Published in final edited form as:
Clin Genet. 2013 November ; 84(5): 464–472. doi:10.1111/cge.12097.

Variants of Uncertain Significance in *BRCA* Testing: Evaluation of Surgical Decisions, Risk Perception, and Cancer Distress

J.O. Culver[1], **C.D. Brinkerhoff**[2], **J. Clague**[1], **K. Yang**[1], **K.E. Singh**[2], **S.R. Sand**[1], and **J.N. Weitzel**[1]

[1]City of Hope, Division of Clinical Cancer Genetics, 1500 E. Duarte Rd., Duarte, CA

[2]University of California, Irvine, Irvine, CA 92697

Abstract

Studies suggest that patients carrying a *BRCA* variant of uncertain significance (VUS) may have lingering confusion concerning results interpretation. Counseling for uninformative *BRCA*-negative (UN) results is thought to be more straightforward, despite the fact that both results lead to similar methods of empiric cancer risk counseling. This study compared surgical choices and perceptions between 71 patients with VUS results and 714 patients with UN results. All patients underwent genetic counseling because of a personal or family history of breast or ovarian cancer between 1997 and 2010, and completed a two-year follow-up survey. Risk-reducing mastectomy rates in both groups were 7% (p=1.00) and risk-reducing oophorectomy rates were 5% and 3%, respectively (p=0.42). The VUS group reported less cancer distress reduction than the UN group (23.0% versus 35.8%, respectively, p=.043). Over 90% of both groups found the counseling process helpful. Overall, the study suggests that VUS results disclosed in genetic counseling did not cause excessive surgery or exaggerated cancer distress, though patients with a VUS found counseling somewhat less informative or reassuring. Future research on communication of VUS results, including pre-and post-test counseling, is essential for full realization of the potential for genomic medicine.

Keywords

BRCA1 gene; BRCA2 gene; genetic counseling; hereditary breast and ovarian cancer syndrome; mutation missense; variant of uncertain significance

Introduction

A variant of uncertain significance (VUS) is a gene mutation identified with an unknown effect on protein function (1). With recent advances in massively parallel sequencing technology (2, 3), multiple cancer-risk causing genes are analyzed simultaneously; hence, the number of VUSs identified in cancer-causing genes is rapidly growing (4). The larger the fraction of the genome assessed, the more likely that VUSs will be encountered (5).

A VUS result is reported in approximately 5% of *BRCA1* and *BRCA2* genetic tests conducted in the United States (6). VUSs in *BRCA* genes are often challenging to interpret

Corresponding Author: Jeffrey N. Weitzel, MD, Division of Clinical Cancer Genetics Mod 173, City of Hope, 1500 E. Duarte Rd., Duarte, CA 91010, (626) 256-8662, Fax: (626) 930-5495, jweitzel@coh.org.

Conflict of Interest Statement:
Julie Culver, Chad Brinkerhoff, Jessica Clague, Kai Yang, Kathryn Singh, Sharon Sand, and Jeffrey Weitzel do not have financial or personal relationships that would bias this work.

for providers and have been described as “flies in the ointment,” (7) a term which refers to the frustration rooted in both the inability of the laboratory to provide a clear interpretation of the result and the prospect of having to explain this information to a patient (8). These challenges include possible misperceptions by patients or physicians that a VUS is deleterious. Published reports have documented physician misinterpretation of VUS results, perhaps due to lack of formal training in genetics (9, 10).

As the reporting laboratory obtains more data over time, a particular variant may ultimately be reclassified as a polymorphism, which is clinically grouped with a *BRCA*-negative result, or as a deleterious mutation. In 2007, Easton et al. evaluated a large dataset of *BRCA1/2* VUSs of Myriad Genetics, the commercial laboratory that holds the *BRCA1/2* patents and conducts all clinical *BRCA* testing in the United States. The study estimated between 12–20% of the VUSs as being deleterious, depending upon the nature of the VUS (1). However, advances in VUS reclassification techniques since 2007 has likely changed this proportion. Deleterious mutations in *BRCA1/2* are associated with a lifetime breast cancer risk of 40–85% and an ovarian cancer risk of 15–40% (11). Preventive strategies such as enhanced surveillance, chemoprevention, risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) are offered to patients with deleterious mutations (12). Therefore, the potential for an altered interpretation of a VUS over time carries with it possible disparate clinical implications.

A *BRCA*-negative result in a family known to have a *BRCA* mutation is highly informative because a patient in a high risk family can usually be counseled as having the population risk for cancer. However, a *BRCA*-negative result in the absence of a known family mutation is an “Uninformative Negative” (UN) (3, 13). The cause of cancer in the family or individual is still unknown after genetic testing, often leaving behind a striking but unexplained personal and/or family history of cancer. Both VUSs and UNs are uninformative and thus recommendations are made in both cases by considering the patient’s personal and family history (12) and considering empiric risks (14, 15).

Previous studies have described the impact of a VUS result, such as subsequent surgical decisions and perceived risk. A series of Dutch studies found that most VUS patients interpreted the VUS result as a predisposition to cancer and almost half had undergone risk-reducing surgery (16, 17). These results are concerning since standard clinical genetics practice dictates that patients with VUS results should be counseled in the same manner as patients with UN results (12). However, another Dutch study found VUS patients and UN patients had very similar post-test perceived risks and distress levels (18). To date, studies comparing VUS and UN patients have only been reported in the Dutch population.

