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Distress among Women Receiving Uninformative *BRCA1/2* Results: 12-month Outcomes

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Abstract

Objective—Few data are available regarding the long-term psychological impact of uninformative *BRCA1/2* test results. This study examines change in distress from pretesting to 12-months post-disclosure, with medical, family history, and psychological variables, such as pretesting perceived risk of carrying a deleterious mutation prior to testing and primary and secondary appraisals, as predictors.

Methods—209 women with uninformative *BRCA1/2* test results completed questionnaires at pretesting and 1-, 6-, and 12-months post-disclosure, including measures of anxiety and depression, cancer-specific and genetic testing distress. We used a mixed models approach to predict change in post-disclosure distress.

Results—Distress declined from pretesting to 1-month post-disclosure, but remained stable thereafter. Primary appraisals predicted all types of distress at 1-month post-disclosure. Primary and secondary appraisals predicted genetic testing distress at 1-month as well as change over time. Receiving a variant of uncertain clinical significance (VUCS) and entering testing with a high expectation for carrying a deleterious mutation predicted genetic testing distress that persisted through the year after testing.

Conclusions—As a whole, women receiving uninformative *BRCA1/2* test results are a resilient group. For some women, distress experienced in the month after testing does not dissipate. Variables, such as heightened pretesting perceived risk and cognitive appraisals, predict greater likelihood for sustained distress in this group and could be amenable to intervention.

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BRCA1/BRCA2 (*BRCA1/2*) gene testing increasingly has become part of routine clinical care for high-risk women. Mutations in *BRCA1/2* confer a 40–66% lifetime risk of developing breast cancer, with up to a 52% lifetime risk of developing a new, contralateral breast cancer, and a 13–46% risk of ovarian cancer [1,2]. *BRCA1/2* testing typically begins with a breast and/or ovarian cancer-affected individual (proband). Testing then is offered to family members if a risk-conferring mutation is detected. However, uninformative test results, in which a deleterious mutation is neither identified nor definitively ruled out, are possible and indeed, quite common [3,4]. Three distinct reasons for an uninformative result include: 1) not detecting a mutation in an affected individual from a high-risk family after fully sequencing the *BRCA1/2* genes (*BRCA1/2* negative); 2) not detecting a mutation in an affected high-risk individual of Ashkenazi Jewish descent after targeted testing for three common founder mutations responsible for the majority of cases in this population (Ashkenazi Panel negative) [5–9]; and 3) detecting a genetic variant of uncertain clinical significance (VUCS).

Research examining distress among women seeking *BRCA1/2* testing has focused on three primary outcomes: situation-specific distress, including cancer-related distress [10] and less commonly, genetic testing-related distress [11], as well as global anxiety and depressive symptoms [12]. Distress generally is heightened pre-testing. This dissipates somewhat after receipt of uninformative *BRCA1/2* test results, reaching levels that are higher than those of women receiving true negative test results and comparable to or slightly lower than those of mutation carriers [3,13–16]. Although the impact of modest ongoing distress in this population is unclear, moderately heightened distress predicts subsequent rates of contralateral prophylactic mastectomy in mutation carriers [17] and "over-adherence" to BSE and CBE among women with strong family histories of breast cancer [18].

In this report, we use Baum, Friedman and Zakowski's [19] adaptation of the Transactional Model of Stress and Coping [20] as a guiding framework to examine predictors of distress. Briefly, the Transactional Model states that when people experience a stressor, they evaluate the relevance of the situation (primary appraisal) and their coping resources (secondary appraisal), implement coping strategies, and experience an emotional outcome. Baum and colleagues propose that these appraisals and overall adjustment to genetic testing is determined by: 1) test result and related uncertainty, 2) personal and family history of disease, 3) risk-reduction and disease management options, and 4) individual differences.

Test Result and Uncertainty

As noted, three types of uninformative *BRCA1/2* test results include: *BRCA1/2* negative, Ashkenazi Panel negative and a VUCS. The latter result indicates that a sequence alteration was detected, but whether this variation is deleterious or a benign polymorphism is unknown, making the associated risk highly variable and difficult to assess [21]. The increased uncertainty associated with receiving a VUCS may result in heightened distress, though previous studies utilizing very small samples have found no effect [3,22].

