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Exploring psychological responses to genetic testing for Lynch Syndrome within the family context

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Abstract

Objective—Genetic testing for hereditary cancer susceptibility syndromes is a family centered process. Nonetheless, little research has explored how the family context affects psychological responses to genetic testing. We examine how personal test results and the test results of immediate and extended family members shape responses to genetic testing.

Methods—Individuals at risk of carrying a mutation associated with an inherited cancer susceptibility syndrome (Lynch syndrome) received genetic testing. Six months after receiving their results, participants reported on cancer distress, cancer worry and depressive symptoms.

Results—Among mutation carriers for Lynch syndrome, the higher the proportion of carriers in their immediate family, the less cancer worry and distress they reported. In contrast, mutation carriers and non-carriers with a high proportion of carriers in their immediate family and mutation carriers with a high proportion of carriers in their extended family were at elevated risk for clinically significant levels of depressive symptoms.

Conclusion—Personal test results alone are not highly predictive of psychological outcomes. Instead, the interaction between personal and family test results, or in some cases, family test results alone, predict key psychological outcomes. The current research has important implications for genetic counseling and intervention efforts.

Keywords

Cancer; Oncology; Genetic testing; Lynch syndrome; Family; Depression

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¹The chronbach's alpha does not adjust for the clustering of participants within families. Thus, the reported values are an approximation.

Genetic testing for hereditary cancer susceptibility syndromes is a family process. Family members often receive testing together, or in sequence, and the test results of relatives have important implications for the health of the rest of the family [1,2]. Nonetheless, research on the psychological outcomes of genetic testing often overlooks the family and focuses on responses to personal test results [3,4]. Although some work has examined the impact of family members' test results, the literature is small, limited to siblings, and only examines breast/ovarian cancer susceptibility (*BRCA1/2*) and Huntington's disease testing [5,6]. The current study is the first to explore how immediate *and* extended family members' genetic test results for Lynch syndrome (LS) shape psychological outcomes (cancer distress, cancer worry, and depression).

LS, also known as Hereditary Nonpolyposis Colorectal Cancer or HNPCC, is a dominantly inherited cancer susceptibility syndrome. Individuals have a 50% chance of inheriting a mutation associated with LS if one parent carries a mutation. Consequently, LS is a family disease, increasing cancer risk for approximately 50% of relatives. Both male and female carriers of LS associated mutations have estimated lifetime risks for colorectal cancer ranging from 43 to 69% when considering the two most common LS associated genes (*MSH2*, *MLH1*). Carriers of LS mutations are also at risk for several other cancers (e.g., endometrial, stomach, urinary tract, small intestine) [7-9].

Despite the cancer risk associated with LS, people do not experience persistently high levels of distress, worry or depression in response to genetic testing [10-14]. Nonetheless, certain subgroups of people are more vulnerable to adverse outcomes than others [15-19]. Identifying factors that moderate responses to genetic testing is critical for efforts to develop effective and targeted counseling and intervention efforts [11].

We propose that the genetic test results of immediate *and* extended family members will moderate the effect of personal test results on psychological outcomes. A small body of literature explored this issue by examining the impact of siblings' test results for *BRCA1/2* or Huntington's disease. Overall, people experience more distress when their test results do not match their siblings' results [5,6,20,21]. Consistently, women who carried a *BRCA1/2* mutation experienced elevated distress when their siblings were identified as non-carriers, whereas non-carrier men experienced elevated distress when their siblings were carriers [6]. Similarly, sibling dyads with discordant test results (mutation carrier with non-carrier) for *BRCA1/2* reported greater anger and less friendly behavior when interacting compared to sibling dyads with concordant results [5].