The current study further evaluated the perceptions and actions of patients after receiving a VUS test result and undergoing genetic counseling. The study compares these post-test reactions of patients with a VUS with those associated with uninformative negative results (UNs). We hypothesized that both groups would have responded to counseling in a similar manner because both were counseled as having uninformative test results, with cancer risks derived from empiric risks rather than from risk associated with a mutation. However, since they were counseled about the ambiguous nature of the VUS result, meaning that the VUS could be reclassified to benign or deleterious, we sought to determine if there were any differences between VUS and UN patients with respect to surgical decisions, risk perception, cancer distress or opinions about the genetic counseling and testing process.

Materials and Methods

Participants

This case control study was designed to compare the responses of patients receiving one of two test results (VUSs or UNs). The study sample was collected from the City of Hope Clinical Cancer Genetics Community Research Network (CCGCRN), an IRB-approved research registry with collaborating sites wherein the clinicians (physicians, advanced-practice nurses, and genetic counselors) had all received core training in an intensive course in cancer risk counseling (19, 20). Patients with a personal or family history of cancer were referred for a genetic cancer risk assessment (GCRA) appointment both by physicians within the cancer center and by outside providers. Patients were enrolled and consented in the registry at the time of their GCRA appointment; 86% of patients receiving GCRA were recruited. Patients receiving genetic testing were provided with pre- and post- test counseling, including cancer risk assessment. Follow-up is obtained via questionnaire mailed two years after the initial visit; the two-year follow-up survey retention rate is 57%.

Participants in this study had enrolled in the registry between 1997 and 2010 and had completed a two-year follow-up survey. This time frame was chosen because most decision-making based on genetic test results typically would occur during the first two years after receipt of the results (31, 32). Additional eligibility criteria included being female and either carrying a VUS or having a UN result in a *BRCA* gene. Patients with a *variant, favor polymorphism* or *variant, suspected deleterious* results were excluded from the study due to more informative counseling strategies and standard healthcare recommendations associated with those subcategories of VUSs. We omitted patients carrying a VUS who were later found to be positive by other *BRCA* genetic testing, such as *BRCA* rearrangement testing. Only patients counseled at the Duarte and Phoenix CCGCRN sites were included because these sites have the longest recruitment period available.

During the study period, there were five VUS patients who had been notified that their variant had been reclassified to “variant, favor polymorphism” or to a polymorphism before completing their follow-up survey. Such patients were retained in the study because they had already been counseled with empiric risks instead of syndromic risks, as the standard of care described above, and therefore the reclassification did not change the risks provided during genetic counseling. There were no study participants whose VUS was reclassified to “variant, suspected deleterious” or “deleterious.”

Risk Assessment

During results disclosure counseling, both VUS and UN patients were provided with a breast and ovarian cancer risk assessment using identical methods. A patent’s personal and family history were considered (3, 12) and empiric risks were provided for a second primary breast cancer (21–24), and for ovarian cancer (25). Women were only counseled about increased risk of ovarian cancer if there was ovarian cancer in the family (26). For unaffected patients, or for the female relatives of cancer patients, risk models were used, such as the Gail model to determine Tamoxifen eligibility (14, 27), as well as the Claus model (15). After the American Cancer Society published MRI screening guidelines in 2007 (28), the Tyrer-Cuzick or BOADICEA models (29, 30) were also used for breast cancer risk assessment. Additional genetic testing such as the Myriad 5-site rearrangement panel or *BRCA* rearrangement testing was offered when such tests became available. VUS patients were offered the opportunity to participate in tracking studies, when appropriate, but it was explained to patients that this was done for research purposes only, to enable the commercial laboratory to pool data from many families, and not to determine pathogenicity of the variant in any particular family. Moreover, it was explained to the patient that tracking

studies are more informative if the VUS does not track with cancer in the family. Patients were given a risk graph with their empiric breast and ovarian cancer risks written and plotted on the graph; the "high risk" section was crossed out, indicating that they are not at high risk of breast and ovarian cancer. A dictation summarizing the visit, including the results interpretation and the empiric risk numbers, was sent to the referring provider, with a copy also mailed to the patient.

Questionnaire items

In the follow-up questionnaire, patients were asked, "Since your last visit with us, have you had a mastectomy to reduce your breast cancer risk (not as part of treatment for breast cancer)?" If "Yes," they were asked, "Did genetic counseling and/or genetic testing influence this decision?" Regarding oophorectomy, patients were asked, "Have you had your ovaries removed since your last visit with us?," and, if "Yes," they were asked whether one ovary or both ovaries were removed and were offered several checkboxes to indicate the reason(s) for having an oophorectomy including: "Preventative to reduce ovarian cancer risk," "Combined with a hysterectomy," "Treatment of ovarian cancer," etc. They were also asked the same question as above regarding the influence of genetic counseling on oophorectomy. Patients were classified as having a bilateral salpingo oophorectomy (BSO) if both ovaries were removed. Patients were classified as having an RRSO if they had a BSO and they indicated that the only reason for the BSO was preventative.

