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Psychological Impact of Learning *CDKN2A* Variant Status as a Genetic Research Result

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Abstract

Objectives: Little is known about genetic research participants' responses to receiving individual research results (IRR) from cancer genetic research. We examined the immediate and delayed psychological impact of returning a *CDKN2A* variant result that is associated with increased risk of pancreatic cancer and melanoma.

Methods: One hundred and thirty-three pancreas research registry enrollees whose samples were tested in a research laboratory for the *CDKN2A* variant were invited by mail to learn the result by telephone and participate in a study about the disclosure process. Self-rated health, quality of life, and emotional responses were surveyed at pre-disclosure and 6-months post-disclosure. Genetic testing-specific distress, uncertainty, and positive experiences were assessed at 6-months post-disclosure.

Results: Eighty individuals agreed to participate; 63 completed the study. Both carriers and noncarriers showed no change over time in self-rated health, quality of life, or anxiety levels. Carriers reported more sadness than non-carriers at pre-disclosure and 6-months post-disclosure. Both carriers and non-carriers showed more hopefulness at 6-months post-disclosure than predisclosure. Carriers experienced greater test-specific distress and uncertainty than non-carriers, but levels were low.

Conclusions: Return of IRR in conjunction with cancer prevention counselling led to low levels of test-specific distress and uncertainty among carriers. No other adverse psychological outcomes were observed.

Keywords

CDKN2A variant; melanoma; pancreatic cancer; psychological outcomes; return of genetic research result

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Conflict of Interest Statement

Authors have no conflicts of interest to disclose.

Introduction

Advances in genetic research have led to a growing volume of individual genetic research results (IRR) that may have health implications for participants providing biological samples for research. Studies have shown that participants in genomic research are interested in learning IRR¹⁻⁴. Return of IRR differs from return of results from clinical genetic testing in important ways, yet research results may have clinical relevance^{5,6}. Researchers are not obligated to return IRR in most cases, yet depending on the research context and the genetic finding, they may feel compelled to do so. Researchers who choose to return IRR are often motivated by feelings of obligation that the genetic information may be valuable to participants, particularly when the information is only available through research as the translation of genetic analysis from research to clinical care can be slow⁷.

Best practices regarding which IRR should be returned to participants and how have yet to be established^{7,8}. The Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network recommend that “at a minimum, researchers should offer individual genomic research results that are valid, medically important, and actionable if discovered purposefully or by chance during the course of data analysis”⁹. This is consistent with the updated guidelines from a National Heart, Lung, and Blood Institute Working Group¹⁰. In addition, CSER and eMERGE acknowledged that the definition of what is actionable would be context dependent and researchers should contemplate what findings would represent the minimum for return in their study in consultation with local institutional review boards (IRBs) and funding agencies⁹. Because return of IRR serves informational purposes only, experts suggest that IRR that have clinical relevance but are not from a Clinical Laboratory Improvement Amendments (CLIA)-certified lab can be returned to participants if clearly labeled as research results and accompanied with a warning that the results should not be used for clinical decisions until they are confirmed in a CLIA-certified lab^{5,10}.

To date, most information about participants’ responses toward receiving genetic research results is based on hypothetical scenarios; few data have been collected regarding research participants’ responses to actual research results^{11,12}. Additional research examining the potential benefits and harms of returning IRR and investigations on what methods are appropriate for returning IRR are needed to inform best practices. The present study reports data from a novel protocol in which IRR, obtained in a research laboratory, were offered by the investigator to consented research participants from a pancreatic cancer research registry.

Pancreatic cancer (PC) is the fourth leading cause of cancer death in the U.S. and remains the most challenging of all cancers¹³. It is often asymptomatic until it has advanced to late stage when treatments are suboptimal, resulting in a 5-year survival rate of approximately 8%¹⁴. About 5–10% of patients with PC have a family history of PC, and a number of gene variants have been identified to be associated with increased risk of PC¹⁵. Currently, routine screening for PC is generally not recommended for asymptomatic individuals; however, asymptomatic individuals with a genetic predisposition are recommended to undergo surveillance for PC with endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) of the pancreas^{16–18}. Therefore, when a genetic risk for PC is uncovered through the

course of research, offering the results to participants has the potential to be actionable (after clinical confirmation) and medically important. The asymptomatic nature of early-stage disease coupled with the rapid progression and lethality of PC make this an important cancer in which to offer genetic information learned in the research context.

In the course of gene discovery for PC, biological samples were analyzed for the presence/absence of the variant *L16R* c.47T>G (p.Leu16Arg) in the *CDKN2A* gene in several large kindreds that segregated this variant. At the time of the study, this variant was classified as a Variant of Uncertain Significance,¹⁹ but our research has shown it is likely pathogenic and it is currently classified as Pathogenic/Likely Pathogenic in CLINVAR.^{20–23} The specific context of this research wherein results could have particular importance for families who experience a high burden of cancer, led the principal investigator (G.M.P.) to disclose the status of the *CDKN2A* variant, positive or negative, as an IRR to participants who wanted to know. We subsequently examined the immediate and delayed psychological outcomes of returning *CDKN2A* variant status as a research result to participants who are from high-risk PC families. Specifically, we sought to understand how learning specific *CDKN2A* variant status may influence individuals' general self-rated health, quality of life, emotional experiences, and genetic testing related concerns.

