Familial Context of Genetic Testing for Cancer Susceptibility: Moderating Effect of Siblings' Test Results on Psychological Distress One to Two Weeks after *BRCA1* Mutation Testing[1]

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Abstract

Objectives. To determine whether psychological distress differs among individuals tested for a *BRCA1* mutation and is moderated by the pattern of their siblings' test results.

Materials and Methods. Participants in this study are members of a large kindred identified with a *BRCA1* mutation. Subjects included 87 males and 125 females who completed a baseline interview, were tested for a *BRCA1* gene mutation, received their results in person from a genetic counselor, completed a follow-up interview 1–2 weeks after the receipt of their test results, and had complete data on all variables used in the analysis. The main outcome of the study was psychological distress as measured by the Impact of Event Scale during the 1–2 week follow-up interview. Data were analyzed based on multiple regression.

Results. Male carriers, relative to noncarriers, experienced significantly more distress if they were the first tested than when all of their tested siblings were already known to be negative. Noncarrier males whose siblings all tested positive also encountered significant test-related distress. The largest adverse psychological consequences for female carriers, relative to noncarriers, were for those who were tested first and those whose tested siblings were noncarriers.

Conclusions. The familial context in which genetic testing is conducted may be important for understanding how individuals react to their own test results.

Introduction

A growing number of investigations have examined the effects of genetic testing on psychological well-being (1–5). The research design and analysis strategies adopted in these studies have been fairly uniform. An individual's psychological health, assessed before counseling, and the receipt of genetic testing results, are compared with his or her psychological health after counseling and testing. Changes in psychological response among carriers and noncarriers are then compared. Changes in distress or anxiety associated with the receipt of test results can then be reasonably attributed to an individual's test result.

Potentially important factors that may alter the context in which results are received and interpreted involve both the timing and results of testing for other family members and whether other relatives are tested at all (6). The psychological effects of chronic and eventful stress have been shown to vary with the social and familial context in which they occur (7–13). Although a growing number of studies have investigated the association between family factors and the effects of being diagnosed with cancer (14–16), few studies have examined how the impact of genetic testing for disease susceptibility for individuals depends on the characteristics of their families (6, 17–18). Some investigators have considered how family history of cancer is shared among relatives (19) and how women with a family history of breast cancer may share hypothetical genetic testing information with other family members (Ref. 20; see also Ref. 21).

With the growing use of gene sequencing and direct mutation testing, such as those involving *BRCA1* and *BRCA2* (22), it is possible for an individual to be the only person in his/her family to be tested. More often, a person is one of several family members tested, either simultaneously or in sequence (*e.g.,* an affected parent is tested first, and then the children, should the parent test positive). Both clinical experiences and the familial nature of genetic testing strongly suggest that tested persons do not contemplate their own test results in isolation but instead evaluate their results vis-à-vis the testing experiences and results of their relatives. Overall, previous studies examining the psychological sequelae of genetic testing have attached primary significance to the role played by the receipt of genetic test results at the individual level, while giving far less attention to issues related to social characteristics of tested families of which these individuals are a part.

The purpose of this study is to determine whether an individual's psychological reaction to genetic test results for a *BRCA1* gene mutation is affected by the familial context in which test results are provided. We focus on the patterns of *BRCA1* mutation test results among all members of adult sibships who undergo testing from a large kindred. The risks of breast and/or ovarian cancer among *BRCA1* mutation carriers are being reevaluated (23). However, the cumulative risk of breast and ovarian cancer by age 70 among female *BRCA1* mutation carriers in the kindred analyzed in this paper is approximately 58 and 67%, respectively; the combined risk of either cancer by age 70 is 88% (24). Men may be carriers and, like women, pass on a genetic risk to their children. Now that testing for *BRCA1* gene mutations is available commercially, it is important to consider both individual and familial factors affecting the psychological response of individuals who test either positive or negative for this mutation.

In this report, we address four specific research questions: (*a*) does the distress experienced by persons who test positive for the

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BRCA1 mutation differ if other siblings are also known to have tested positive or negative? Mutation carriers whose siblings all test positive may experience either a "collective" adverse reaction or they may be comforted to know that they will not be alone as gene carriers. Conversely, those who test positive but whose siblings are not gene mutation carriers may feel resentful toward or isolated from others in the family; (*b*) does the potential relief experienced by persons who test negative change if some siblings are known to be gene carriers? This question addresses the possibility that a form of "survivor guilt" may be felt among individuals testing negative; (*c*) is there a psychological penalty paid by persons who test positive for the *BRCA1* mutation when they are the first (and possibly only) person to receive test results in their sibship? and (*d*) do individuals respond differently when their sisters, as opposed to their brothers, test positive? Because the presence of a *BRCA1* mutation will affect women primarily [recognizing a possible elevated risk of colon and prostate cancer for male gene carriers (25–27)], it is reasonable to anticipate that for a given sibling, male or female, having sisters who are carriers will have a larger impact than having carrier brothers.

Materials and Methods

Subjects

Details of the study protocol have been published elsewhere (28) but are summarized here. Subjects in this study are part of a large, on-going, longitudinal investigation of the psychosocial and behavioral effects of *BRCA1* mutation testing. All participants in the larger main study are members of Kindred 2082 (K2082), the largest known kindred identified with a *BRCA1* mutation (29). The specific *BRCA1* mutation in this kindred creates a stop codon at codon 1313 (22). More than 750 living adult members of K2082 have been identified. Adult kindred members were invited to participate in the study, including persons affected with breast or ovarian cancer. Adult members of K2082 who are ineligible for the study are those who are not competent to consent to participate in the study, based on an evaluation by family and genetic counselors and a psychiatrist, or those who are unable to attend two in-person genetic counseling sessions at the University of Utah.