Personal and Family History of Disease

Residual risk estimates for women receiving uninformative *BRCA1/2* test results are highly variable and dependent primarily upon personal and family cancer history. Cancer-affected women report higher levels of cancer-related distress than unaffected women, as do those with higher pedigree-based risk [14] and those diagnosed more recently [15]. These clinical features also predict how likely women with uninformative *BRCA1/2* test results believe they are to carry a deleterious mutation [3], potentially impacting long-term outcomes. Research has not examined whether other risk-conferring variables impact distress [23].

Risk Reduction and Disease Management Options

Women at high risk for breast and/or ovarian cancer can manage their cancer risk through risk-reducing surgery [24] and enhanced screening [25]. While specific screening guidelines exist for mutation carriers, no established guidelines exist for women who receive uninformative *BRCA1/2* test results [26]. In addition to uncertainty regarding future risk-management decisions, the impact of having had prophylactic mastectomy *prior* to receiving uninformative *BRCA1/2* test results is unclear [14], potentially resulting in regret or relief from having to make further risk-management decisions [27].

Individual Difference Factors

Individual differences, such as sociodemographics, personality, and cognitive appraisals may predict distress. According to our guiding conceptual model, appraisals regarding the stressfulness of genetic testing (primary appraisals) and perceived coping ability (secondary appraisals) should predict adjustment. Carriers report stronger primary appraisals than other groups post-testing, as do those with higher trait anxiety [28], but we do not know whether appraisals predict emotional outcomes. Further, younger women, those who retain heightened post-testing perceived breast cancer risk, and those reporting discomfort when confronting uncertain information report greater post-testing distress [15].

Using a mixed models approach, we examined medical and psychological predictors of post-disclosure distress during the year after receiving uninformative *BRCA1/2* test results. We predicted that distress would be highest pretesting, decrease considerably in the month post-disclosure, decreasing slightly thereafter [13–15]. Predictors of heightened and sustained distress would include 1) variables suggestive of higher residual cancer risk (family history of ovarian cancer, 2+ family members with breast cancer, no previous risk-reducing surgery); 2) variables associated with heightened uncertainty (not having made a cancer risk-management decision, receiving a VUCS result, higher perceived likelihood of carrying a mutation at pretesting); 3) demographics previously associated with heightened distress (younger age); and 4) psychological variables (stronger primary and weaker secondary appraisals, perceived risk of carrying a deleterious mutation).

Methods

Participants

Participants were 214 female probands who received uninformative *BRCA1/2* test results through the clinical research genetic counseling programs at one of three sites [Lombardi Comprehensive Cancer Center (Washington DC), Ruttenberg Cancer Center (New York, NY), or Englewood Hospital (NJ)] from April 2001-June 2003. Eligible probands had a personal history of either breast or ovarian cancer and a family cancer history resulting in approximately ≥10% prior probability of having a *BRCA1/2* mutation. Five women with uninformative *BRCA1/2* test results were excluded due to missing data (final N=209); 89% completed four assessments, 8% completed three assessments, and 3% completed two assessments. A strength of multilevel modeling is its ability to handle unbalanced data of this type [29].

Procedure

Measures were completed at pretesting and one, six, and 12-months post-disclosure. As part of a larger intervention trial designed to encourage informed decision making among mutation carriers, trained research assistants determined eligibility. Eligible participants completed a structured interview and were offered an appointment with a genetic counselor.

All participants received standard genetic counseling (details described elsewhere [13]). Each participant received her test result at a genetic counseling disclosure session during which the counselor discussed test result implications and cancer risk management options. The genetic counselor provided a qualitative estimate of residual risk for breast/ovarian cancer that was based on test results and the individual's personal/family history of breast and ovarian cancer, confirmed via medical records whenever possible. Given this was a high-risk population, surveillance recommendations were consistent with recommendations for high-risk individuals [26]. A summary letter outlined all guidelines and recommendations. Participants could discontinue their participation at any time.

Measures: Predictor Variables

Sociodemographics—Participants provided demographic information at pretesting including age, race, education, marital and employment status, and income. Men were not included due to our inclusion of risk management decisions in our analyses.

Medical—Participants provided self-report information regarding personal and family cancer history. Participants also were asked, "Have you made a final decision about how to manage your breast cancer risk?" Although some women may perceive themselves to have made a final decision, they may face future risk-management decisions. Consequently, decision status is a psychological indicator, not an objective behavioral endpoint.