Although prior research demonstrates the importance of the family context, it overlooks the broader scope of family relationships by focusing only on siblings. Furthermore, research has only explored the influence of relatives' test results for *BRCA1/2* and Huntington's disease. Huntington's disease, a severe neurological disorder for which no medical interventions exist, is distinct from LS. *BRCA1/2* and LS share important similarities, however, they differ in the extent to which the condition affects both men and women. Women with *BRCA1/2* mutations are at far greater risk for cancer than men with *BRCA1/2* mutations, whereas LS puts both men and women at a high risk of cancer. However, women with LS, like women with *BRCA1/2* mutations, have the added risk of gynecological

cancers. The current study explores how personal genetic test results and immediate and extended family members' test results for LS shape subsequent cancer distress, cancer worry and depression.

In line with past research [5,6,20,21], we hypothesized that participants with test results that were discordant from their immediate family (parents, siblings, adult children) would experience more adverse psychological outcomes than those with concordant results. Among *mutation carriers* for LS, we predicted that a lower proportion of carriers in their immediate family would be associated with greater cancer distress, cancer worry, and depressive symptoms. Mutation carriers with a high, compared to low, proportion of carriers in their immediate family may experience fewer adverse outcomes because they may have more positive interactions with carriers than non-carriers [22,23]. Furthermore, simply knowing that others share their condition may increase wellbeing by making the condition seem less severe [24] and by creating a shared identity [25,26]. We also predicted that *non-carriers* would experience the most adverse outcomes when their results were discordant from their immediate family due to feelings of guilt and strained relationships [5,27].

To date, no research has examined the effect of extended family genetic test results on psychological outcomes. Broadly, we hypothesize that the effect of extended family test results will differ from that of the immediate family. There are several reasons to expect a difference. For one, immediate family relationships are socially closer than extended family relationships, potentially making the results of immediate family members more impactful [3,28]. In addition, individuals are likely to learn about the test results of immediate family members through direct communication, but may learn about extended family members' results indirectly, through other family members, or not at all [3,28-30]. Thus, carriers may not be directly affected by the test results of all of their extended family, either because they lack a close relationship or because they are unaware. Consistent with theories of social contagion and diffusion of innovations [31-34], the effect of extended family results on psychological outcomes may be largely indirect, influencing more closely related or affiliated family members who then influence the focal participant.

Methods

Participant recruitment

Data came from a study which explored outcomes related to the option of receiving genetic services for LS (IRB approved, 95-HG-0165, NNMC.1995.0045) [1,35]. See previous articles for methodological details [1,35]. Recruitment began with invitations to adults with LS associated cancer (microsatellite instability and family history). These individuals were identified as index cases for each family. Index cases who consented to testing, after counseling/education, and identified to carry a deleterious mutation in an LS mismatch repair gene, could invite adult first-degree relatives (parents, siblings, adult children) to participate. In some cases, adult second-degree relatives were invited if the intervening first-degree relative was deceased. Recruitment continued in a cascading fashion to include as many at risk relatives as family communication extended. The sample examined in the current study excluded index cases since no relatives had undergone testing prior to them.

Procedure

Participants, all of whom had a relative with an identified mutation, consented and completed a baseline questionnaire prior to education/counseling. Participants then received a detailed, scripted education session to learn about LS, the benefits/limitations of genetic testing, and cancer screening recommendations. A client-centered counseling session followed to explore interest in testing. A Certified Genetic Counselor or an Advanced Practice Nurse with genetics training conducted both sessions. Participants who consented to testing had a blood sample drawn. Once results were available (1-2 months), participants met with the Genetic Counselor or Nurse and received their results along with education/counseling. Six months after receiving results, participants completed a follow-up questionnaire, which included the outcomes of interest. All services were free to participants.

Predictor Measures

Personal mutation status—Participants' mutation status, carrier (43%) or non-carrier, were obtained from the CLIA approved laboratory that conducted testing.

Immediate and extended family mutation status—We took the number of first-degree relatives identified as mutation carriers divided by the total number of first-degree relatives who completed testing to calculate the proportion of carriers in the immediate family ($M = .60$, $SD = .38$). Similarly, we divided the number of second and third-degree relatives (e.g. aunts/uncles, grandchildren, cousins) identified as carriers by the number of second and third-degree relatives who completed testing to calculate the proportion of carriers in the extended family ($M = .45$, $SD = .28$).

