premenopausal women pursuing RRO assume additional risks due to loss of normal ovarian hormone secretion, including osteoporosis and sexual dysfunction.

In our study population, reclassification occurred up to 9 years after initial testing, and 22.7% of women followed up for 8 or more years after initial testing had results that remained classified as a VUS. To facilitate communication in the event of reclassification, it is important for clinics offering genetic counseling and testing to maintain a reliable system for contacting patients who have received a VUS result. As it may be unrealistic to expect clinics to assume the responsibility of maintaining current contact information for all patients who received a VUS result, it is important to emphasize the patient's role in alerting medical providers to changes in address and to periodically request updates on the status of VUS reclassification. In

Table 4 Reported risk-reducing surgery uptake in *BRCA* mutation carriers and noncarriers

Study	*BRCA1/2* status	*N*	RRM uptake	RRO uptake	RRM and RRO uptake	Follow-up (yr[a])	Ethnicity/ nationality	Age (yr)
Lerman et al.[36]	Deleterious	84	3%	13%	NR	1	US	>25
Meijers-Heijboer et al.[34]	Deleterious	220 families	35%	49%	81%	NR	Netherlands	NR
Schwartz et al.[38]	Deleterious	79	NR	27%	NR	1	US 94% white	Mean 47 (SD 11)
	Negative	44	NR	2%	NR			
	Uninformative	166	NR	5%	NR			
Schwartz et al.[39]	Deleterious	31	48%	NR	NR	NR	US 84% white	<40 28% >40 72%
	Uninformative	136	24%					
Wainberg et al.[35]	Deleterious	37[b]	0%	46%	NR	1–2	US	>25
		26[c]	54%	50%	NR	1	Netherlands	>25
		194[d]	15%	51%	NR	2 (mean)	US	>25
Uyei et al.[27]	Deleterious	132	12.1%	12.1%	24.2%	NR	White 71.6%	<50 74%
	No mutation	410	15.6%	3.4%	4.9%		Jewish 12.5%	>50 26%
							Hispanic 9.4%	
							Black 3.8%	
							Asian 2.7%	
Bradbury et al.[37]	Deleterious	88	35%	70%	NR	4	White 89%	42 (23–71)
							Black 9%	
							Hispanic 2%	
Metcalfe et al.[33]	Deleterious	517	33.5%	67.1%	NS	4.5	Canadian	47 (25–79)
Metcalfe et al.[33]	Deleterious	48	10.4%	52.1%	NR	4.1	Austria	46 (25–79)
		766	11.5%	57.3%	NR	4.4	Canada	
		31	3.2%	71%	NR	5.9	France	
		165	2.4%	66.7%	NR	4.1	Israel	
		46	4.3%	50%	NR	4.8	Italy	
		177	3.4%	73.4%	NR	3.6	Norway	
		660	1.4%	34.8%	NR	2.6	Poland	
		81	22.2%	64.2%	NR	4.3	Holland	
		703	16.4%	71.1%	NR	4.4	US	
Evans et al.[30]	Deleterious	211	39.8%	45.5%	NR	4.2	NS	NS
Beattie et al.[31]	Deleterious	285	23%	51%	NR	3.7	White 59–91%	45 (20–79)
							Jewish 19–45%	
Morgan et al.[32]	Deleterious	7	42.9%	71.4%	42.9%	2–9	US	51 (23–75)
	Uninformative	62	13%	23%	NR			
Stuckey et al.[43]	Deleterious	90	7.8%	36.7%	6.7%	NR	NR	45 (18–75)
Skytte et al.[29]	Deleterious	306	30.1%	50.7%	20.6%		Danish	37 (18–86)

[a]Median unless noted.
[b]Botkin et al., 2003.[40]
[c]Lodder et al., 2002.[41]
[d]Scheuer et al., 2002.[42]

addition, it may be advisable to discuss with the patient how and whether to communicate reclassification information to their family in the event of their death as reclassification could be informative for medical decision making in family members. Recontact for updated information or at the time of reclassification also presents an opportunity to invite patients or family members for further genetic counseling and consideration of genetic testing that may not have been previously available. As recontact by the provider may be unexpected, our common practice has been to mail a brief letter informing the patient or family that updated information on the genetic variant is available and requesting them to call the clinic for further information. This allows the individual to initiate the conversation at a time and in a setting they feel appropriate.

