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Understanding of *BRCA1/2* genetic tests results: the importance of objective and subjective numeracy

Yaniv Hanoch[1]*, Talya Miron-Shatz[2], Jonathan J Rolison[3] and Elissa Ozanne[4]
[1]*University of Plymouth, Plymouth, UK*
[2]*Ono Academic College, Kiryat Ono, Israel*
[3]*Queen's University Belfast, Belfast, UK*
[4]*The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth, MA, USA*

**Correspondence to: School of Psychology, University of Plymouth, Cognition Institute, Drake Circus, Plymouth, Devon, PL4 8AA, UK. E-mail: yaniv.hanoch@gmail.com*

Abstract

***Background*: The majority of women (71%) who undergo *BRCA1/2* testing—designed to identify genetic mutations associated with increased risk of cancer—receive results that are termed 'ambiguous' or 'uninformative negative'. How women interpret these results and the association with numerical ability was examined.**

***Methods*: In this study, 477 women at increased risk for breast and ovarian cancer were recruited via the Cancer Genetics Network. They were presented with information about the four different possible *BRCA1/2* test results—positive, true negative, ambiguous and uninformative negative—and asked to indicate which of six options represents the best response. Participants were then asked which treatment options they thought a woman receiving the results should discuss with her doctor. Finally, participants completed measures of objective and subjective numeracy.**

***Results*: Almost all of the participants correctly interpreted the positive and negative *BRCA1/2* genetic test results. However, they encountered difficulties interpreting the uninformative and ambiguous *BRCA1/2* genetic test results. Participants were almost equally likely to think either that the woman had learned nothing from the test result or that she was as likely to develop cancer as the average woman. Highly numerate participants were more likely to correctly interpret inconclusive test results (ambiguous, OR = 1.62; 95% CI [1.28, 2.07]; $p < 0.001$; uninformative, OR = 1.40; 95% CI [1.10, 1.80]).**

***Discussion*: Given the medical and psychological ramifications of genetic testing, healthcare professionals should consider devoting extra effort to ensuring proper comprehension of ambiguous and uninformative negative test results by women.**

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Introduction

Mutations in the *BRCA1* or *BRCA2* gene have been linked to breast and ovarian cancers. Women who are tested for *BRCA1* or *BRCA2* have to grapple with their genetic test results, whether positive (the woman has inherited a known harmful mutation in *BRCA1/2*), true negative (the woman has not inherited the harmful mutation in *BRCA1/2*), ambiguous (the genetic test found alteration in *BRCA1/2* that has not previously linked to cancer), or uninformative negative (a person is the first person in their family to be tested, but no mutation was found via current *BRCA1/2* testing). How women interpret their genetic test results can impact a woman's decision to undergo prophylactic mastectomy [1] and their anxiety and distress levels [2].

Receiving positive or true negative results can help women decide about medical options, whether to inform relatives, and cope with the uncertainty of whether they will develop the disease [3]. Obtaining ambiguous or uninformative negative results, although useful in some circumstances, complicates risk communication and the decision-making process [4,5]. Given that 71% of women who undergo *BRCA1/2* testing receive ambiguous or uninformative negative test results [6], which do not generally lower a woman's projected risk to that of the average population, it is essential to gain a better understanding of how women interpret this kind of test result and to identify factors that might mitigate their understanding.

Positive and true negative test results are understood fairly well [7]. In contrast, inconclusive (i.e., ambiguous and uninformative negative) results have been rather poorly understood. Following a cohort of 30 women who had received inconclusive *BRCA1/2* test results, researchers [5] found that about a third believed that they were definitely not carriers of the gene mutation and about a quarter believed that they were mutation carriers with certainty. Similar results were obtained in another study [8], where, additionally, 52% of the women were uncertain about their carrier status. Others [1] have reported that women who receive unclassified and uninformative test

results tend to either underestimate or overestimate their cancer risk likelihood.