Regarding recall of cancer risks, patients were asked, "Do you recall the breast cancer risk we gave you?" If "Yes," patients were asked if the risk was *average*, *moderate*, or *high*. The same questions were asked about ovarian cancer risk. Regarding cancer concerns, patients were asked a series of questions (33), "During the past month, how often have thoughts about cancer concerned you?" The answer choices were: "Never/Rarely (one time or not at all)," "Sometimes (about once a week or less)," "Often (about 3 times a week)," or "All the time (daily)." They were also asked "Do you think the frequency of these thoughts has changed as a result of genetic counseling and/or genetic testing?" If the answer was "Yes," they were asked whether the frequency increased or decreased. Regarding the genetic counseling process associated with their GCRA appointment, patients were asked, "Was genetic counseling helpful to you?" Depending on whether the answer was "Yes" or "No," they were asked to select from checkboxes with as many reasons as were applicable. Patients were also asked "How do you feel about your decision to have genetic counseling?" on a 5-point Likert scale, with answer choices ranging from "Extremely displeased" to "Extremely pleased."

Statistical methods

Standard summary statistics, including *t*-tests and χ^2 tests, were used to characterize and compare patients within the two groups. The Pearson's Chi-square test was used to evaluate differences in patient satisfaction and feelings about the genetic cancer risk assessment process, general cancer-related distress, and healthcare decisions post-testing between the VUS and UN groups. The Fisher's exact test was used when it was necessary to compensate for small response rates to individual questions within the follow-up questionnaire. All statistical analyses were performed using Stata Statistical Software, Release 11 (College Station, TX: StataCorp LP), and analytical tests were two-sided with a Type I error rate of 5%.

Medical records review

Review of medical records for the VUS patients who had undergone risk-reducing surgery was performed to determine the appropriateness of surgical risk reduction procedures in an attempt to determine whether surgical actions might be consistent with other guidelines such

as the National Comprehensive Cancer Network (NCCN), Society of Surgical Oncology (SSO), American College of Obstetrics and Gynecology, Society of Gynecologic Oncologists, and National Institutes of Health (NIH) Guidelines (Table 1) (34–39). In other words, using clinical guidelines summarized in Table 1, patients who warranted prophylactic action (RRM or RRSO) based on their residual risk due to family history, personal cancer history, or other criteria of the professional organizations discussed above, were differentiated from those who may have acted based on their VUS result.

Patient characteristics influencing GCRA outcomes

We conducted an additional analysis of whether the patient's age, having a cancer diagnosis, ethnicity, or education level had any effect on RRM or RRSO decisions, increases in cancer distress as a result of genetic counseling, feelings that genetic counseling was not helpful, or displeasure with the genetic testing decision. For this analysis we combined VUS and UN patients, given that we found very few differences between these groups. An additional analysis was performed to determine whether the year of study entry was correlated with any of these GCRA outcomes. This analysis was done because genetic counseling trends may have changed over time, especially with respect to VUSs, given that many have now been reclassified to polymorphisms and relatively few have been reclassified to deleterious.

Results

This study analyzed patient 2-year follow-up questionnaire data, including data from 71 participants in the VUS group and 714 participants in the UN group. The mean enrollment year was 2004 for the VUS group and 2005 for the UN group (p=.39). The two groups differed in race/ethnicity; the VUS group was 51% White, Non-Hispanic and the UN Group was 71% White, Non-Hispanic (p<.01). There were no other statistically significant differences between the groups in their demographic characteristics, cancer diagnoses, or surgical history (Table 2). The mean time from initial visit to follow-up was 2.5 years in the VUS group and 2.3 years in the UN group (p=.46).

Patient follow-up data indicated that surgical decisions did not vary significantly between the two groups (Table 3). RRM was undertaken by 7% of both groups (p=1.0). Among those who had RRM, genetic counseling and/or genetic testing influenced 33% (1/3) of respondents from the VUS group and 29% (10/35) from the UN group in decisions for RRM (p=1.00). For the VUS group, 12% of patients opted for bilateral salpingo-oophorectomy (BSO), while 7% of respondents in the UN group underwent BSO (p=0.19). Five percent of VUS patients and 3% of UN patients underwent BSO for risk reduction purposes only (RRSO) (p=.42). Genetic counseling and/or testing was reported to have influenced the RRSO decisions 100% (3/3) and 53% (9/18) of the time, respectively (p=.24).

For patients in the VUS group opting for risk-reducing surgery, a review of medical records was conducted to determine if the patients met criteria in professional guidelines for the surgery (Table 1), regardless of the VUS status. Cosmesis was the rationale for three out of four, meeting SSO guidelines (37); one was conducted because of young age at breast cancer diagnosis (35 years old), which was previously an SSO criteria (40) but the patient also indicated that the VUS was considered in her decision. Of three BSOs, two were deemed appropriate based on family history of ovarian cancer, and one BSO was conducted as an adjunct to the treatment of pre-menopausal estrogen-positive breast cancer. Hence all BSOs in the VUS group met professional guidelines for BSO independent of genetic status.

Patients were asked if they could recall the BC and OC risk category to which they were assigned during their GCRA appointment (Table 4). Approximately 75% of both groups could recall their BC risk category, but the recall rate was 56% for OC risk. Of those who

could recall their BC risk, 15% of VUS and 10% of UN patients believed that they were in the high-risk category, while 85% and 90% recalled average or moderate risk, respectively (p=0.31). Of those able to recall ovarian cancer risk, 16% of VUS patients versus 9% of UN patients recalled a high risk (p=0.29).