The example of *BRCA1* and *BRCA2* VUSs reflects emerging issues in clinical application of genetic technologies. As uptake of genetic services and utilization of sequencing increase, the frequency of VUS detection will also increase. Recently discovered genes are likely to have even more complexity in prediction of risk because of limited data on the effects of variants.[40]

The ambiguities that accompany VUSs detected by the well-established *BRCA* genetic tests speak to the importance of administering genetic tests in a clinical setting accompanied by genetic counseling and the need for accurate and efficient classification tools, such as functional assays or statistical models. Providers of genetic services and patients who receive VUS results should discuss a plan for recontact in the event that new information become available. Moreover, because patients with VUS results may undergo irreversible interventions with associated risks and unclear benefits, periodic communication may help ensure patient understanding of this type of result and its conferred disease risk. An ongoing dialog about the most current understanding of a VUS will minimize the likelihood of surgical decisions based on misunderstood genetic information.

There are several limitations to this study. This report is based on retrospective chart review, and it is possible the nuances of the counseling session are not exhaustively documented in available records. Because we have not interviewed these patients nor are they research participants, we can only make assumptions about patient's subjective interpretation of VUS result and the role this type of result played in subsequent decisions to undergo cancer risk-reducing surgeries. As the majority the women who pursued RRO were treated by the same surgeon, we cannot evaluate the impact of the surgeon on patient decision making. Similarly, this report is limited to the experience of a single center and includes primarily non-Ashkenazi whites; it is possible that the findings do not generalize to all populations. Finally, post-VUS disclosure medical records are unavailable for 27.1% of our study population, likely because many were referred from unaffiliated providers to whom they returned for subsequent care. Despite these limitations, the available data offer insight into surgical outcomes in *BRCA* VUS carriers receiving clinical care at our institute over the first 11 years of *BRCA* clinical availability.

There are several areas for future research addressing patient understanding and use of genetic information postdisclosure of a VUS result. Qualitative studies with women receiving VUS results may offer insight into their experiences and concerns and suggest methods to improve the counseling process. Analysis of patient characteristics, such as demographics, personal medical history, and family history, may reveal factors associated with pursuit of cancer risk-reducing surgeries after VUS disclosure to ensure appropriate follow-up and additional counseling if necessary. Although the median age of the women in our study was 45, many of the women were of reproductive age; women with a VUS may alter reproductive decision making based on genetic testing. In addition, our findings reflect the practices of a single tertiary care academic center; it would be useful to characterize the experience of several sites, including a diversity of practice settings. Finally, it will be useful to investigate patient decision making after VUS disclosure in other highly penetrant cancer predisposition syndrome genes for which cancer risk-reducing surgeries are typically offered, such as the genes associated with Lynch syndrome or *RET*-associated familial medullary thyroid carcinoma.

As genetic testing for cancer susceptibility is offered to more moderate or low-risk women, the potential harm from risk-reducing surgeries for women identified with a VUS may be greater. For example, a VUS identified in a woman with a first-degree relative with postmenopausal breast cancer would have a low a priori risk of developing breast or ovarian cancer or of testing *BRCA* mutation positive. This compares with ovarian cancer where 10–15% may be attributable to *BRCA1* and *BRCA2* mutations,[41,42] thus a woman with a VUS with a first-degree relative with ovarian cancer may be more likely to be counseled to consider bilateral salpingo-oophorectomy. Interestingly, our study sample had no women referred for family history of ovarian cancer alone, but this is becoming a much more common referral.

In conclusion, variants of unknown significance will continue to present both patients and providers with an uncertain measure of disease risk, thereby complicating decisions regarding cancer surveillance and prevention. Our experience described in this study shows that women who received *BRCA1* or *BRCA2* VUS results in the context of practices concordant with NSGC guidelines pursued cancer risk-reducing surgeries at rates overlapping reported uptake rates both in women with and without clearly pathogenic mutations. In addition, on the basis of the observation that VUS reclassification may occur at 9 or more years after testing, we endorse all providers offering genetic testing to establish a reliable tracking system and discuss with the patient a plan to communicate reclassification information to them or their family members in the event of their death. Challenges in medical decision making after identification of a genetic VUS are not unique to *BRCA* testing, and further research both in *BRCA* VUS disclosure and in other highly penetrant cancer predisposition genes will be helpful to guide future genetic counseling practices.

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