Perceived likelihood of carrying a deleterious mutation—Participants rated their pretesting perceived risk for carrying a deleterious mutation on a 4-point scale (*not at all likely-very likely*) [30].

Appraisals—The 10-item genetic testing appraisal measure [28] assesses primary and secondary appraisals related to the receipt of genetic test results on a 4-point scale (*not at all-very*) at the 1-month assessment. Primary appraisals (α=.81) assess the stressfulness of cancer risk, risk-reduction efforts, and family communication regarding genetic testing results. Secondary appraisals (α=.64) assess confidence in dealing with these issues.

Genetic test result—Participants included probands for whom no mutation was detected after full sequencing of the *BRCA1* and *BRCA2* genes (*BRCA1/2 negative),* Ashkenazi Jewish women for whom a mutation was not detected in targeted testing for the three Ashkenazi Jewish founder mutations (*Ashkenazi panel negative)* [5–7], and women receiving a VUCS result.

Measures: Outcome Variables

Anxiety and depression—We used 12 items of the Brief Symptom Inventory (BSI) [12] to assess anxiety and depressive symptoms at each timepoint (α=.89–.91). The original BSI uses a 5-point response scale; we used a modified 4-point scale (*not at all-extremely*), indicating the discomfort caused during the past two weeks. Scales were summed due to large correlations (rs≥.70, ps<.001).

Cancer-specific distress—The 15-item Impact of Event Scale (IES) [10] was used to measure cancer-specific distress at each timepoint (α=.87–.90), indicating intrusive and avoidant thoughts/behaviors associated with a trauma/stressor (in this case, the experience of familial cancer). Items are scored on a 4-point scale (*not at all-often*), indicating how frequently each thought/behavior occurred during the past week.

Genetic testing distress—We used the Multidimensional Impact of Cancer Risk Assessment Questionnaire (MICRA) [11] to assess post-disclosure genetic testing distress. The MICRA contains 25 items on a 4-point scale (*not at all-often*) measuring specific responses to the receipt of genetic test results, including three factors (Distress, Uncertainty, Positive Experiences), combined as a total score. It has demonstrated adequate reliability previously [15,31,32]. However, in this study, the Positive Experiences factor did not converge with other factors at the six and 12-month timepoints, lowering reliability. Therefore, we excluded this factor in our analysis; remaining scale reliability was adequate (.80–.85).

Data Analysis

We developed multilevel models using Hierarchical Linear Modeling (HLM) for Windows (full maximum likelihood estimation) in order to analyze our hierarchically structured data (assessments nested within participants). Level 1 analyses estimate each individual's unique initial status and rate of change for each outcome. Level 2 analyses, modeled simultaneously, enable examination of between-person predictors of average initial status and rate of change (*fixed effects*) as well as variation around average initial status and rate of change (*random effects*). We examined post-disclosure trajectories of distress, with "initial status" referring to the 1-month post-disclosure assessment (Time was coded 0, 1, 2 corresponding to post-disclosure timepoints), controlling for scores at pretesting.

After examining descriptive statistics, including variable distributions, we tested multilevel models to investigate post-disclosure trajectories for each outcome. We specified an unconditional growth model (to examine the extent and direction of mean individual change over time) followed by a conditional growth model (in which predictors explain fixed and random variation [33]). Non-significant effects were dropped to yield parsimonious final models. All continuous predictors were grand mean centered to facilitate interpretation [29]. To protect against inflated Type I error, we used partial Bonferroni correction. Taking into account the three outcomes and mean intercorrelations=.50, the adjusted significance level was .029 [34]. Sample sizes are sufficient to find effect sizes of .04, .11 and .06 for anxiety and depression, cancer-specific and genetic testing distress, respectively, with a power of 99%.

Results

Descriptive Statistics

Descriptive statistics appear in Tables 1 and 2. Participants had been affected with only breast cancer (89%), only ovarian cancer (7%), or both (4%) and were the first member of their family to seek *BRCA1/2* testing. Average age at diagnosis was 46.3 (*SD*=8.9, range 27–71). Diagnosis occurred, on average, just under 7 years before assessment (*M*=6.8, *SD*=7.9). Forty-three percent of participants received *BRCA1/2* negative results, 48% received Ashkenazi panel negative results, and 9% received VUCS results. Five percent had a bilateral mastectomy for treatment of breast cancer prior to enrolling in the study, 12% reported having a prophylactic mastectomy prior to enrolling, and another 1% reported having a prophylactic mastectomy between pretesting and 1-month post-disclosure. Nineteen percent had oophorectomy prior to enrollment, and one woman had the surgery between pretesting and 1-month post-disclosure. Having prophylactic surgery postdisclosure was not significantly associated with test result.