Dorval *et al*. [5] compared at-risk women who tested true negative with women who had received inconclusive test results: the latter reported elevated cancer risk perception, more anxiety, less reassurance by the test results and a diminished quality of life. Other investigations [2,9] revealed that receiving inconclusive test results is especially taxing for women who have difficulty coping with uncertainty. Along similar lines, researchers [9,10] compared women who received positive, true negative and uninformative test results with regard to their perception of being a carrier of a harmful gene mutation. Only the uninformative group were confused about their carrier status: some women perceived it to be 'certain', whereas others assumed it to be 'non-existent'.

What factors affect women's understanding of genetic test results? Researchers [11] have shown that at-risk women, including those who have undergone genetic testing, encounter difficulties in understanding their test results, even in cases when they accurately recall their test results [12]; and others [13–15] have found that cognitive process, communication style, emotions, personal experience and presentation format can affect risk comprehension. An additional factor that plays a role in women's better understanding of lifetime risk is numeracy—typically understood as the ability to understand basic mathematical concepts [16]. Indeed, a substantial body of literature illustrates the essential role numeracy plays in a wide spectrum of medical decision-making [17,18], such as undergoing mammography screening [16], genetic testing [19] and making informed decisions [20]. Low objective numeracy, in addition, has been linked to decreased health management abilities, worse health-related knowledge and inferior health outcomes across a spectrum of diseases [21–25]. Furthermore, it has been argued that numeracy is an independent factor from education or cognitive ability [18]. Despite these extensive findings, we are not aware of previous studies that have examined whether numeracy (objective or subjective) is associated with more accurate understanding of ambiguous and uninformative negative test results.

The present study was designed to test at-risk women's ability to interpret genetic test results and to examine the link between numeracy and accurate understanding. Information about *BRCA1/2* test results was taken from the website of the National Cancer Institute (NCI, USA; see http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA) and presented to at-risk women, as the NCI represents one of the most trusted, informative and accessible publically available resource on cancer.

A number of hypotheses guided our research. It was predicted that women would have little to no misunderstanding when interpreting positive and true negative test results but that they would exhibit greater confusion when encountering ambiguous and uninformative negative test results. Second, it was hypothesised that, compared with lower numeracy women, women with higher numeracy would be more accurate in their understanding of ambiguous and uninformative negative test results.

Methods

Participants

The study protocol was approved by the appropriate institutional review boards, and all participants provided informed consent. In this study, 1007 women were contacted via an email distributed by a local branch of the Cancer Genetics Network (CGN; Table 1) to complete an online survey. Four hundred and seventy-seven women (47% response rate) consented to participate in the study (http://www.cancergen.org/). The CGN maintains a registry of people interested in participating in research studies. Participation in the study was restricted to unaffected or cancer-free women at increased risk for breast cancer. Participants were women who had no prior history of breast cancer but were considered at increased risk [26] of developing breast cancer because of having at least one of the following: (1) at least one relative diagnosed with breast cancer at 45 years or younger, (2) two or more relatives diagnosed with breast cancer at 50 years or younger or (3) at least one relative diagnosed with ovarian cancer or male breast cancer. The CGN also provided us with a de-identified database that included information about participants' demographic, family and disease history data.

Procedure

Participants received an email from the CGN and were asked to complete an online survey about *BRCA1/2* test results, objective and subjective numeracy and demographic. All participants were offered a $30 gift card and were not required to answer any questions that made them uncomfortable.

Interpreting *BRCA1/2* test results

Participants were presented descriptions of four different possible *BRCA1/2* test results taken in 2012 from the NCI official website. The short descriptions provided information about the meaning of positive, true negative, ambiguous and uninformative negative *BRCA1/2* test results (Appendix A). Only for the scenario presenting a positive test result, participants were also asked, 'Which treatment options do you think she should discuss with her doctor?' Participants were instructed to choose as many options as they wished (Appendix A).