Most kindred members live in Utah and Idaho and are members of the Church of Jesus Christ of Latter-day Saints (Mormons). Members of K2082 are primarily Caucasian and of northern European descent.

Data Collection

Kindred members age 18 or older were invited by letter to participate in a study that provided an opportunity for free genetic counseling and testing for a *BRCA1* gene mutation. The letters asked if the individual either wanted to participate, wanted more information, or did not wish to be contacted again. Persons who declined our invitation to participate were not contacted further. Those who agreed to be subjects were sent an informed consent document to read, sign, and return. Some subjects chose to be interviewed but not to be tested for the *BRCA1* mutation. The informed consent procedure and the overall design of the project were approved by two Institutional Review Boards at the University of Utah, as well as by staff of the National Cancer Institute and the Ethical, Legal, and Social Implications branch of the National Human Genome Research Institute.

Our recruitment strategy was designed to limit the possibility of testing adult children prior to their at-risk parent. Therefore, the protocol staged recruitment within a lineage from the oldest to the youngest. Adult siblings were recruited without regard to their age (*i.e.*, older siblings were just as likely to be recruited first as younger siblings). Each subject was asked about other living adult blood relatives and asked for their permission to recruit these relatives into the study. This allowed us to recruit previously unknown kindred members and maximized our chances of including all known living kindred members. If individuals declined to participate, their children were not contacted (unless the parent provided consent) to prevent parents from obtaining unwanted genetic information based on their children's results, especially without the benefits of informed consent and genetic counseling.

Once subjects provided written informed consent to participate, trained interviewers in a centralized and supervised facility scheduled and administered a baseline questionnaire using computer-assisted interviewing software. After the baseline questionnaire was completed, subjects who still wished to be tested received extensive pre- and post-test family and genetic counseling with a genetic as well as a marriage/family counselor. After the first genetic counseling (pre-testing) session, subjects had blood drawn for DNA analysis by the DNA Diagnostic Laboratory at the University of Utah. Results were then provided to participants at a post-test counseling session if subjects still elected to receive their results. One to 2 weeks later, participants were contacted for the first follow-up interview. Additional questionnaires were administered at various points in time up to 2 years after the receipt of test results, although data from these later surveys are not used here.

Contact letters and response forms were mailed to 759 potential subjects. Five-hundred of these individuals received full information about the project by telephone. Subjects who did not receive full project information ($n = 259$) did so because they refused to participate in the study at the time of the initial invitation to the study ($n = 124$) or project staff were unable to reach them (after repeated attempts) after the initial contact letter had been sent ($n = 135$). In comparing available information about both nonparticipants and participants, we found that nonparticipants were more likely to be young (<35), to have parents who had already tested negative, or to not have a family cancer history. On the basis of these differences, we infer that nonparticipants largely viewed the study as being less important or less relevant because they had lower perceived levels of cancer susceptibility compared with participants.

Of the 500 subjects, 81.6% ($n = 408$) completed the baseline interview, 59.2% ($n = 296$) also completed the first genetic counseling session, and 54% ($n = 269$) had blood drawn for the purposes of mutation testing. The uptake rate of 54% is similar to that reported by Lerman *et al.* (4) in a similar study. Thus, 91% (269 of 296) of the subjects who received genetic counseling decided to be tested for the mutation. Of the 269 who had completed the baseline interview and had their blood drawn, 88% ($n = 238$) received their test results in person from a genetic counselor, and 86% ($n = 230$) completed the follow-up interview 1–2 weeks after the receipt of their test results. Of these 230 subjects, 92% ($n = 212$) were tested for a *BRCA1* gene mutation, received their results from a genetic counselor, completed the 1–2 week follow-up interview, and had complete data on all relevant variables. These 212 subjects comprise the sample used in this analysis.

Measures

Measure of Psychological Response: Test-related Distress. The IES[4] (30) is a 15-item scale that measures an individual's

[4] The abbreviation used is: IES, Impact of Event Scale.

level of event-related distress and was administered as part of the 1–2-week follow-up interview. This measure was used to evaluate responses to the receipt of genetic test results and therefore was not administered during the baseline interview. The IES yields a total score comprised of Intrusion and Avoidance subscores. For the sample data used here, the IES scale at the 1–2 week interview showed high internal consistency with a Cronbach's α of 0.88 (.89 for females and .84 for males). The Intrusion and Avoidance subscales have a simple Pearson correlation coefficient of 0.64 ($P < .01$).

Test-related Independent Variables: Patterns of Individual and Sibship *BRCA1* Mutation Test Results. Subjects received their test results from a genetic counselor and completed the interview given at 1–2 weeks. At the time of the interview, some subjects were among several siblings who had received their test results, whereas others learned of their carrier status before their siblings learned theirs. A few subjects were either only children or the only member of their sibship who elected to be tested.

Two different measures of test results were used:

(*a*) We constructed separate measures for subjects and their siblings' test results. For subjects, the variable CARRIER equals one if they were carriers and zero if they were noncarriers. For siblings, they were grouped into one of four categories at the time of the subject's 1–2-week interview: all siblings tested positive (POS), all tested negative (NEG), there were both positive and negative results (MIX), or no other siblings had received their their test results (NULL). For the NULL group, only 2 of 23 men and 2 of 56 women were the only siblings tested within their sibship. Nearly all subjects in the NULL group were the first to be tested, whereas their siblings were in earlier stages of the protocol.

The main effects of these variables were estimated, as well as the interactions between them. Testing for interactions between personal and sibling test result variables allowed us to consider whether persons identified as carriers had different responses to their test result depending on their siblings' pattern of results.