Outcome measures were highly intercorrelated (*p*s<.001). Primary and secondary appraisals were negatively correlated (r=−.37, p<.001): Women who rated genetic testing as more stressful felt less confident as well. Item means indicated that participants had stronger

primary and weaker secondary appraisals when considering how to deal with their cancer risk (1.80, 3.41, respectively) and their personal cancer risk-management decisions (1.64, 3.51, respectively) than for communicating with their family about their test result (1.30, 3.69, respectively) or dealing with the impact of the test result on their family (1.32, 3.68, respectively). Not surprisingly, women who had undergone a prior bilateral prophylactic mastectomy were most likely to report that they had reached a final breast cancer management decision ($p<.01$).

Anxiety and Depression

Anxiety and depression declined significantly from pretesting to 1-month post-disclosure ($t(206)=3.99$, $p<.001$), but not significantly thereafter (Table 2). This pattern described women who received *BRCA1/2* negative results and Ashkenazi panel negative results better than those who received VUCS results, whose anxiety and depression stayed stable pretesting through 6-months post-disclosure and then decreased from 6- to 12-months post-disclosure ($t(17)=2.88$, $p=.01$). Women who received VUCS results had higher anxiety and depression at the 1- and 6-months post-disclosure assessments than other women (ps=.01–.07).

The unconditional growth model revealed significant fixed, $\gamma=16.36$, $t(208)=41.50$, $p<.001$, and random, $\tau_{00}=23.97$, $\chi^2(201)=750.39$, $p<.001$, effects for initial status. Thus, anxiety and depression were significantly greater than zero at the 1-month post-disclosure assessment, and women varied significantly at 1-month. The fixed, $\gamma=-.19$, $t(208)=-1.20$, $p=.23$, and random, $\tau_{11}=.24$, $\chi^2(201)=204.49$, $p=.42$, effects for rate of change from 1- to 12-months post-disclosure were non-significant, indicating flat trajectories. Consequently, we tested rate of change as a fixed effect in the conditional growth model, allowing us to examine potential moderators of longitudinal change.

The final conditional growth model for anxiety and depression (Table 3) indicated that higher pretesting anxiety and depression predicted higher 1-month post-disclosure anxiety and depression $\gamma=.60$, $t(203)=7.57$, $p<.001$, as did stronger primary appraisals, $\gamma=1.65$, $t(203)=3.53$, $p=.001$. The effects of primary appraisals remained stable throughout the year following disclosure.

Pretesting anxiety and depression, $\gamma=-.09$, $t(583)=-2.80$, $p=.01$, and ethnicity, $\gamma=.92$, $t(583)=2.29$, $p=.02$, predicted post-disclosure rate of change. We probed these interactions by graphing trajectories of predicted scores. Women with lower pretesting anxiety and depression demonstrated an increase in these across time, though at each assessment, their scores were lower than the scores of women with higher pretesting anxiety and depression. Furthermore, although White women were slightly less distressed than non-White women at 1-month post-disclosure, their distress increased over the post-disclosure period until they were slightly more distressed than non-White participants by 12-months post-disclosure. The final model explained 67% of the between-person variance at 1-month post-disclosure.

Cancer-Specific Distress

Overall, cancer-specific distress declined significantly from pretesting to 1-month post-disclosure, $t(205)=6.55$, $p<.001$, but did not change significantly thereafter (Table 2). This pattern described women who received all types of genetic test results, although this decline was only marginally significant for women who received VUCS results. The unconditional growth model revealed a significant fixed effect for initial status, $\gamma=13.07$, $t(208)=14.19$, $p<.001$; however, the fixed effect for rate of change was non-significant, $\gamma=-.48$, $t(208)=-1.17$, $p=.24$. The random effects for both initial status, $\tau_{00}=133.81$, $\chi^2(201)=774.70$, $p<.001$, and rate of change, $\tau_{11}=7.16$, $\chi^2(201)=254.64$, $p=.006$, were significant.