Objective and subjective numeracy

Respondents completed a three-item Objective Numeracy Scale [27], which examines individuals' capacity to answer

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Table 1. Demographic characteristics of participants ($N = 477$)

Characteristic	Value
Cancer genetics network site	
Duke University	40 (8.4%)
Emory University	25 (5.2%)
Johns Hopkins University	75 (15.7%)
MD Anderson Cancer Center	25 (5.2%)
University of North Carolina	26 (5.5%)
University of Utah	129 (27.0%)
University of Colorado	157 (32.9%)
Age (years)	
Mean (SD)	50.5 (7.4)
Range	30–61
Education	
High school or less	29 (6.1%)
Some college	106 (22.2%)
College graduate	342 (71.7%)
Marital status	
Not married or living together	107 (22.4%)
Married or living together	370 (77.6%)
Race	
Asian	3 (0.6%)
Black or African American	6 (1.3%)
White	455 (95.4%)
More than one race	5 (1.1 %)
Other	4 (0.8%)
Unknown or not reported	4 (0.8%)
Tested for *BRCA1/2* gene mutations	
No	39 (8.2%)
Yes	91 (19.1%)
Not reported	347 (72.7%)
Family member tested for *BRCA1/2* gene mutations	
No	132 (27.7%)
Yes	34 (7.1%)
Not reported	311 (65.2%)
Number of family members with ovarian or breast cancer	
One	107 (22.4%)
Two	97 (20.3 %)
Three	83 (17.4%)
Four	49 (10.3%)
Five	26 (5.5%)
Six	21 (4.4%)
Seven	12 (2.5%)
More than seven	15 (3.1%)
Not reported	67 (14.0%)
Objective numeracy (SD)[1]	1.76 (0.86)
Subjective numeracy (SD)	4.71 (0.84)

[1]Objective numeracy data were missing for eight participants.

basic probability and ratio problems. The Objective Numeracy Scale measure has been utilised in hundreds of studies, with different populations, in multiple medical decision-making domains, and its psychometric properties are well founded. Questions were scored as either correct (coded '1') or incorrect (coded '0'). Individual item responses and total number of correct were analysed. We combined the scores for the three questions and treated the overall numeracy scores as a continuous variable (range from 0 to 3) [28].

We also administered the Subjective Numeracy Scale (SNS) [29,30], a self-report measure that evaluates participants' perceived capacity to perform different mathematical problems and preference for numerical rather than prose information. The SNS has been validated in participants' samples of broad age and education ranges [31]. The SNS contains eight items, of which four require participants to evaluate their numerical ability in various settings and four require participants to indicate their preferences for the presentation of numerical information as numbers or prose. Each question was scored on a 6-point Likert-like scale, and the overall score was computed as the average rating across all eight questions (with one question reversed scored).

Analysis strategy

Logistic regression analyses were conducted on participants' understanding of the test results for harmful *BRCA1/2* gene mutations. The analyses were conducted on whether participants interpreted the result to mean 'she is as likely as the average woman to develop breast cancer' or 'she has learned nothing from the test result' and were conducted separately for uninformative negative and ambiguous test results. Missing responses ranged from 1 to 7 (of 477; 0.21–1.47% of the sample). None of the participants had more than 1 missing response. Education and marital status were included as categorical predictors, and age and overall objective numeracy scores and subjective numeracy ratings were included as continuous predictors. Objective and subjective numeracy were included in separate regression models because of a high correlation between objective and self-reported ability. The majority of responses were missing for items that identified whether women had been tested previously for *BRCA1/2* gene mutations (347/477; 72.7%) and whether they had a family member who had been tested previously for *BRCA1/2* gene mutations (311/477; 65.2%). For this reason, these factors were included as additional categorical predictors in a final regression block that controlled for age, education and marital status but did not include numeracy scores. The McNemar's test for repeated-measures nominal data was conducted to test for significant changes in participants' response as a function of screening test results.