(*b*) We constructed an eight-category typology that classified all subjects in terms of the joint pattern of their results and their siblings' results. Subjects who tested positive for the *BRCA1* mutation fell into four groups, determined at the time of the subject's 1–2-week interview:

1. All of their tested siblings tested positive (POSPOS, $n = 17$);
2. All of their tested siblings included those who tested positive and negative (POSMIX, $n = 17$);
3. All of their tested siblings tested negative (POSNEG, $n = 13$);
4. No other siblings had yet received results (POSNUL, $n = 29$).

Similarly, subjects who tested negative for the *BRCA1* mutation also fell into four groups, determined at the time of the subject's 1–2-week interview:

1. All of their tested siblings tested positive (NEGPOS, $n = 21$);
2. All of their tested siblings included those testing positive and negative (NEGMIX, $n = 17$);
3. All of their tested siblings tested negative (NEGNEG, $n = 50$);
4. No other siblings had yet received results (NEGNUL, $n = 48$).

Seven dummy variables were constructed for use in multiple regressions. The eighth category, NEGNEG, served as the reference group. This measurement approach differs from the interaction approach in that it allows us to rank subjects across all eight categories to determine which combination of test results posed the greatest psychological risk to subjects.

Measures of the Social and Medical Context in Which Test Results Are Provided

Subjects received their test results in a potentially wide range of personal and social contexts. We considered several variables that may confound the relationship between sibship-specific patterns of test results and psychological morbidity. All variables were measured during the baseline interview. These variables include initial level of State Anxiety as measured by the 20-item State Anxiety scale of the State-Trait Anxiety Inventory Form X (31), age in years, total number of living brothers and sisters (all ages, including both participants and nonparticipants), measures of social integration [marital status, number of close friends, whether a devout member of the Church of Jesus Christ of Latter-day Saints (Mormons)], education in years, and medical history (personal history with cancer or cancer-related surgeries, whether knew that a tested parent was a carrier, whether parent from K2082 died from breast, ovarian, or colon cancer). In our study sample, the 20-item State Anxiety scale at baseline had high internal consistency, with a Cronbach's α of 0.92.

Statistical Methods

Ordinary least squares regression equations are used to estimate all of the models stratified by sex. The regressions take one of four forms (confounder variables are included in the model but are not shown here for simplicity):

Main Effects Model without Sibling Results:

$$(1)\ IES = a0 + (a1 \times CARRIER) + e$$

Main Effects Model with Sibling Results:

$$(2)\ IES = b0 + (b1 \times CARRIER) + (b2 \times ALLPOS) + (b3 \times MIX) + (b4 \times NULL) + e$$

Interaction Effects Model:

$$(3)\ IES = c0 + (c1 \times CARRIER) + (c2 \times ALLPOS) + (c3 \times MIX) + (c4 \times NULL) + (c5 \times (CARRIER \times ALLPOS)) + (c6 \times (CARRIER \times MIX)) + (c7 \times (CARRIER \times NULL)) + e$$

Rank-of-Effects Model:

$$(4)\ IES = d0 + (d1 \times POSPOS) + (d2 \times POSNEG) + (d3 \times POSMIX) + (d4 \times POSNUL) + (d5 \times NEGPOS) + (d6 \times NEGMIX) + (d7 \times NEGNUL) + e$$

For each of these models, IES is the dependent variable, test results are the independent variables, regression coefficients are designated by *a*, *b*, *c*, or *d*, and the residual term is denoted by *e*. All models are estimated, stratified by sex. Measures of the siblings' results are also analyzed by sex. This means that instead of considering all siblings, we measure the pattern of sibling test results for either sisters only or brothers only. This approach allows us to assess whether an individual's psychological reaction, after learning their carrier status, de-

Table 1 Means and SD of distress, personal and sibling test results, and confounder variables, by sex

	Men ($n = 87$)		Women ($n = 125$)	
	Mean	SD	Mean	SD
IES (1–2-week follow-up)	8.95	9.21	13.30	12.56
State Anxiety Scale (baseline)	29.41	7.79	33.16	10.33
% *BRCA1* mutation carrier	33.30	47.40	37.60	48.63
Siblings results by subject's 1–2-week interview				
% all carriers (POS)	14.94	35.86	20.00	40.16
% carriers and noncarriers (MIX)	21.84	41.55	12.00	32.63
% all noncarriers (NEG)	36.78	48.22	23.20	42.21
% none tested (NULL)	26.44	44.36	44.80	49.93
Variables measured at baseline				
Age in years	46.32	16.72	46.14	13.98
Total number of living siblings	4.36	2.06	4.54	2.01
Education in years	14.47	2.10	13.60	1.89
% devout Mormon	85.06	35.86	88.00	32.63
% married	89.66	30.63	82.40	38.24
% ever diagnosed with cancer or had cancer-related surgery	20.69	40.74	34.40	47.70
Number of friends	4.95	0.43	4.78	0.92
% knew parents were carriers	14.94	35.86	10.40	30.65
% K2082 parent died of breast, ovarian, or colon cancer	34.48	47.81	31.20	46.52

pends upon their entire sibships' pattern of results or whether it varies by the gender of their siblings.

Results

Sex-specific means and SD for all variables used in the analysis are listed in Table 1. Approximately one in three subjects were carriers for the *BRCA1* gene mutation. Over 60% of subjects had siblings who had not yet received their results (or opted not be tested) or had tested negative by the time of the subjects' 1–2-week interview.