The third category within the follow-up questionnaire focused on cancer distress (Table 5). Over 75% of respondents in both groups indicated that thoughts of cancer concerned them at least sometimes. Patients were then asked if genetic counseling changed the frequency of these concerning thoughts. Patients from the VUS group indicated that genetic counseling had changed the frequency of their concerning thoughts about cancer at a rate of 23% compared to 36% of UN patients (p=0.043), almost always by decreasing the frequency (92% VUS, 83% UN, p=0.67). In summary, a higher percentage of the UN group had reduction in cancer distress when compared to the VUS group.

Patient responses to the genetic counseling and testing process were investigated. Over90% of both groups answered that GC was helpful to them (Table 6). In both groups, the majority responded that GC was educational and helped with their understanding of genetics and their family's risk, and about one-third of patients indicated that it helped them make medical decisions or understand how to reduce their cancer risk. About half of the individuals in each group indicated that genetic counseling helped reduce worry. The majority in both groups were extremely pleased with their decision to test (Table 6).

A small portion of each study group did not find the GC process to be helpful (7.5% VUS, 5.9% UN). There was only one difference identified between the unsatisfied VUS and UN patients regarding the reason for this opinion; 5/5 VUS (100%) patients versus 10/40 UN patients (25%) claimed that "GC did not provide me with any new knowledge." (Table 6)

We combined the VUS and UN groups and conducted an additional analysis of whether the age of the women, having a cancer diagnosis, ethnicity, or education level had any correlation with study outcomes such as RRM or RRSO decisions, increases in cancer distress as a result of genetic counseling, feelings that genetic counseling was not helpful, or being displeased with the genetic testing decision. The only significant findings of these analyses related to the RRM decision. The mean age of RRM patients were younger than non-RRM patients (44 years versus 48 years, p=.0091). Additionally, patients with a cancer diagnosis were more likely to have RRM (6.6% versus 1.0%, p=.002). There were no trends in the year of study entry on any of these outcomes.

Discussion

Despite the inherent uncertainty associated with a VUS result in *BRCA* testing, the findings of this study indicate that VUS results do not appear to undermine the goals of genetic counseling. In this population, VUSs and UNs were both treated as clinically uninformative, and were counseled with similar strategies and identical risk assessment methods. VUS results did not lead to a higher rate of surgical intervention, distress, or increased risk perception when compared to patients receiving UN results.

The two groups differed in race/ethnicity, with the VUS group having a significantly lower proportion of White, Non-Hispanic patients. This discrepancy reflects the experience of the *BRCA* testing laboratory, with individuals of European ancestry having a lower rate of VUS results than Latin American, African, Native American, Middle Eastern or Asian populations (6). The rate of VUSs is now less than 5%, but it is still higher in these less represented ethnic groups due to less testing experience with these groups and thus less opportunity to collect the data necessary for variant reclassification.

Risk reducing surgery

There was a low rate of risk reducing surgery in both groups. Furthermore, the vast majority of these procedures in VUS patients were found to have a clear indication after consulting established practice guidelines. Along with the RRM data, the very low rate of RRSO in both groups is encouraging as these findings suggest that VUSs do not lead to an excessive rate of surgery when the genetic testing and counseling is performed by an experienced multidisciplinary team.

A few previous studies have reported the rate of risk-reducing surgeries in a VUS population. Preventive surgery attributed solely to VUSs has been found to occur among 42% of patients in one Dutch study (n=24) (16). This study attributed the high preventive surgery rate to patients incorrectly interpreting the VUS as pathogenic; their decision could not be explained by personal or family history of cancer or any socio-demographic characteristics. While the 7% RRM rate in our VUS population was similar to the 10% rate found in a Seattle study (N=107), the rate of RRSO in our study was much lower (5% versus 21%). Possible surgeon/provider bias was cited in the Seattle study (the majority of RRSOs were performed by the same surgeon) (41). The Seattle study did not compare VUS patients to UN patients but commented that their observed surgery rates in VUS patients overlapped the 2–24% rate of RRM and 2–23% rate of RRSO in the published literature for women with UN results (32, 42–45). Varying rates of prophylactic surgeries in general could also be attributed to cultural and geographic differences in opinion (46). Additionally, the interpretation of a VUS may differ by clinical setting or testing laboratory used.

Risk perception

In the current study, there was no significant difference in breast or ovarian cancer risk perception of VUS patients in comparison to UN patients, which supports the hypothesis that risk-appropriate VUS counseling does not cause excess perception of risk.

Similarly to our study, a Dutch study compared women with VUSs (N=10) to women with other *BRCA* results including UNs (N=37), finding no increase in perceived risk of cancer when compared to their pre-test perceptions (18). However, a more recent Dutch study comparing VUS patients (N=76) and UN patients (N=76) found that VUS patients recalled higher cancer risks and interpreted a higher likelihood of their cancer being hereditary (17). The providers of these patients may have used somewhat different counseling strategies, or perhaps the study method was able to pick up more subtle differences between these two groups.

Cancer distress

Over 30% of patients in both groups have concerning cancer thoughts often or all of the time. Most of these patients had cancer already, thus their prior diagnosis would be expected to affect cancer distress. However, no suggestion of a higher frequency of concerning thoughts about cancer was found in patients with a VUS compared to those with an UN. Both groups reported that distress generally decreased or stayed the same after receiving their test result. However, the UN group reported significantly more distress reduction as a result of genetic counseling than the VUS group. The difference in frequencies of cancer distress in our study could be evidence that UN patients are falsely reassured into feeling some reduction of risk, while VUS patients do not experience this. Some qualitative studies have shown that individuals receiving a UN result in *BRCA* testing may misinterpret that result as a true negative, believing that not finding a mutation relieves them of genetic risk (47). Van Dijk, et al. showed that genetic counseling tends to reduce cancer distress and worry in a UN population (48), with a similar reduction of distress between UN and VUS patients (18). This is generally supported by our findings.