Results

When asked to imagine a woman who had tested positive, the majority (98.3%) correctly interpreted that the woman was more likely than the average woman to develop cancer. Because very few participants interpreted the information incorrectly, we did not include them in the analysis. Given a positive test result for a harmful *BRCA1/2* gene mutation, most women recommended surveillance (93.1%) as a treatment option that should be discussed with a physician, followed by risk avoidance (80.9%), prophylactic surgery (59.1%) and chemoprevention (49.5%).

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When participants were asked to imagine a woman who had received a true negative result, most participants (91.6%) correctly interpreted that the woman was as likely as the average woman to develop cancer. A minority of participants incorrectly interpreted the scenario.

In contrast, participants' answers were not as uniform in the uninformative negative and ambiguous cases. First, in the uninformative negative scenario, a similar proportion of participants interpreted that the woman had learned nothing from the test result (44.8%) as those who incorrectly interpreted that she was as likely as the average woman to develop cancer (43.5%). Some participants thought the woman was more likely than the average woman to develop cancer (9.0%), and few participants incorrectly interpreted that the woman was less likely than the average woman to develop cancer (2.6%) or would not develop cancer (0.2%).

Our regression analysis for the uninformative test results revealed that education (some college vs. high school or less, OR = 0.98; 95% CI [0.40, 2.41]; $p = 0.965$; college graduate vs. high school or less, OR = 0.74; 95% CI [0.33, 1.70]; $p = 0.479$) and marital status (married or living together vs. not married or living together; OR = 0.87; 95% CI [0.54, 1.39]; $p = 0.560$) did not relate to participants' responses. Age was a marginally significant positive predictor of participant's interpreting that the woman was as likely as the average woman to develop cancer rather than that she had learned nothing from the test result (OR = 1.03; 95% CI [1.00, 1.05]; $p = 0.053$). Higher objective numeracy (OR = 1.40; 95% CI [1.10, 1.80]; $p = 0.007$), higher subjective numeracy (OR = 1.34; 95% CI [1.06, 1.71]; $p = 0.015$) and previous testing for the *BRCA1/2* gene mutations (OR = 4.21; 95% CI [1.13, 15.63]; $p = 0.032$), but not having a family member with a positive test result for *BRCA1/2* gene mutations (OR = 0.38; 95% CI [0.12, 1.19]; $p = 0.095$), were associated with a shift from interpreting that the woman was as likely as the average woman to develop cancer to interpreting that she had learned nothing from the test result.

Participants' responses when asked to imagine a woman who had received an ambiguous test result for the *BRCA1/2* gene mutations were also varied. A large proportion of participants believed that the woman had learned nothing from the test result (52.4%) or that the woman was as likely as the average woman to develop cancer (40.6%). Some participants correctly believed that the woman was more likely than the average woman to develop cancer (5.7%), and few participants interpreted the results as meaning the woman was less likely than the average woman to develop cancer (1.1%) or would definitely develop cancer (0.2%).

In our regression analysis, education (some college vs. high school or less, OR = 0.95; 95% CI [0.38, 2.36]; $p = 0.913$; college graduate vs. high school or less, OR = 0.68; 95% CI [0.29, 1.58]; $p = 0.372$) and marital status (married or living together vs. not married or living together; OR = 1.31; 95% CI [0.81, 2.14]; $p = 0.270$) were unrelated to participants' answers. Consistent with our previous analysis of an uninformative negative test result, when participants evaluated an ambiguous result, age predicted that participants would incorrectly interpret that the woman was as likely as the average woman to develop cancer rather than that she had learned nothing from the test result (OR = 1.03; 95% CI [1.01, 1.06]; $p = 0.019$). Higher objective numeracy (OR = 1.62; 95% CI [1.28, 2.07]; $p < 0.001$) and higher subjective numeracy (OR = 1.41; 95% CI [1.11, 1.78]; $p = 0.004$) were again associated with a shift towards a more accurate responses, that is, from interpreting that the woman was as likely as the average woman to develop cancer to interpreting that she had learned nothing from the result. Previous testing for *BRCA1* gene mutations (OR = 3.27; 95% CI [0.88, 12.20]; $p = 0.077$), but not having a family member with a positive test result for *BRCA1/2* gene mutations (OR = 0.51; 95% CI [0.16, 1.65]; $p = 0.264$), was a marginally significant predictor that participants would interpret that the woman had learned nothing from the result.