Main and Interaction Effects Models. Results from the main effects and interaction regression models are reported for males and females in Tables 2 and 3, respectively. Starting with the main effects models among males (models A–D), we found that carrier status, by itself, had little impact on their 1-week, test-related distress as measured by the IES. Comparisons of R^2 (goodness-of-fit) between the main effects and interaction models suggested that the interaction models performed better with the exception of the brother-only model. The best fitting model was the interaction model that considered all siblings (model G). Results from this model showed that relative to a noncarrier, a carrier male experienced more distress if he was the first sibling tested than when all of his siblings tested negative (CARRIER × NULL; $P < 0.10$). Noncarrier men whose siblings tested positive also reported more distress than noncarriers whose siblings all tested negative (POS, $P < .10$). This effect appears to be largely a function of carrier sisters than carrier brothers. The results of model G for men are summarized in Fig. 1, where the adjusted IES scores were generated by evaluating the covariates at their mean values.

For women (Table 3), the adverse effect of being a carrier *versus* a noncarrier on test-related distress was significant (models A–D). This effect was somewhat larger when the results of all siblings were considered (model D). Similar to the analysis of males, the best-fitting model was an interaction model that considered all siblings (model G). There were two important interactions in Model G. The undesirable effects of testing positive (relative to testing negative) were attenuated when tested siblings were all positive (CARRIER × POS; $P < 0.10$) and when siblings had mixed results (CARRIER × MIX; $P < 0.01$). These findings strongly suggest that the largest adverse consequences for carrier women were among those whose tested siblings were noncarriers. The lack of a significant interaction between CARRIER and NULL indicated that carrier women who were the first to receive their results had elevated levels of distress comparable with carrier women whose siblings tested negative. The results of model G for women are summarized in Fig. 2.

Rank-of-Effects Models. The purpose of rank-of-effects models was not to conduct formal tests of significance for interaction effects but rather to identify patterns of test results among individuals and their siblings that pose the greatest psychological risk to tested persons. To accomplish this, we used the eight-category typology described earlier and compared the average levels of distress among seven test-result categories to the low-risk reference group (subject and tested siblings were all noncarriers). These comparisons could be derived from the interaction models shown in Tables 2 and 3 except that for rank-of-effect models, the tests of significance now refer specifically to comparisons between a given test-result category and the low-risk reference category (NEGNEG).

Relative to those who were noncarriers and whose siblings were also noncarriers, a man who tested positive and was the first sibling tested (POSNUL) experienced the largest psychological risk after learning his test result (Table 4). Men who tested negative but whose siblings all tested positive (NEGPOS) also encountered significant albeit somewhat weaker test-related distress (*i.e.*, consistent with survivors' guilt). This response pattern was also observed when sibships were restricted to sisters but not brothers.

For women, distress was greatest among those who learned that they were carriers, although there was variation among these women. Specifically, carrier women whose siblings all tested negative (POSNEG) or whose siblings had not yet been tested (POSNUL) experienced the greatest levels of test-related distress. For both sets of women, there may have been a sense that they were alone in their experience or they were isolated to some degree from their siblings. For women in sibships where everyone was a carrier (POSPOS), elevated distress was also observed but to a lesser degree.

Discussion

Our understanding of the potential family and social implications engendered by the development of genetic testing technology will only come when genetic screening for cancer susceptibility becomes more widely available. Studies of high-risk families, such as those in the kindred studied here, provide an opportunity to preview how genetic testing results may affect individuals within a familial context.

We are aware of only a few studies that explicitly examined how siblings might affect an individual's reaction to their genetic test results. Given the small number of participants, we consider the findings from these studies to be more anecdotal than compelling. In studies that have examined the effects of testing negative for Huntington's disease, researchers have found that some noncarriers report that gene-positive or untested siblings are hostile or resentful of noncarriers (32, 33), and that expected relief was short-lived and soon replaced by depression, emotional numbness, and feelings similar to survivor's guilt (34, 35). Tibben *et al.* (36) examined the reactions of nine noncarriers in their study of 18 individuals who were tested for the *HD* gene. They found that six of the nine noncarriers, upon receipt of results, avoided contact

Table 2 Males: Main effects model with and without sibling results and an interaction model

Dependent variable is IES measured 1–2 weeks after receipt of test results. Entries are unstandardized ordinary least squares regression coefficients ($n = 87$). All models control for initial level of State Anxiety, age (in years), total number of living brothers and sisters, marital status, number of close friends, whether a devout member of the Church of Jesus Christ of Latter-day Saints (Mormons), education (in years), personal history with cancer or cancer-related surgeries, knew that tested parent is a carrier, and whether parent from K2082 died from breast, ovarian, or colon cancer.

Test result	A. Main effects without sibling results	Main effects with sibling results			Interaction model		
		B. Brothers only	C. Sisters only	D. All siblings	E. Brothers only	F. Sisters only	G. All siblings
Subject tested positive (CARRIER)	2.19	2.30	2.21	2.34	−0.95	−1.50	−0.01
Sibling results							
All positive (POS)		0.54	3.49	3.98	0.84	5.95	6.13[a]
Mixture of positive and negative (MIX)		−2.77	0.62	−1.19	−3.84	0.47	−0.98
None yet tested (NULL)		−0.36	2.25	3.67	−1.47	−1.11	−0.57
Interactions							
CARRIER × POS					−0.66	−4.65	−5.97
CARRIER × MIX					4.83	0.66	−0.23
CARRIER × NULL					4.34	10.40[a]	10.25[a]
R^2	0.19	0.20	0.21	0.23	0.21	0.29	0.30
P for changes in R^2 (models being compared)		$P > 0.05$ (B *vs.* A)	$P > 0.05$ (C *vs.* A)	$P > 0.05$ (D *vs.* A)	$P > 0.05$ (E *vs.* B)	$P < 0.05$ (F *vs.* C)	$P < 0.05$ (G *vs.* D)

[a] $P < 0.10$.