Opinions about genetic counseling

With regard to patient satisfaction and feelings toward genetic counseling and testing, both groups reported very high levels of helpfulness from the process, mostly because it helped them gain a better understanding of cancer genetics and cancer risk. Despite the lack of informative results, over 40% of VUS and UN patients who found genetic counseling helpful felt this way because counseling helped them make decisions regarding medical care. Patients from the VUS group who did not find genetic counseling helpful attributed that opinion, at least in part, to a feeling that counseling/testing did not provide them with any new knowledge. This finding is somewhat intuitive. After all, no mutation was reported in UNs, whereas VUS patients still have an ambiguous result.

Future directions

Further research on VUS and the effect on risk perception and medical management will be imperative given that next-generation sequencing strategies allow for concurrent testing of multiple genes, thus multiplying the likelihood of receiving a report with one or more variants of uncertain significance (VUS). Analysis of well characterized genes such as *BRCA1* and *BRCA2* still yields an approximately 5% rate of VUS by Sanger sequencing, more than 16 years after introduction of commercial laboratory testing and after experience with more than a million genotypes. When multiple genes are analyzed at one time, the potential for identifying an uncertain variant is multiplied. For example, a clinically available test for seven hereditary colon cancer genes estimates a 10% rate of identifying a VUS (49); higher rates will likely persist, especially among lesser represented racial/ethnic groups (4). This reflects the need for further development of counseling tools for VUS and ongoing research in the communication of these results.

Physician misinterpretation of genetic test results can lead to inappropriate care, neglect, or misinformation given to patients, including those with a VUS (9, 10). It is important to note that in the United States, not all *BRCA* testing is ordered by genetics professionals, and results are not disclosed in uniform methods nationwide. It is quite possible and even probable that the differences among healthcare providers regarding their test disclosure strategies are instrumental in the differences among patients with respect to their comprehension of VUSs. Future studies could compare clinical actions of VUS patients who had their results disclosure by genetics professionals versus other health professionals or whether genetic testing included pre- and post-test counseling.

Limitations

While it was possible to determine that all VUS patients having risk reducing surgery met clear guidelines, the precise rationale used by the patient for undergoing a risk-reducing surgery could not always be determined. In many cases, we lacked access to other medical information that could influence surgical decisions or risk perception.

This study included patients who were representative of a cancer center population, with almost 90% of study participants affected with cancer. Thus, the findings may not apply to patients who have not had cancer and are undergoing genetic testing due to a family history only.

The patients in the VUS group had a higher proportion of ethnic and racial minorities than in the UN group. Given potential cultural and/or language barriers inherent in counseling, this difference may have introduced a bias in the responses to the follow-up survey that may have not been possible to detect.

Conclusion

With counseling based on risk management guidelines, patients with a VUS acted appropriately for their level of risk, did not worry at an increased rate, and found genetic counseling and testing helpful. A patient-centered approach, sound medical strategy, a clear understanding of the VUS by the cancer risk counseling team, and emphasis on a patient's post-test risk and management are crucial in a successful results disclosure session. A conscious effort on the part of clinicians should be made to not only interpret test results but to guide the patient to a sound plan of action. Future research on communication of VUS results is essential for full realization of the potential for genomic medicine.

Acknowledgments

We would like to acknowledge the efforts of Josef Herzog for researching VUSs and applying functional prediction models, Lacolle Robinson for data collection, Hazel Mariveles for registry coordination, Benjamin Weissman for data entry, and Tracy Sulkin for manuscript preparation.

Funding Sources:

The project described was supported in part by awards number RC4CA153828 and number R25CA085771 (PI: J. Weitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

References

1. Easton DF, Deffenbaugh AM, Pruss D, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. Am J Hum Genet. 2007; 81:873–883. [PubMed: 17924331]
2. Walsh ER, Pisitkun P, Voynova E, et al. Dual signaling by innate and adaptive immune receptors is required for TLR7-induced B-cell-mediated autoimmunity. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109:16276–16281. [PubMed: 22988104]
3. Weitzel JN, Blazer KR, MacDonald DJ, et al. Genetics, genomics and cancer risk assessment: state of the art and future directions in the era of personalized medicine. CA Cancer J Clin. 2011; 61:327–359.
4. Stuenkel, AJ.; Tandy, SL.; Siegfried, JD. Estimated variant rate for a next-generation sequencing panel of 13 genes associated with hereditary colon cancer. American Society of Human Genetics Annual Meeting; San Francisco, CA. 2012.
5. Tucker T, Marra M, Friedman JM. Massively parallel sequencing: the next big thing in genetic medicine. Am J Hum Genet. 2009; 85:142–154. [PubMed: 19679224]
6. Saam, J.; Burbidge, L.; Bowles, K., et al. Decline in rate of BRCA1/2 variants of uncertain significance: 2002–2008. 27th Annual Education Conference of the National Society of Genetic Counselors; Los Angeles. 2008.
7. Domchek S, Weber BL. Genetic variants of uncertain significance: flies in the ointment. J Clin Oncol. 2008; 26:16–17. [PubMed: 18165634]
8. Ardern-Jones A, Kenen R, Lynch E, et al. Is no news good news? Inconclusive genetic test results in BRCA1 and BRCA2 from patients and professionals' perspectives. Hered Cancer Clin Pract. 2010; 8:1. [PubMed: 20180951]
9. Brierley KL, Campfield D, Ducaine W, et al. Errors in delivery of cancer genetics services: implications for practice. Conn Med. 2010; 74:413–423. [PubMed: 20806621]
10. Brierley KL, Blouch E, Cogswell W, et al. Adverse events in cancer genetic testing: medical, ethical, legal, and financial implications. Cancer J. 2012; 18:303–309. [PubMed: 22846730]
11. Pruthi S, Gostout BS, Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. Mayo Clin Proc. 2010; 85:1111–1120. [PubMed: 21123638]