A majority of participants (69.8%) who responded to the statements regarding an uninformative negative test result and an ambiguous test result provided similar response for the two statements. Of the 141 participants who gave different answers for the two statements, a significantly larger proportion of participants changed their correct answer that a woman had learned nothing from an ambiguous test result to an incorrect response that she was as likely as the average woman to develop cancer following an uninformative negative test result (35.5%) than vice versa (15.6%; McNemar = 10.13, $p = 0.001$). Moreover, a significantly larger proportion of participants changed their incorrect response that a woman was as likely as the average woman to develop cancer following an ambiguous test result to a correct answer that she was more likely than the average woman to develop cancer following an uninformative negative test result (18.4%) than vice versa (8.5%; McNemar = 4.45, $p = 0.035$).

Discussion

As the majority of women who undergo *BRCA1/2* testing receive results that are termed 'ambiguous' or 'uninformative negative', they are faced with the question, what do my *BRCA1/2* genetic test results mean? Women, as our results reveal, demonstrate solid understanding of positive and true negative test results, as the vast majority provided the correct answer.

Understanding of ambiguous or uninformative negative test results turned out to be more challenging. When faced with uninformative negative results, about half thought a woman facing such results would learn nothing from them, and a similar proportion thought that such a woman

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would have a similar probability of developing cancer to that of the average woman. Yet this test result does not generally lower a women's projected risk to that of the average population. Consequently, as much as half of women who receive an uninformative negative result may falsely believe that their cancer risk has reduced. When faced with ambiguous results, a similar picture emerged: slightly more than half of our sample thought that the results were not informative, close to 40% assumed that such a woman would have a similar probability of developing cancer to that of the average woman, and a minority believed that such a woman would face a greater probability of developing cancer.

Our results, along with those of others [4,7,32,33], further highlight the increased complexity associated with obtaining ambiguous or uninformative negative test results. Leaving the consultation room with better comprehension could help reduce a patient's psychological distress [34] and improve long-term quality of life [35]. Practitioners should ensure that women accurately understand the meaning of their test results and to verify that (mis)understanding does not cloud the decision to inform relatives or their ability to convey the information to relatives [6] or affect their treatment decisions [36]. Genetic counsellors and clinicians should be aware that an inability to reduce uncertainty levels—one of the main motivations to undergo genetic testing in the first place—is a key factor in women's stress [34].

Our data revealed that objective numeracy, subjective numeracy and being previously tested were associated with better interpretation of inconclusive genetic test results. Our results, thus, reveal a link between high levels of objective and subjective numeracy and the ability to interpret ambiguous or uninformative negative test results.

Two additional factors could help explain our results with regard to understanding of uninformative and ambiguous results. Confusion could stem from the lack of consistency and validity in professionals' communication of DNA test results [37]. It is also feasible that counselees' tendency to transform objective risk information into personally relevant information [15] has hampered their understanding. Patients' particular difficulties understanding uninformative and ambiguous test results could be the result of their inability to assign personal meaning to these results.

Our current study has some limitations. Joining the CGN is voluntary, which could have biassed the study population [26]. Participants, although geographically diverse, were largely well-educated White women. As such, our sample might not be representative of a more diverse population that includes minority groups. A more representative sample may have generated a different set of results, as minorities and less educated people might experience greater difficulties understanding medically related information. Furthermore, close to 20% of the women in our sample reported having had genetic counselling and were more familiar with the test results and their meaning (some of the 72% who did not respond may also have had counselling). Our findings lend support to this idea, as prior personal experience of genetic testing, but not through family member, was associated with more accurate interpretations. However, we caution against drawing strong conclusions from these findings as the majority of participants did not identify whether they (or a family member) had been previously tested.