Table 3 Females: Main effects model with and without sibling results and an interaction model

Dependent Variable is IES Measured 1–2 weeks after receipt of test results. Entries are unstandardized ordinary least squares regression coefficients ($n = 125$). All models control for initial level of State Anxiety, age (in years), total number of living brothers and sisters, marital status, number of close friends, whether a devout member of the Church of Jesus Christ of Latter-day Saints (Mormons), education (in years), personal history with cancer or cancer-related surgeries, knew that tested parent is a carrier, and whether parent from K2082 died from breast, ovarian, or colon cancer.

Test result	A. Main effects without sibling results	Main effects with sibling results			Interaction model		
		B. Brothers only	C. Sisters only	D. All siblings	E. Brothers only	F. Sisters only	G. All siblings
Subject tested positive (CARRIER)	10.20[a]	11.11[a]	11.21[a]	12.27[a]	3.11	17.54[a]	20.21[a]
Sibling results							
All positive (POS)		1.20	−3.36	−1.21	3.74	3.38	3.20
Mixture of positive and negative (MIX)		−9.76	−6.10	−9.45[b]	−3.81	3.40	1.92
None yet tested (NULL)		5.58[c]	0.61	1.62	3.13	1.60	2.23
Interactions							
CARRIER × POS					−4.52	−14.56[c]	−13.33[c]
CARRIER × MIX						−18.55	−22.94[a]
CARRIER × NULL					10.35	−4.01	−4.97
R^2	0.32	0.37	0.34	0.38	0.41	0.37	0.44
P for changes in R^2 (models being compared)		$P < 0.05$ (B *vs.* A)	$P > 0.05$ (C *vs.* A)	$P < 0.05$ (D *vs.* A)	$P > 0.05$ (E *vs.* B)	$P > 0.05$ (F *vs.* C)	$P < 0.05$ (G *vs.* D)

[a] $P < 0.01$.
[b] $P < 0.05$.
[c] $P < 0.10$.

with siblings. Two of the noncarriers had not told their siblings about their results because they did not want their siblings to feel pressured to also be tested, although it was not clear whether untested siblings learned about the status of their noncarrier siblings from others in the family. All noncarriers experienced feelings toward their affected or at-risk siblings similar to survivor's guilt and felt an obligation to be continuously available to these relatives for support.

This study is the first to report the short-term psychological effects of *BRCA1* testing among tested family members. Our results suggest that individuals' immediate reaction to test results varies by the results of their siblings, although this association varies by gender. We found that carrier men who received their results first and noncarrier men whose siblings all tested positive experienced adverse short-term psychological reactions. For women, we support an earlier finding that carrier women experienced elevated distress shortly after receiving their test results (2) but extend these findings by showing that women who learned their positive carrier status first report the highest levels of distress.

Had we ignored the familial context in which testing was done, we would have reached different conclusions than those reported here. For men, ignoring their siblings' test results would have led us to conclude that men in general did not experience significant distress if they were carriers. We found that female carriers have higher levels of distress compared with female noncarriers when siblings' results are not considered; however, female carriers with no carrier siblings have a remarkably high level of psychological distress, to the point

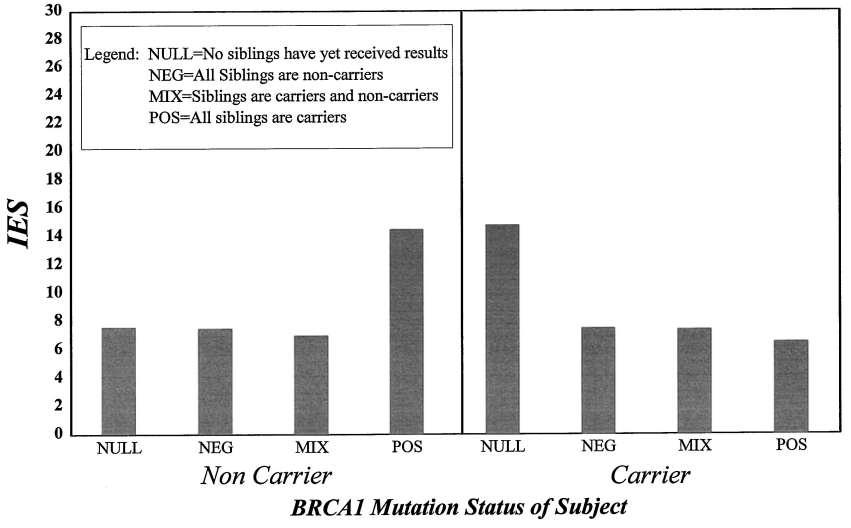

Fig. 1. Differences in distress (IES) 1–2 weeks after receipt of test results by carrier status and sibling results: males.

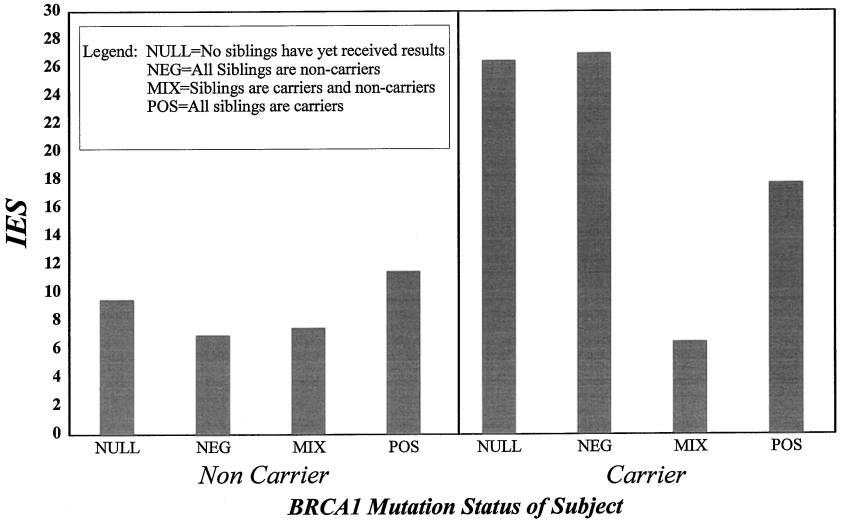

Fig. 2. Differences in distress (IES) 1–2 weeks after receipt of test results by carrier status and sibling results: females.

that their mean IES scores exceeded the mean scores reported for cancer patients 10 weeks after their diagnosis (37).