12. NCCN. NCCN Clinical Practice Guidelines. 2012. NCCN clinical practice guidelines in oncology V.1.2012: Genetic/familial high-risk assessment: breast and ovarian.
13. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. J Genet Couns. 2012; 21:151–161. [PubMed: 22134580]
14. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989; 81:1879–1886. [PubMed: 2593165]
15. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer: Implications for risk prediction. Cancer. 1994; 73:643–651. [PubMed: 8299086]
16. Vos J, Otten W, van Asperen C, et al. The counsellees' view of an unclassified variant in BRCA1/2: recall, interpretation, and impact on life. Psycho-Oncol. 2008; 17:822–830.
17. Vos J, Oosterwijk JC, Gomez-Garcia E, et al. Perceiving cancer-risks and heredity-likelihood in genetic-counseling: how counselees recall and interpret BRCA 1/2-test results. Clin Genet. 2011; 79:207–218. [PubMed: 21114486]
18. van Dijk S, van Asperen CJ, Jacobi CE, et al. Variants of uncertain clinical significance as a result of BRCA1/2 testing: impact of an ambiguous breast cancer risk message. Genet Test. 2004; 8:235–239. [PubMed: 15727245]
19. MacDonald DJ, Blazer KR, Weitzel JN. Extending comprehensive cancer center expertise in clinical cancer genetics and genomics to diverse communities: the power of partnership. J Natl Compr Canc Netw. 2010; 8:615–624. [PubMed: 20495088]
20. Blazer KR, MacDonald DJ, Culver JO, et al. Personalized cancer genetics training for personalized medicine: Improving community-based healthcare through a genetically literate workforce. Genet Med. 2011; 13:832–840. [PubMed: 21629123]
21. Kurian AW, McClure LA, John EM, et al. Second primary breast cancer occurrence according to hormone receptor status. J Natl Cancer Inst. 2009; 101:1058–1065. [PubMed: 19590058]
22. Hemminki K, Vaittinen P. Familial risks in second primary breast cancer based on a family cancer database. Eur J Cancer. 1999; 35:455–458. [PubMed: 10448299]
23. Hemminki K, Ji J, Forsti A. Risks for familial and contralateral breast cancer interact multiplicatively and cause a high risk. Cancer Res. 2007; 67:868–870. [PubMed: 17283115]
24. Harris RE, Lynch HT, Guirgis HA. Familial breast cancer: risk to the contralateral breast. J Natl Cancer Inst. 1978; 60:955–960. [PubMed: 642037]
25. Stratton JF, Pharoah P, Smith SK, et al. A systematic review and meta-analysis of family history and risk of ovarian cancer. Br J Obstet Gynaecol. 1998; 105:493–499. [PubMed: 9637117]
26. Kauff ND, Mitra N, Robson ME, et al. Risk of ovarian cancer in BRCA1 and BRCA2 mutation-negative hereditary breast cancer families. J Natl Cancer Inst. 2005; 97:1382–1384. [PubMed: 16174860]
27. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst. 1998; 90:1371–1388. [PubMed: 9747868]
28. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007; 57:75–89. [PubMed: 17392385]
29. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004; 23:1111–1130. [PubMed: 15057881]
30. Antoniou AC, Pharoah PP, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer. 2004; 91:1580–1590. [PubMed: 15381934]
31. Weitzel JN, McCaffrey SM, Nedelcu R, et al. Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Arch Surg. 2003; 138:1323–1329. [PubMed: 14662532]
32. Schwartz MD, Lerman C, Brogan B, et al. Impact of BRCA1/BRCA2 counseling and testing on newly diagnosed breast cancer patients. J Clin Oncol. 2004; 22:1823–1829. [PubMed: 15067026]
33. MacDonald DJ, Choi J, Ferrell B, et al. Concerns of women presenting to a comprehensive cancer center for genetic cancer risk assessment. J Med Genet. 2002; 39:526–530. [PubMed: 12114489]