Only relatives who were notified of their results prior to the participant's six-month follow-up were included in the family mutation status. Due to the cascading recruitment, participants in the same family did not necessarily have the same proportion of carriers in their tested family at the time of follow-up. Thus, family mutation status reflects each individual's family environment at the time of his/her follow-up.

Importantly, 97% of participants reported that they told their immediate family about their test results within the follow-up period; this, together with past research [3,28-30] suggests that participants were aware of their immediate family's test results. Participants did not report about disclosure to their extended family, however, communication with the extended family is typically lower. Follow-up interviews suggest that indirect communication of extended relatives' mutation results sometimes occurred through connecting relatives. Thus, the influence of extended family test results may be more indirect, influencing family members who are aware of the test results who then influence the focal participant.

Outcome Measures

Family cancer distress—Participants completed the Impact of Events Scale Revised [36] to assess intrusive and avoidant thoughts about cancer within their family on scales from 1 (*not at all*) to 4 (*often*). We created a composite with the mean of the baseline ($M =$

1.62, $SD = .58$) and follow-up items ($M = 1.34$, $SD = .48$); both were highly reliable (baseline: $\alpha = .90$; follow-up: $\alpha = .89$).

Cancer worry—Participants answered three validated questions [37] about their colon cancer worry (e.g. “During the past month, how often have thoughts about... colon cancer affected your mood?”) on scales from 1 (*Not at all/rarely*) to 4 (*A lot*). We created composites with the mean of the baseline ($M = 1.52$, $SD = .60$) and follow-up items ($M = 1.27$, $SD = .44$). Reliability was adequate (baseline: $\alpha = .69$; follow-up: $\alpha = .65$).

Depressive symptoms—Participants completed a 20-item depressive symptomology questionnaire (CES-d). Although the scale does not provide a psychiatric diagnosis, it is correlated with clinical ratings of depression severity [38]. A score at or above 16 (on 0 to 60 scale) is generally accepted as suggesting clinically significant levels of depression [38]. We dichotomized scores ($0 < 16$, $1 \geq 16$) for baseline (15% depressed) and follow-up (17% depressed).

Analytic Strategy

We controlled for the baseline measurements of the outcome variables, participant age, cancer status of participants and their relatives, and adverse health changes from baseline to follow-up. To account for the cascading recruitment and long interval between the start and finish of data collection as a whole, we controlled for the time between each participant's test receipt and the beginning of their own family's testing (index case's test receipt) along with the time between each participant's test receipt and the beginning of data collection for the entire study (first participant's test receipt).

To account for clustering of individuals within families, we used generalized estimating equations (GEE) with an exchangeable covariance structure. We used logistic regression to examine depression and linear regression to examine distress and worry. We entered the predictors into the model in three hierarchical steps [39]. In step 1, we entered the covariates and the three predictor variables to test for main effects. In step 2, we included the step 1 variables and added in all 2-way interactions between the predictor variables. In step 3, we included all the step 2 variables and added in the 3-way interaction between the predictor variables.

Results

Participants

We limited the sample to families with at least two participants with completed data. We excluded one family whose relatives' test results were unknown to us because they were tested elsewhere. Families with inconclusive genetic test results (e.g. variant of unknown significance) were also excluded. Because we included immediate and extended family test results in the same statistical model, participants with missing values on either variable were automatically dropped from the analyses. This method allowed us to compare the effect of immediate and extended family test results for the same set of participants and to control for the effect of immediate family when examining the effect of extended family (and visa-

versa). Alternative analyses incorporating the participants dropped from the main analyses yielded the same results.²

Our sample consisted of 179 participants from 26 families. The majority of participants were White (97%), female (58%), married (60%) and health insured (97%). Ages ranged from 18 to 72 years ($M = 39$). Twelve percent of participants had a cancer diagnosis. At baseline, participants reported 2 first-degree and 3 second-degree relatives with cancer, on average (participants did not report on third-degree relatives). At follow-up, 19% of participants reported one or more adverse change in their own and/or relatives' health. Participants' immediate and extended family members were comparable in terms of gender and age, but varied in size as participants tended to have more extended than immediate family members who received testing (Table 1).