Two important questions regarding the linkage between siblings were also considered: (*a*) does it matter whether an individual has no siblings? Our sample included only one person who was an only child. Excluding this person from the analysis made no difference in the results, although this question requires further study; and (*b*) a second issue concerns our participants' awareness of their siblings' test results. When a sibling receives their test results, will others in the sibship know about it? For those who test first, we know that they could not have heard about their siblings' results because the information did not exist. Awareness of test results among tested siblings is generally the rule. Although our survey instruments contain explicit questions about direct communications between siblings with respect to sharing test results, it does not fully track all of the possible paths by which test results might be communicated among family members. We know from our data that reports of direct exchanges between siblings are an important and large component of family communication, but they provide an underestimate of such conversations because some siblings hear about their siblings' test results indirectly from other family members. Open-ended comments from respondents given at various points in the interview indicate that many subjects hear of a sibling's test result indirectly from other family members. (Solicited and unsolicited comments are captured at the time they are made. For example, if we were asking about age and the person instead chose to discuss at that point the fact that a sister was a carrier, we documented that information.) Despite the possibility that direct communications between siblings may not reflect the full flow of information about test results, we repeated the analysis by restricting the analysis to those who had heard directly from three or more family members, at least two of which were tested siblings. This restriction provides a large enough sample comprising those who received test result information directly from tested siblings. If we add to this subsample those in the NULL group, we obtain a sample of 50 men and 87 women. The pattern and significance levels of the effects reported in Table 4 were largely replicated. The only meaningful difference between these results and those reported earlier was for carrier women whose siblings all tested negative; only one woman was in this category, and her

Table 4 Rank-of-effects models for males and females

Entries are differences in IES scores for each pattern of *BRCA1* mutation test results compared to a noncarrier group (subject tests negative, all siblings test negative). All models control for initial level of State Anxiety, age (in years), total number of living brothers and sisters, marital status, number of close friends, whether a devout member of the Church of Jesus Christ of Latter-day Saints (Mormons), education (in years), personal history with cancer or cancer-related surgeries, knew that tested parent is a carrier, and whether parent from K2082 died from breast, ovarian, or colon cancer.

Pattern of test results Subject/Siblings		Males (87)[a]	Females (125)[a]
All siblings			
Positive/All positive	(POSPOS)	0.15 (5)	10.08[b] (12)
Positive/Mixed	(POSMIX)	−1.22 (7)	−0.08 (10)
Positive/All negative	(POSNEG)	−0.01 (7)	20.21[b] (6)
Positive/None tested	(POSNUL)	9.68[c] (10)	17.48[b] (19)
Negative/All positive	(NEGPOS)	6.13[d] (8)	3.20 (13)
Negative/Mixed	(NEGMIX)	−0.98 (12)	1.92 (5)
Negative/None tested	(NEGNUL)	−0.57 (13)	2.24 (37)
Negative/Negative	(NEGNEG)	0.0 (25)	0.0 (23)
Sisters only			
Positive/All positive	(POSPOS)	−0.21 (6)	6.36[d] (15)
Positive/Mixed	(POSMIX)	−0.37 (3)	2.39 (3)
Positive/All negative	(POSNEG)	−1.50 (7)	17.54[b] (6)
Positive/None tested	(POSNUL)	7.79[c] (13)	15.13[b] (23)
Negative/All positive	(NEGPOS)	5.95 (8)	3.38 (10)
Negative/Mixed	(NEGMIX)	0.47 (5)	3.40 (2)
Negative/None tested	(NEGNUL)	−1.11 (22)	1.60 (44)
Negative/Negative	(NEGNEG)	0.0 (23)	0.0 (22)
Brothers only			
Positive/All positive	(POSPOS)	−0.76 (3)	2.32 (4)
Positive/Mixed	(POSMIX)	0.04 (2)	−0.71 (4)
Positive/All negative	(POSNEG)	−0.95 (4)	3.11 (3)
Positive/None tested	(POSNUL)	1.92 (20)	16.59[b] (36)
Negative/All positive	(NEGPOS)	0.84 (6)	3.74 (7)
Negative/Mixed	(NEGMIX)	−3.84 (5)	–(0)
Negative/None tested	(NEGNUL)	−1.47 (31)	3.13 (60)
Negative/Negative	(NEGNEG)	0.0 (16)	0.0 (11)

[a] Numbers in parentheses are sample sizes.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] $P < 0.10$.

elevated distress levels were no longer statistically significant. The similarity of these findings with the larger sample suggests that individuals are largely aware of the test results of their siblings.

We also collected extensive information during the baseline interview about social networks within the family. We used two questions to select those siblings who reported that they stay in touch with at least two-thirds of their living brothers and sisters either by phone or in-person and who "talk to each other about your problems (when) you have difficult times in your lives." When the analysis was repeated with this subset (58 males, 94 females) of closely communicating siblings, we found once again comparable patterns of psychological reaction to those reported based on the larger sample.