34. NCCN. NCCN clinical practice guildelines in ocology V.2.2012: Breast Cancer. NCCN Clinical Practice Guidelines. 2012
35. Giuliano AE, Boolbol S, Degnim A, et al. Society of Surgical Oncology: position statement on prophylactic mastectomy. Approved by the Society of Surgical Oncology Executive Council, March 2007. Ann Surg Oncol. 2007; 14:2425–2427. [PubMed: 17597344]
36. National Institutes of Health (NIH). NIH Consensus Conference. Ovarian cancer. Screening, treatment, and follow-up. NIH Consensus Development Panel on Ovarian Cancer. JAMA. 1995; 273:491–497. [PubMed: 7837369]
37. SGO. Society of Gynecologic Oncologists Clinical Practice Committee Statement on Prophylactic Salpingo-oophorectomy. Gynecol Oncol. 2005; 98:179–181. [PubMed: 15979696]
38. ACOG. ACOG Practice Bulletin No. 89. Elective and risk-reducing salpingo-oophorectomy. Obstet Gynecol. 2008; 111:231–241. [PubMed: 18165419]
39. NCCN. NCCN Guidelines Breast Cancer Risk Reduction V.1.2012. NCCN Guidelines for Detection, Prevention, & Risk Reduction. 2012
40. Bilimoria MM, Morrow M. The woman at increased risk for breast cancer: evaluation and management strategies. CA Cancer J Clin. 1995; 45:263–278. [PubMed: 7656130]
41. Murray ML, Cerrato F, Bennett RL, Jarvik GP. Follow-up of carriers of BRCA1 and BRCA2 variants of unknown significance: variant reclassification and surgical decisions. Genet Med. 2011; 13(12):998–1005. [PubMed: 21811163]
42. Schwartz MD, Kaufman E, Peshkin BN, et al. Bilateral prophylactic oophorectomy and ovarian cancer screening following BRCA1/BRCA2 mutation testing. J Clin Oncol. 2003; 21:4034–4041. [PubMed: 14581427]
43. Uyei A, Peterson SK, Erlichman J, et al. Association between clinical characteristics and risk-reduction interventions in women who underwent BRCA1 and BRCA2 testing: a single-institution study. Cancer. 2006; 107:2745–2751. [PubMed: 17109443]
44. Morgan D, Sylvester H, Lucas FL, et al. Cancer prevention and screening practices among women at risk for hereditary breast and ovarian cancer after genetic counseling in the community setting. Fam Cancer. 2009; 8:277–287. [PubMed: 19347608]
45. Schwartz MD, Isaacs C, Graves KD, et al. Long-term outcomes of BRCA1/BRCA2 testing: risk reduction and surveillance. Cancer. 2012; 118:510–517. [PubMed: 21717445]
46. Julian-Reynier CM, Bouchard LJ, Evans DG, et al. Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another. Cancer. 2001; 92:959–968. [PubMed: 11550171]
47. Hallowell N, Foster C, Ardern-Jones A, et al. Genetic testing for women previously diagnosed with breast/ovarian cancer: examining the impact of BRCA1 and BRCA2 mutation searching. Genet Test. 2002; 6:79–87. [PubMed: 12215246]
48. van Dijk S, Otten W, Tollenaar R, et al. Putting it all behind: long-term psychological impact of an inconclusive DNA test result for breast cancer. Genet Med. 2008; 10:745–750. [PubMed: 18813137]
49. Pritchard CC, Smith C, Salipante SJ, et al. ColoSeq provides comprehensive lynch and polyposis syndrome mutational analysis using massively parallel sequencing. J Mol Diagn. 2012; 14:357–366. [PubMed: 22658618]

Table 1

Professional Guidelines for Consideration of Risk-Reducing Surgery

Risk Reducing Mastectomy and Risk-Reducing Contralateral Mastectomy		**Risk Reducing Salpingo-Oophorectomy**		
National Comprehensive Cancer Network 2012 (34, 39)	**Society of Surgical Oncology 2007 (35)**	**National Institutes of Health 1995 (36)**	**Society of Gynecologic Oncologists 2005 (37)**	**American College of Obstetrics and Gynecology 2008 (38)**
• *BRCA* or other strong pre-disposing mutation • Compelling family history • Thoracic radiation therapy < age 30 • Lobular carcinoma in-situ ----AND---- • Patient desires this form of risk reduction	• *BRCA* or other strong pre-disposing mutation • Strong family history • High-risk histology • Difficult surveillance • Improved breast symmetry	• *BRCA* or other strong pre-disposing mutation • Strong family history of ovarian cancer • Moderate family history and other abdominal surgery such as hysterectomy	• *BRCA* mutation • Family history of breast/ ovarian cancer and multi-disciplinary team guidance	• *BRCA* or other strong pre-disposing mutation • Estrogen receptor-positive breast cancer • Hysterectomy with genetic susceptibility to ovarian cancer based on family history • Hysterectomy in a post-menopausal woman

Table 2

Demographics and Clinical Characteristics

		VUS (N=71) N (%)	UN (N=714) N (%)	p-value
Age	Mean years ± SD	45.4 ± 12.6	48.1 ± 10.0	0.081[a]
Education	Less than a college degree	34 (50.8)	291 (43.0)	0.22
	College degree or higher	33 (49.3)	386 (57.0)	
Ethnicity	White, Non-Hispanic	36 (50.7)	510 (71.4)	<0.001[b]
	Hispanic/Latino	17 (23.9)	130 (18.2)	
	Asian	10 (14.1)	42 (5.9)	
	Native American	3 (4.2)	17 (2.4)	
	African American	4 (5.6)	3 (0.4)	
	Unknown/Other	1 (1.4)	12 (1.7)	
Clinical Diagnosis	Breast Cancer Only	58 (81.7)	567 (79.4)	0.074[b]
	Ovarian Cancer Only	2 (2.8)	34 (4.8)	
	Breast and Ovarian Cancer	4 (5.6)	10 (1.4)	
	No Cancer	7 (9.8)	103 (14.4)	
Gene with VUS	*BRCA1*	21 (29.6)	--	--
	BRCA2	51 (70.4)	--	--
Bilateral Mastectomy Before Study Entry	Yes	12 (17.7)	87 (12.4)	0.21
	No	56 (82.4)	617 (87.6)	
BSO Before Study Entry	Yes	11 (16.2)	95 (13.7)	0.57
	No	57 (83.8)	600 (86.3)	