The final conditional growth model (Table 3) revealed that higher pretesting cancer-specific distress predicted higher distress 1-month post-disclosure, γ=.43, t(205)=9.89, p<.001, while older age predicted lower cancer-specific distress at 1-month post-disclosure, γ=−.21, t(205)=−3.25, p=.002. Stronger primary appraisals predicted higher distress 1-month after testing, γ=6.20, t(205)=5.86, p<.001. The only variable to interact with time was age: younger women reported greater cancer-specific distress at 1-month post-disclosure, though their distress declined over time. By 12-months post-disclosure, there were no age differences. The final model explained 71% of the between-person variance at 1-month post-disclosure and 16% of the variance in between-person post-disclosure rate of change.

Genetic Testing Distress

Genetic testing distress was not measured at pretesting. Overall, mean post-disclosure genetic testing distress decreased from 1- to 6-months post-disclosure, t(194)=3.53, p=.001; the decline between 6- and 12-months post-disclosure was not significant, t(176)=1.95, p=.053 (Table 2). This pattern described women who received *BRCA1/2* negative results and Ashkenazi panel negative results (although the decline from 1- to 6-months post-disclosure was only marginally significant for the latter group), but not those who received VUCS results; genetic testing distress stayed stable from 1- to 6-months post-disclosure (t(17)=1.52, p=.15) and then decreased somewhat from 6- to 12-months post-disclosure (t(16)=1.93, p=.07). Women who received a VUCS had higher genetic testing distress than women in the other groups at all assessments (ps=<.001–.05).

The unconditional growth model revealed significant fixed effects for initial status, γ=8.11, t(208)=12.45, p<.001, and rate of change, γ=−1.59, t(208)=−5.47, p<.001. The random effect for initial status was significant, τ_{00}=63.85, χ^2(201)=727.62, p<.001, reflecting significant individual variation around the mean at 1-month post-disclosure. However, the random effect for rate of change was non-significant, τ_{11}=2.26, χ^2(201)=231.83, p=.07, suggesting no significant individual variation around the mean for rate of change over time. Rate of change was tested as a fixed effect in the conditional growth model.

The final conditional growth model revealed several significant effects (Table 3). First, women's genetic test results predicted genetic testing distress at 1-month post-disclosure: Women who received an uninformative *BRCA1/2* negative test result, γ=−4.65, t(203)=−2.47, p=.01, or an Ashkenazi panel negative test result, γ=−4.46, t(203)=−2.41, p=.02, reported significantly lower distress at 1-month post-disclosure than women receiving a VUCS, such that adjusted distress scores for those who received a VUCS result were approximately half a standard deviation higher than other women. Test results did not predict rate of change, indicating that these differences persisted throughout the year post-disclosure. Second, women who had higher pretesting perceived risk for carrying a deleterious mutation reported higher genetic testing distress at 1-month post-disclosure, γ=1.25, t(203)=2.47, p=.02; this effect did not vary over time. Third, women with stronger primary appraisal scores reported significantly higher genetic testing distress at 1-month post-disclosure, γ=7.10, t(203)=5.84, p<.001, and those with stronger secondary appraisal scores reported significantly lower genetic testing distress at 1-month post-disclosure, γ=−6.40, t(203)=−5.46, p<.001, each moderated by significant interactions with rate of change: Although women with stronger primary appraisal and weaker secondary appraisal scores at 1-month post-disclosure reported greater distress at that timepoint, their scores declined more steeply over time. Yet, at 12-months post-disclosure, their genetic testing distress remained higher than those with weaker primary appraisal and stronger secondary appraisal. Notably, having made a final cancer risk-management decision did not predict genetic testing distress, nor did any demographic, medical, or family history characteristics. The final model explained 61% of the between-person variance at 1-month post-disclosure.

Discussion

We examined the impact of receiving uninformative *BRCA1/2* test results on trajectories of psychological adjustment, as assessed by measures of cancer-related and genetic testing distress, as well as anxiety and depressive symptoms, in the year following testing. Generally, distress declined significantly from pretesting to 1-month post-disclosure, but remained stable thereafter. Rates of distress are comparable to those found in previous studies and, similar to these studies [13,14], our results suggest that as a group, our participants report modest distress. Likewise, post-testing decreases in distress appear to be clinically significant. For example, using IES criteria [10], 59 (28%) participants were in the medium category for symptomatology at pretesting, while 90 (43%) were in the high category. This decreased to 39 (19%) and 64 (31%), respectively, at 1-month and 40 (19%) and 50 (24%), respectively, at 12-months.