Our study presented participants with a short description of genetic test results taken from the NCI Web page. Participants were unable to ask questions or receive clarification. In contrast, in genetic counselling sessions, there is room for more extensive dialogue. For example, in the uninformative negative and the ambiguous test results, we assumed the correct response to be 'learned nothing from the test result' and 'more likely than the average woman to develop cancer', respectively. These statements, however, are unlikely to represent the entire consultation process. Furthermore, knowing that one might not be a carrier of *BRCA1/2* mutations can be helpful as one learns that one may actually be true negative (if another family member would subsequently test positive), which would put them at no more than an average risk. It is important that further research compares our results with ones that emerge during or after the genetic counselling experience. It is also important to acknowledge that women deciding whether to undergo genetic testing may not have more information than that presented to our sample as direct-to-consumer testing becomes more available.

As the NCI website provides information about available cancer treatments (surveillance, prophylactic surgery, risk avoidance and chemoprevention), this study also probed women's willingness to discuss treatment options with their physician. The majority of our participants stated that hypothetical woman would be interested, primarily, in exploring less aggressive options, such as surveillance (93.1%) and risk avoidance (80.9%). At the same time, close to 60% of our sample indicated that they would discuss prophylactic surgery (59.1%) and almost half (49.5%) chemoprevention. These findings are especially important for attending clinicians who should be cognizant that women may prefer to explore more moderate options first but are also willing and interested in discussing more aggressive options. This point might be important given the Food and Drug Administration (FDA) warning letter to 23andME (39), indicating that the company was marketing their genetic test without proper clearance or approval. In fact, the FDA letter specifically addressed direct-to-consumer marketing of *BRCA1/2* test, highlighting the link between difficulties understanding the result and the important treatment decisions that are made on the basis of this test.

Genetic testing is rapidly increasing in prevalence, and more companies now offer it directly to consumers.

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Indeed, genetic testing is playing a greater and more vital role in women's decisions about their health behaviour, treatments decisions, communication with family members and quality of life. Ensuring that women fully grasp the nature of their genetic test results, especially when the majority of the testing results are ambiguous or uninformative negative, is paramount. This might be especially the case for women low in numeracy, who, as our study illustrates, can experience greater difficulties in making sense of their ambiguous or uninformative negative test results.

Appendix A

Participants were then asked, 'Imagine a woman who tested positive (true negative, ambiguous and uninformative negative) for a harmful mutation in the *BRCA1*/*BRCA2* genes. Based on the information below, how likely is she to develop cancer?' They were provided with six possible options and asked to identify the answer that was most applicable to the scenario: (1) she has learned nothing from the test result, (2) she will not develop breast cancer, (3) she is less likely than the average woman to develop breast cancer, (4) she is as likely as the average woman to develop breast cancer, (5) she is more likely than the average woman to develop breast cancer and (6) she will definitely develop breast cancer.

For the scenario that presented a positive test result, participants were also asked, 'Which treatment options do you think she should discuss with her doctor?' This time, however, participants were instructed to choose as many options as they wished. The four treatment options and their meaning were, again, taken from the same NCI website and presented in the order in which they appear on the website. The options were as follows:

(1) Surveillance—cancer screening or a way of detecting the disease early. Screening does not, however, change the risk of developing cancer. The goal is to find cancer early, when it may be more treatable.
(2) Prophylactic surgery—this type of surgery involves removing as much of the 'at-risk' tissue as possible in order to reduce the chance of developing cancer.
(3) Risk avoidance—certain behaviours have been associated with increased breast and ovarian cancer risk. These include not using alcohol or hormone replacement therapy, maintaining a healthy weight and physical activity.
(4) Chemoprevention—this approach involves the use of natural or synthetic substances to reduce the risk of developing cancer or to reduce the chance that cancer will come back.

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