Changes in family dynamics before and after testing need to be investigated further to help us better understand why we detected the patterns of distress reported here. We are beginning several analyses of the processes that may explain our findings: (*a*) it is possible that siblings' reaction to their own results may play an important role in the process. For example, two men might each have a sister who tests positive for a *BRCA1* mutation. One sister might experience a dramatic adverse reaction to her test result, whereas the second sister does not. In such a case, it may the sister's reaction to her own results rather than the test results *per se* that might explain how and why her brother responds to his own test results; (*b*) sibling relationships are quite variable, with some siblings being closer to each other than others. Individuals with siblings with whom they feel emotionally close may react more strongly when they learn of their test results compared with their reaction when they hear the results of more distant siblings; (*c*) adult sibling ties are generally strong but are not immutable (38, 39). We have little understanding about changes that may arise in sibling relationships attributable to experiences related to genetic testing. Such changes may unfold over a period of time longer than we have considered in this study; (*d*) sibling results are an important element of an individual's family, but certainly carrier status of other relatives may also play a role. Although we have considered information about an individual's parents in this analysis, we intend to extend these analyses to other close relatives who have been tested; (*e*) the study relies on a single, albeit very large, kindred whose members are members of a religious minority. The family interaction patterns exhibited in our sample should be compared with other families and social groups, should they be provided similar opportunities for genetic testing; and (*f*) the familial patterns of results communication measured in this study were based on a large number of survey questions, and yet more detail may still be necessary to capture all of the needed complexity regarding this phenome-

non. We hope to join others in addressing further the methodological challenges of collecting this type of information.

It is important to emphasize that the patterns of psychological distress reported here were observed within the context of a research-based genetic testing protocol. Accordingly, subjects were provided thorough informed consent and extensive genetic and family counseling at no cost. Future investigators should anticipate how psychological consequences and family dynamics may change when genetic testing is conducted in other settings, where individuals do not have access to such counseling services.

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References

1. Codori, A-M., and Brandt, J. Psychological costs and benefits of predictive testing for Huntington's disease. Am. J. Med. Genet., *54:* 174–184, 1994.

2. Croyle, R. T., Smith, K. R., Botkin, J. R., Baty, B., and Nash, J. Psychological responses to *BRCA1* mutation testing: preliminary findings. Health Psychol., *16:* 63–72, 1997.

3. Croyle, R. T., and Lerman, C. Psychological impact of genetic testing. *In:* R. T. Croyle (ed.), Psychosocial Effects of Screening for Disease Prevention and Detection, pp 11–38. New York: Oxford University Press, 1995.

4. Lerman, C., Narod, S., Schulman, K., Hughes, C., Gomez-Caminero, A., Bonney, G., Gold, K., Trock, B., Main, D., Lynch, J., Fulmore, C., Snyder, C., Lemon, S. J., Conway, T., Tonin, P., Lenoir, G., and Lynch, H. *BRCA1* testing in families with hereditary breast-ovarian cancer: a prospective study of patient decision making and outcomes. J. Am. Med. Assoc., *275:* 1885–1892, 1996.

5. Wiggins, S., Whyte, P., Huggins, M., Adam, S., Heilman, J., Block, M., Sheps, S. B., Schechter, M. T., Hayden, M. R., and the Canadian Collaborative Study of Predictive Testing. The psychological consequences of predictive testing for Huntington's disease. N. Engl. J. Med., *327:* 1401–1405, 1992.

6. Chapman, M. A. Canadian experience with predictive testing for Huntington disease: lessons for genetic testing centers and policy makers. Am. J. Med. Genet., *42:* 491–498, 1992.

7. Pillemer, K., and Suitor, J. Family stress and social support among caregivers to persons with Alzheimer's disease. *In:* G. R. Pierce, B. R. Sarason, and I. G. Sarason (eds.), Handbook of Social Support and the Family, pp. 467–494. New York: Plenum Publishing Corp., 1996.

8. Turk, D. C., and Kerns, R. D. The family in health and illness. *In:* D. C. Turk and R. D. Kerns (eds.), Health, Illness, and Families: A Life-Span Perspective, pp. 1–22. New York: Wiley, 1985.

9. Ross C., Mirowsky, J., and Goldsteen, K. The impact of the family on health. J. Marr. Family, *52:* 1059–1078, 1990.

10. MacIntyre, S. The effects of family position and status on health. Soc. Sci. Med., *35:* 453–464, 1992.

11. Pearlin, L., and Turner, H. A. The family as a context of the stress process. *In:* S. V. Kasl and C. L. Cooper (eds.), Stress and Health: Issues in Research Methodology, pp. 143–165. NY: Wiley, 1987.

12. House, J. S., Landis, K. R., and Umberson, D. Social relationships and health. Science (Washington DC), *241:* 540–545, 1988.

13. Thoits, P. A. Stress, coping, and social support processes: Where are we? What next? J. Health Soc. Behav., Spec. No.: 53–79, 1995.

14. Friedman, L. C., Baer, P. E., Nelson, D. V., Lane, M., Smith, F. E., and Dworkin, R. J. Women with breast cancer: perceptions of family functioning and adjustment to illness. Psychosom. Med., *50:* 529–540, 1988.

15. Lewis, F. M., Hammond, M. A., and Woods, N. F. The family's functioning with newly diagnosed breast cancer in the mother. J. Behav. Med., *16:* 351–370, 1993.

16. Northhouse, L. L., Cracchiolo-Caraway, A., and Appel, C. P. Psychologic consequences of breast cancer on partner and family. Semin. Oncol. Nursing, *7:* 216–223, 1991.

17. Dudokdewit, A. C., Tibben, A., Frets, P. G., Meijers-Heijboer, E. J., Devilee, P., Klijn, J. G. M., Oosterwijk, J. C., and Niermeijer, M. F. *BRCA1* in the family: a case description of the psychological implication. Am. J. Med. Genet., *71:* 63–71, 1997.