Our results also suggest that some women report elevated distress after testing that does not dissipate. Furthermore, certain testing-related variables predict greater likelihood for sustained genetic testing-related distress, underscoring the importance of identifying those who might be particularly vulnerable to ongoing, situation-specific distress and providing additional resources. Based on appraisal item means, participants reported greater difficulty dealing with their cancer risk and their personal cancer risk management decisions than communicating with their family about their test result or dealing with the impact of the test result on their family, perhaps because uninformative results are shared less frequently with family members than mutation-positive results [35]. Decision support materials could be developed to address the risk management strategies available to these women in order to facilitate the coping process. Most intervention research of this kind has focused on mutation carriers [35–37]. The fact that appraisals were most strongly predictive of genetic testing distress suggests that interventions should address issues specific to that form of distress as opposed to global distress.

A number of variables predicted distress in the month following disclosure. In particular, primary appraisals predicted all three types of distress at 1-month post-disclosure. Primary and secondary appraisals predicted genetic testing distress at 1-month as well as change over time. Appraisals have differentiated *BRCA1/2* carriers from those receiving other results [28], and our results suggest that they also predict adjustment among women with uninformative *BRCA1/2* test results. Although women who perceived greater stress surrounding genetic testing and who felt less confident about coping with genetic testing issues reported elevated genetic testing distress 1-month after disclosure of their test results, their genetic testing distress also declined more steeply over time. These results might suggest that these women demonstrate improved adaptation and coping over time, though this must be examined further.

With the exception of age and primary appraisals, no variables predicted cancer-specific distress other than pretesting distress, as found previously [13,15,38,39]. This complements other studies that report limited post-testing differences in cancer-specific distress among affected women [13,31]. While this adds to questions about the sensitivity of measures of cancer-specific distress among affected women [31,40], it also suggests that providers need not be unduly concerned about offering cancer survivors *BRCA1/2* testing [38]. Varying trajectories emerged for anxiety and depression based on race, though our sample's ethnic homogeneity tempers this finding. In contrast, several variables predicted genetic testing distress, highlighting the importance of measuring relevant constructs. Women with VUCS results reported higher, and more sustained, genetic testing distress than women with other uninformative *BRCA1/2* test results immediately after testing. This finding conflicts with previous studies that found no such differences [22]. This may be due to the substantially

larger sample size in our study, as well as measurement of genetic testing distress, which the previous study did not assess.

Pretesting perceived risk for carrying a deleterious mutation also predicted genetic testing distress; those who entered the study with higher, sustained perceived risk reported higher genetic testing distress. This result may suggest that, for various reasons, these women did not fully adjust their post-testing perceived risk [41]. Alternatively, these women may continue to interpret the uncertainty around their risk status in a more negative light; perhaps due to personal and family histories conferring greater risk, they may continue to believe that they carry an undetected mutation.

Several predictors did not reach significance, most notably, family cancer history, risk-management decision status, and most demographic and medical variables. Because women with a more extensive family history are counseled that they remain at elevated risk following an uninformative *BRCA1/2* test result, we expected to see higher levels of distress within this group, replicating previous studies [14]. This difference may be explained by our inclusion of only cancer-affected women and our high risk sample; the previous report included affected and unaffected women. These factors may have affected other null findings.

This study has several limitations. First, all participants received free genetic services and likely differ from those receiving testing in true clinical settings. Likewise, not all women who receive testing in a clinical setting would have the strong family history or other criteria needed to meet our recruitment guidelines. These women may react differently to the receipt of an uninformative result, especially a VUCS result than our sample. A better understanding of the experience of this growing group of women is an important area of future study. Second, most participants were White, college educated, employed, and affluent. Although these demographics are similar to other studies of this type, they are not representative of more diverse groups who might begin to utilize these tests in coming years as they become more commonly integrated into clinical care [42] and used to inform treatment decisions [43]. It is increasingly important to seek representative samples [44,45]. Further, our sample consisted only of cancer-affected women who, on average, received their diagnosis several years prior. Unaffected women report lower levels of distress [14] and may have different predictors of distress, as might women who are newly diagnosed with cancer. Third, although our sample of women who received a VUCS result was larger than that of previous studies, these women still represent a small percentage of our sample. This, in combination with the varied interpretation of VUCS results, makes it difficult for us to learn more about this group and specifically, to further examine patterns of distress. Fourth, our measure of perceived risk was measured by one item and only at pretesting, limiting our ability to further examine this potentially important construct. Finally, our measure of residual risk was relatively crude. Increasingly, patients who receive uninformative *BRCA1/2* test results are counseled regarding their residual risk using qualitative and quantitative approaches. It is possible that had we better characterized residual risk, we might have observed the predicted associations between residual risk and distress outcomes. Despite these limitations, this study contributes to the growing understanding of the impact of receiving uninformative *BRCA1/2* test results and highlights several clinical and theoretical issues requiring further exploration.