Family cancer distress

There were no main effects of personal, immediate family, or extended family mutation status. The only significant interaction was between personal mutation status and immediate family mutation status, $b = .55$, $p = .017$. Among mutation carriers, the greater the proportion of carriers in their immediate family, the marginally less distress they reported after test receipt, $b = -.38$, $p = .057$. There was no relationship between immediate family mutation and distress among non-carriers, $b = .17$, $p = .14$. To further explore the interaction we plotted immediate family mutation status at .20 (20% of tested immediate family were carriers) and .80 (80% of tested immediate family were carriers).³ Carriers experienced more distress than non-carriers, but only when they had a low proportion of immediate family carriers, $b = -.34$, $p = .021$. In contrast, carriers had a similar low level of distress as non-carriers, $b = -.014$, $p = .81$, when they had a high proportion of immediate family carriers (Table 2 and Figure 1). As predicted, carriers expressed the most post-test distress when their results diverged from their family.

Cancer worry

There was a main effect of personal mutation status on worry; carriers reported greater worry than non-carriers, $b = -.24$, $p = .002$. There was also a main effect of extended family mutation such that a higher proportion of carriers in the extended family predicted greater worry, $b = .21$, $p = .002$. There was no main effect of immediate family mutation status.

The only significant interaction was between immediate family and personal mutation status, $b = .48$, $p = .011$. Among mutation carriers, the greater the proportion of carriers in their immediate family, the less cancer worry they reported after test receipt, $b = -.37$, $p = .053$. There was no relationship between immediate family mutation status and worry among

²By including immediate and extended family test results in the same model, the main analyses omitted participants who did not have any immediate family who received testing and omitted participants who did not have any extended family who received testing. To include these participants, we analyzed two separate models; one examining the interaction between personal and immediate family mutation status and one examining the interaction between personal and extended family mutation status. The pattern of results remained the same.

³We chose to plot the simple slopes at .2 and .8 to represent a high proportion versus a low proportion of family carriers. The benefit of selecting set values is that they can be applied consistently to the analyses for immediate and extended family test results. Since the means and standard deviations differ for immediate versus extended family test results, using one standard deviation above and below the mean would result in different high and low values to plot for each variable.

non-carriers, $b = .10$, $p = .14$. We plotted immediate family mutation status at a low (.20) and high (.80) proportion of immediate family carriers. Carriers reported greater distress than non-carriers when they had a low proportion of carriers in the immediate family, $b = -.46$, $p < .001$. When carriers had a high proportion of carriers in the immediate family they still reported greater worry than non-carriers, but the difference was smaller, $b = -.18$, $p = .010$ (Table 2 and Figure 2).

As predicted, carriers expressed the most worry when they had a low proportion of immediate family carriers. However, the main effect for extended family suggests that carriers and non-carriers expressed less worry when they had a low proportion of extended family carriers.

Depressive symptoms

There was a main effect of immediate family mutation status, $b = 1.02$, $p = .040$, and a marginally trending effect of extended family mutation status on depressive symptoms, $b = 1.20$, $p = .076$. A higher proportion of carriers in the immediate and extended family predicted a greater likelihood of clinically significant levels of depressive symptoms. There was no effect of personal mutation status. Additionally, there were no significant interactions involving immediate family mutation status.