[a] Unequal variances: Satterthwaite t-test

[b] Cell count<5: Fisher's exact test

Table 3

Surgical Decisions

Surgical Action	VUS N (%)	UN N (%)	p-value
BSO[a]			
No	50 (87.7)	548 (92.7)	0.19[d]
Yes	7 (12.3)	43 (7.3)	
RRSO[a,b]			
No	54 (94.7)	573 (96.9)	0.42[d]
Yes	3 (5.3)	18 (3.1)	
RRSO influenced by GC/GT			
No	--	8 (47.1)	0.24[d]
Yes	3(100.0)	9 (52.9)	
RRM[c]			
No	52 (92.9)	552 (93.4)	1.00[d]
Yes	4 (7.1)	39 (6.6)	
RRM Influenced by GC/GT			
No	2 (66.7)	25 (71.4)	1.00[d]
Yes	1 (33.3)	10 (28.6)	

Abbreviations: BSO = Bilateral salpingo-oophorectomy, RRSO = Risk-reducing salpingo-oophorectomy, GC = genetic counseling, RRM=Risk-reducing mastectomy

[a]Patients with a BSO before study entry were removed from this analysis

[b]RRSO is a BSO that was performed for risk-reduction ONLY

[c]Patients with a bilateral mastectomy before study entry were removed from this analysis

[d]Cell count<5: Fisher's exact test

Table 4

Risk Perception

Aspects of Risk Perception	VUS N (%)	UN N (%)	p-value
Do you recall the BC risk we provided you?			
No	14 (26.4)	129 (22.5)	0.52
Yes	39 (73.6)	443 (77.5)	
What is your BC risk?			
Average/Moderate	33 (84.6)	398 (89.8)	0.31
High	6 (15.4)	45 (10.2)	
Do you recall the OC risk we provided you?			
No	21 (43.7)	220 (43.4)	0.96
Yes	27 (56.3)	287 (56.6)	
What is your OC risk?			
Average/Moderate	23 (85.2)	262 (91.3)	0.29[a]
High	4 (15.8)	25 (8.7)	

Abbreviations: BC = breast cancer, OC = ovarian cancer, VUS = variant of uncertain significance

[a]Cell count<5: Fisher's exact test

Table 5

Cancer Distress

Aspects of Cancer Distress	VUS N (%)	Uninformative Negatives N (%)	p-value
How often have thoughts of cancer concerned you?			
1 (Never, Rarely)	16 (23.5)	167 (24.6)	0.99
2 (Sometimes)	28 (41.2)	280 (41.2)	
3 (Often)	14 (20.6)	130 (19.1)	
4 (All the time)	10 (14.7)	103 (15.1)	
Did GC change the frequency of these thoughts?			
Yes	14 (23.0)	234 (35.8)	0.043
No	47 (77.0)	419 (64.2)	
If yes, did it increase or decrease?			
Increase	1 (8.3)	36 (16.9)	0.67[a]
Decrease	11 (91.7)	177 (83.1)	

[a]Cell count<5: Fisher's exact test

Table 6

Responses to the Genetic Counseling/Testing Process

Response to Genetic Counseling/Testing	VUS (N) %	UN (N) %	p-value
Was genetic counseling (GC) helpful to you?			
Yes	62 (92.5)	636(94.1)	0.61
No	5 (7.5)	40 (5.9)	
Among those who answered Yes[a]			
GC helped me have a better understanding of cancer genetics.	45 (72.6)	465 (73.1)	
GC helped me have a better understanding of my own/my family's risk.	43 (69.4)	486 (76.4)	
GC helped me understand how to reduce risk for cancer.	19 (30.6)	194 (30.5)	
GC helped me make decisions for medical care.	26 (41.9)	267 (42.0)	
GC was informative/educational.	44 (71.0)	433 (68.1)	
GC relieved my anxiety/stress/worry.	29 (46.8)	347 (54.5)	
Among those who answered No[a]			
GC caused anxiety/stress/worry.	2 (40.0)	4 (10.0)	
GC did not give me a better understanding of my own/my family's risk.	--	--	
GC did not help me to make decisions for medical care.	3 (60.0)	12 (30.0)	
GC did not provide me with any new knowledge.	5 (100.0)	10 (25.0)	
How do you feel about your decision to have genetic testing? (Likert scale)			
Extremely pleased	40 (60.6)	463 (69.0)	0.58
Somewhat pleased	17 (25.8)	128 (19.1)	
Neutral	6 (9.1)	50 (7.4)	
Somewhat displeased	1 (1.5)	10 (1.5)	
Extremely displeased	2 (3.0)	20 (3.0)	

Abbreviations: GC = Genetic counseling

[a]May not add up to 100% due to patients having the ability to select multiple options.