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Table 1

Descriptive statistics for predictors

Variable	*n*	*M(SD)*
Medical and Family History		
Personal cancer history		
Breast	186	
Ovarian	15	
Breast/Ovarian	8	
Family cancer history (first- and second-degree relatives)		
Breast (≥2)	100	
Ovarian (≥1)	37	
Genetic test result		
BRCA1/2 negative	89	
Ashkenazi panel negative	101	
VUCS	19	
Mastectomy history		
Bilateral treatment mastectomy	10	
Prophylactic mastectomy	27	
Oophorectomy history	40	
Made final risk-management decision	156	
Perceived likelihood of carrying mutation[1]		2.26(.71)
Psychological		
Primary appraisals[1]		1.51(.60)
Secondary appraisals[1]		3.64(.46)

Note:

[1]Range=1–4

Table 2

Descriptive statistics for distress outcomes

		----------Post-disclosure----------		
Variable	**Pretesting**	**1-month**	**6-months**	**12-months**
Anxiety+depression[1,c]				
M	17.76_a	16.43_b	16.00_b	16.05_b
SD	6.08	5.90	5.42	5.24
N	207	209	194	190
Cancer-specific distress[2,d]				
M	18.63_a	13.09_b	12.26_b	11.80_b
SD	14.58	13.75	13.21	13.16
N	206	209	195	191
Genetic testing distress[3,e]				
M		8.30_a	6.13_b	5.14_b
SD		9.91	8.48	7.33
N		209	195	184

Note:

[1]Range=12–48;

[2]Range=0–75;

[3]Means are for two of three factors on the MICRA (range=0–75).

Means in the same row with different subscripts are significantly different ($p<.05$).

Table 3

Final Multilevel Models Predicting Post-Disclosure Distress

		Anxiety and Depression	Cancer-Specific Distress	Genetic Testing Distress
Fixed Effects		**Coefficient (*SE*)**	**Coefficient (*SE*)**	**Coefficient (*SE*)**
Mean initial status (π_{0i})	Intercept	6.85(1.38)***	13.05(.63)***	12.25(1.79)***
	Pre-disclosure score	.60(.08)***	.43(.05)***	
	White ethnicity	−1.08(1.06)*		
	Age		−.21(.06)***	
	Married			
	Treatment bilateral mastectomy			
	Prophylactic mastectomy			
	Uninformative *BRCA* negative (vs. VUCS)			−4.65(1.88)*
	Ashkenazi panel negative (vs. VUCS)			−4.46(1.85)*
	Perceived risk for positive result			1.25(.51)*
	Primary appraisal	1.65(.47)**	6.20(1.44)***	7.10(1.22)***
	Secondary appraisal			−6.40(1.17)***
Mean rate of change (π_{1i})	Intercept	.52(.57)	−.47(.40)	−1.60(.27)***
	Pre-disclosure score x Time	−.09(.03)**		
	Age x Time		.10(.04)*	
	White ethnicity x Time	.92(.40)*		
	Prophylactic mastectomy x Time			
	Primary appraisal x Time			−1.71(.68)*
	Secondary appraisal x Time			1.83(.64)**

Random Effects	**Parameter**	**Variance**	**Variance**	**Variance**
Initial status	(τ_{00})	6.46***	39.35***	16.89***
Rate of change	(τ_{11})		6.03*	
Within person[a]	(σ^2)	10.12	51.08	29.93

* $p<.029$ (adjusted p-value).

** $p<.01$.

*** $p<.001$.

[a] Test of significance undefined for this parameter