There was, however, a significant interaction between extended family and personal mutation status, $b = -4.05$, $p = .029$. Among carriers, the greater the proportion of carriers in their extended family, the *greater* their odds of reporting clinically significant levels of depressive symptoms, $b = 3.17$, $p = .001$. There was no relationship between extended family mutation status and depressive symptoms among non-carriers, $b = -.88$, $p = .46$. We plotted extended family mutation status at a low (.20) and high (.80) proportion of extended family carriers. Carriers were actually less likely to report depressive symptoms than non-carriers when they had a low proportion of carriers in their extended family, $b = 1.21$, $p = .050$. Carriers and non-carriers did not differ in depressive symptoms when they had a high proportion of family carriers, $b = -1.23$, $p = .14$ (Table 2 and Figure 3).

Carriers were the most likely to report depressive symptoms when they had a high proportion of carriers in the extended family. Unexpectedly, a main effect of immediate family suggested that a higher proportion of immediate family carriers predicted depressive symptoms for carriers and non-carriers.

Discussion

Despite the family centered nature of genetic testing for hereditary cancer susceptibility, the literature has focused on responses to personal test results. Our research suggests that personal test results alone are not highly predictive of psychological outcomes. Instead, the interaction between personal and family test results, or in some cases, family test results alone, predict cancer worry, cancer distress, and depressive symptoms. Importantly, extended family test results predict a distinct pattern of results that has been overlooked in past research on siblings.

Immediate family

Consistent with previous literature, carriers of cancer predisposing mutations experienced the greatest distress and worry when they had a low proportion of carriers in their immediate family [5,6,20,21]. Past research suggests that carriers have more positive interactions with carriers than non-carriers [5]. Thus, carriers may receive more social support to alleviate their distress and worry [22,23] when they have a high proportion of immediate family carriers. Furthermore, knowing that other relatives are faced with similar risks may make LS seem less alarming [24] and increase solidarity [25,37].

The current work did not find elevated worry or distress among non-carriers with a high proportion of immediate family carriers. This is not surprising given that most of the evidence of guilt and distress among non-carriers is from Huntington's disease research [5]. Furthermore, consistent with our results, one *BRCA1/2* study suggests that female non-carriers with sibling carriers do *not* experience elevated distress [6]. Women testing for *BRCA1/2* are comparable to both men and women testing for LS because they all have a similarly high cancer risk.

Unexpectedly, the results for depressive symptoms differed from the cancer-specific measures. Regardless of personal mutation, carriers and non-carriers were more likely to report clinically significant levels of depressive symptoms when they had a high proportion of carriers in their immediate family. A high proportion of carriers in the immediate family may alleviate cancer-specific distress and worry (for carriers) but may be more globally stressful, increasing the demands placed on individuals and heightening vulnerability to depression.

Extended family

Extended family test results have a unique influence on cancer worry and depressive symptoms. Research which only examines siblings' test results overlooks an influential aspect of the genetic testing process. Regardless of personal mutation, carriers and non-carriers experienced more cancer worry the higher the proportion of carriers in their extended family. Similarly, carriers (but not non-carriers), were at greater risk for depressive symptoms the higher the proportion of carriers in their extended family.

Future research is needed to verify and explain the extended family findings. Preliminarily, we suggest that the effect of extended family test results on psychological outcomes may be indirect, influencing closely affiliated relatives who then influence the focal participant. An individual with a high proportion of carriers in his/her extended family may receive diminished support and attention from certain immediate family members because they may be busy supporting carriers in the extended family. In other words, support resources may be spread thin in contexts with a high proportion of extended family carriers [3,28] and this may put people at greater risk of worry and depression [22,23]. This explanation contrasts, however, with our earlier assertion that having a higher proportion of carriers in the immediate family diminishes distress and worry because carriers may provide each other with support and solidarity. The current research cannot resolve this discrepancy because we did not directly measure how family test results impact social support exchange. Future

research should examine the relational mechanisms that explain why immediate and extended family test results influence psychological outcomes.