18. Quaid, K. A., and Wesson, M. K. Exploration of the effects of predictive testing for Huntington's disease on intimate relationships. Am. J. Med. Genet., *57:* 46–51, 1995.

19. Green, J., Richards, M. P. M., Statham, H., Murton, F., and Hallowell, N. Family communication and genetic counselling: the case of hereditary breast and ovarian cancers. J. Genet. Counsel., *6:* 45–60. 1997.

20. Julian-Reynier, C., Eisinger, F., Vennin, P., Chabal, F., Aurran, Y., Nogues, C., Bignon, Y. J., Machelard-Roumagnac, M., Maugard-Louboutin, C., Serin, D., Blanc, B., Orsoni, P., and Sobol, H. Attitudes toward cancer predictive testing and transmission of information to the family. J. Med. Genet., *33:* 731–736, 1996.

21. Richards, M. P. M. Families, kinship, and genetics. *In:* T. Marteau and M. P. M. Richards (eds.), The Troubled Helix: Social and Psychological Implications of the New Human Genetics. Cambridge: Cambridge University Press, 1996.

22. Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P. A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., Bennett, L. M., Ding, W., Bell, R., Rosenthal, J., Hussey, C., Tranh, T., McClure, M., Frye, C., Hattier, T., Phelps, R., Haugen-Strano, A., Katcher, H., Yakumo, K., Gholami, Z., Shaffer, D., Stone, S., Bayer, S., Wray, C., Bogden, R., Dayanath, P., Ward, J., Tonin, P., Narod, S., Bristow, P. K., Norris, F. H., Helvering, L., Morrison, P., Rosteck, P., Lai, M., Barrett, J. C., Lewis, C., Neuhausen, S., Cannon-Albright, L., Goldgar, D., Wiseman, R., Kamb, A., Skolnick, M. H. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. Science (Washington DC), *266:* 66–71, 1994.

23. Easton, D. F. Breast cancer genes–what are the real risks? Nat. Genet., *16:* 210–211, 1997.

24. Easton, D. F., Ford, D., and Bishop, D. T. Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. Breast Cancer Linkage Consortium. Am. J. Hum. Genet., *56:* 265–271, 1995.

25. Bishop, D. T., and Kiemeney, L. A. Family studies and the evidence for genetic susceptibility to prostate cancer. Semin. Cancer Biol., *8:* 45–51, 1997.

26. Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., Goldgar, D. E., and the Breast Cancer Linkage Consortium. Risks of cancer in *BRCA1*-mutation carriers. Lancet, *343:* 692–695, 1994.

27. Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., Timmerman, M. M., Brody, L. C., and Tucker, M. A. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. N. Engl. J. Med., *336:* 1401–1408, 1997.

28. Botkin, J. R., Croyle, R. T., Smith, K. R., Baty, B. J., Lerman, C., Goldgar, D. E., Ward, J. M., Flick, B. J., and Nash, J. E. A model protocol for evaluating the behavioral and psychosocial effects of *BRCA1* testing. J. Natl. Cancer Inst., *88:* 872–882, 1996.

29. Goldgar, D. E., Fields, P., Lewis, C. M., Tran, T. D., Cannon-Albright, L. A., Ward, J. H., Swensen, J., and Skolnick, M. H. A large kindred with the 19q-linked breast and ovarian cancer: genetic, phenotypic, and genealogical analysis. J. Natl. Cancer Inst., *86:* 200–209, 1994.

30. Horowitz, M., Wilner, A., and Alvarez, W. The impact of event scale: a measure of subjective stress. Psychosom. Med., *41:* 209–218, 1979.

31. Spielberger, C. D. State-trait anxiety inventory for adults (Form Y). Palo Alto, CA: Mind Garden, 1983.

32. Crauford, D., Dodge, A., Kerzin-Storrar, L., and Harris, R. Uptake of presymptomatic predictive testing for Huntington's disease. Lancet, *2:* 603–605, 1989.

33. Meissen, G. J., Myers, R. H., Mastromauro, C. A., Koroshetz, W. J., Klinger, K. W., Farrer, L. A., Watkins, P. A., Gusella, J. F., Bird, E. D., and Martin, J. B. Predictive testing for Huntington's disease with use of a linked DNA marker. N. Engl. J. Med., *318:* 535–542, 1988.

34. Lifton, R. J. The Broken Connection: On Death and The Continuity of Life, pp. 63–101. New York: Simon and Schuster, 1979.

35. Tibben, A., Vegter-van der Vlis, M., Niermeijer, M. F., van der Kamp, J. J. P., Roos, R. A. C., Rooijmans, H. G. M., Frets, P. G., and Verhage, F. Testing for Huntington's disease with support for all parties. Lancet, *ii:* 553, 1992.

36. Tibben, A., Vegter-van der Vlis, M., Skraastad, M. I., Frets, P. G., van der Kamp, J. J. P., Niermeijer, M. F., van Ommen, G. B., Roos, R. A. C., Rooijmans, H. G. M., Stronks, D., and Verhage, F. DNA-testing for Huntington's disease in the Netherlands: a retrospective study on psychosocial effects. Am. J. Med. Genet., *44:* 94–99, 1990.

37. Epping-Jordan, J. E., Compas, B. E., and Howell, D. C. Predictors of cancer progression in young adult men and women: avoidance, intrusive thoughts, and psychological symptoms. Health Psychol., *13:* 539–547, 1994.

38. White, L. K., and Riedmann, A. Ties among adult siblings. Social Forces, *71:* 85–102, 1992.

39. Connidis, I. Siblings as friends in later life. Am. Behav. Scientist, *33:* 81–93, 1989.