Clinical Implications

Scientific consideration of the family context of genetic testing can ultimately aid the development of more effective genetic counseling and intervention efforts. Genetic education and counseling should explore the family's history with genetic testing and how it may influence social support, communication, and psychological outcomes. In addition, the influence of the extended family should be given greater consideration due to the important consequences of extended family test results for wellbeing. Finally, family test results could be used to target interventions. Carriers and non-carriers with a high proportion of carriers in their immediate family and carriers with a high proportion of carriers in their extended family may be a point of intervention as they have an elevated risk for clinically significant depression symptoms.

Limitations and Future Directions

The generalizability of the current study is limited because our sample consisted of predominantly upper to middle class White participants. An examination of the implications of genetic testing for diverse populations is greatly needed. The scope of the current study is also limited in that it only examines a six month follow-up. Psychological outcomes may change over time in response to relatives who pursue genetic testing at a later date. Future work should explore the impact of family test results as they unfold over time. Additionally, research is needed to explore how relationship closeness influences responses to relatives' test results. We assumed that immediate family relationships were closer than extended family relationships, but we did not directly measure closeness or support and communication. Future research should assess whether the impact of family members' test results depends on level of relationship closeness and support exchange. Finally, research should explore the role of gender in the context of family test results for LS. Previous research suggests that women play a central role in communicating information about genetic testing [40]. Families with a higher number of female testers may communicate about their results to a greater extent than families with fewer female testers. Thus, psychological responses to family members' test results may depend on the number of women who received testing.

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Figure 1.

Immediate family mutation status (plotted at .2 and .8) $\times$ Personal mutation status on distress about family cancer. * $p < .05$, $^\dagger p < .06$

Figure 2. Immediate family mutation status (plotted at .2 and .8) $\times$ Personal mutation status on worry about colon cancer. * $p < .05$

Figure 3. Extended family mutation status (plotted at .2 and .8) $\times$ Personal mutation status on probability of clinically significant level of depressive symptoms. The b values are unstandardized log-odds. $*p < .05$

Table 1

Family characteristics

	Immediate Family	Extended Family
Number of family members tested		
<i>Mean</i>	2.7	4.98
<i>Range</i>	1-7	1-15
Number of mutation carriers in family		
<i>Mean</i>	1.44	2.25
<i>Range</i>	0-5	0-6
Proportion of carriers in family		
<i>Mean</i>	.60	.45
<i>Range</i>	0-1	0-1
Age		
<i>Mean</i>	44	46
<i>Range</i>	18-72	18-83
Gender (% Male)	39%	38%

Table 2

Step 1 and Step 2 Analyses

	Distress Step 1		Distress Step 2		Worry Step 1		Worry Step 2		Depression Step 1		Depression Step 2	
	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)	b(SE)
Personal mutation status (0= Carrier, 1= Non-carrier)	-.097(.07)	-.12(.07)	-.24(.08)**	-.27(.07)**	.34(.43)	.15(.46)						
Immediate family mutation status (Mean centered)	.032(.10)	-.38(.20) [†]	-.052(.08)	-.37(.19)*	1.02(.50)*	.065(1.37)						
Extended family mutation status (Mean centered)	.13(.12)	-.18(.23)	.21(.07)**	-.067(.16)	1.20(.68)	3.17(.94)**						
Personal X Immediate		.55(.23)*		.48(.19)*		2.27(1.84)						
Personal X Extended		.33(.25)		.21(.17)		-4.05(1.86)*						
Immediate X Extended		.084(.31)		.19(.22)		2.11(2.16)						

Notes: Step 3 was not significant ($ps > .37$). All steps controlled for the baseline measures of the outcome variables, age, family and personal cancer history, health changes, and the time variables. At step 1, the predictors can be interpreted as main effects. At step 2, the predictors can be interpreted as simple effects conditional on other predictors, e.g., the effect of immediate family on worry when personal mutation = 0 (carrier) and extended family = 0 (mean number of carriers).

[†] p .06.
* p .05.
** p .01