Methods

Participants

This study, “Learning About Research Gene Outcomes” (LARGO) was reviewed and approved by the Mayo Clinic Institutional Review Board. This study was a sub-project under the PC family registry at Mayo Clinic that consists of PC patients having at least one blood relative with PC (probands) and their family membersⁱ. Methodology of the registry is described in detail elsewhere²⁴. Briefly, at the time of enrollment, all registry participants provided a blood or saliva sample and completed a demographic and risk factor questionnaire. The electronic health record was abstracted to ascertain history of cancer when the risk factor questionnaire was incomplete. Participants of the LARGO study were 133 individuals who enrolled in the registry and provided a sample between 2009 and 2012. Their samples were tested between 2013 and 2015 for the presence/absence of a missense variant *L16R* in the *CDKN2A* gene. LARGO participants did not have a diagnosis of PC but some had been diagnosed with melanoma (Table 1).

Procedures

Eligible participants were notified via mail that their sample was analyzed for a specific genetic variant associated with cancer and invited to learn their genetic research result by phone, and also to participate in the LARGO study. Participants could choose to (1) learn the result and participate in LARGO, (2) learn the result but not participate in LARGO, or (3) decline both opportunities. A scheduled phone call was chosen as the disclosure method because the participants lived across the U.S.; for many individuals, traveling to Mayo Clinic

ⁱFamily members included first-degree, second-degree, and third-degree blood-relatives plus spouses/partners or other relatives who would make the pedigree informative for linkage.

for in-person disclosure would have been impractical. If individuals chose option (1), they were asked to complete and return a pre-disclosure survey (Survey 1) that was enclosed in the mailing. Survey 1 contained measures of general self-rated health, quality of life, emotional experiences, cancer risk perceptions, and cancer screening and prevention behaviors. Non-responders were mailed a second invitation after four weeks.

IRR was disclosed over the phone by the principal investigator of the Mayo Clinic PC family registry, who is certified in Medical Genetics by the American Board of Medical Genetics. The disclosure calls were audio-recorded with participants' consent. First, background information regarding the *CDKN2A* gene in relation to familial PC and familial melanoma was provided along with the rationale for having tested their sample. The investigator emphasized that testing was performed in a research laboratory, explained the differences between a research lab and a clinical/CLIA-certified lab, and recommended that participants follow-up with their physician and repeat the genetic test in a clinical lab. Next, the IRR in terms of carrier (positive for the variant) or non-carrier (negative for the variant) status was disclosed, and its meaning with regard to cancer risk was reviewed.

Carriers were informed that if the IRR is confirmed in a CLIA-certified lab, their lifetime risk for PC could be up to 60–70% and lifetime risk for melanoma could be up to 30–40%.^{20,25–28} They were then counselled about screening and prevention options for PC and melanoma. For PC, it was noted that currently there is no routine screening, but carriers were advised to consult with their physician about screening options, such as EUS. In cases where a participant asked about insurance coverage, the participant was advised to contact his or her particular insurance company for an answer prior to scheduling the screening. For melanoma, carriers were advised to have routine skin exams by a clinician and to protect their skin from sun exposure. Non-carriers were informed that if the IRR is confirmed in a CLIA-certified lab, they would not be at increased risk for PC or melanoma relative to others their age in the general population. They were then advised to follow the National Cancer Institute's cancer prevention guidelines, such as eating a balanced diet rich in fruits and vegetables, no smoking, exercising often, drinking alcohol in moderation, and protecting their skin from sun exposure. Participants were reassured that they would receive a letter in the mail containing the information discussed during the disclosure call.

Following result disclosure, participants completed a post-disclosure survey (Survey 2) on the phone with a trained interviewer who was present for the disclosure. Survey 2 measured recall of the IRR, followed by an open-ended question assessing their feelings after learning the result. Other questions in Survey 2 included behaviors related to receiving genetic information.

Participants were mailed a 6-month post-disclosure survey (Survey 3). Survey 3 contained the same measures as Survey 1, plus the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire²⁹.

This manuscript reports findings on the psychological impact of IRR disclosure. Findings regarding cancer perceptions and behaviors will be reported separately.

Key Measures

Sociodemographic information included age, sex, education level, marital status, race/ethnicity, and number of biological children. Participants who were found to carry the variant were classified as **carriers**, and participants who were not found to carry the variant were classified as **non-carriers**. **Cancer history** was determined by self-report and medical records.

In Surveys 1 and 3, **General Self-rated Health** (GSRH) was measured with the item: “In general, would you say your health is:” (5-point scale: 1=*Poor*, 5=*Excellent*)³⁰. **Quality of life** (QoL) was measured with the Linear Analog Scale Assessment³¹: “How would you rate your overall well-being over the past 6 months?” (11-point scale: 0=*As bad as it can be*, 10=*As good as it can be*). **Emotional Experience** measures in Surveys 1 and 3 were from the Health Information National Trends Survey³². Following the stem “In the past 30 days, how often have you felt...” the words “Happy,” “Angry,” “Anxious,” “Hopeful,” and “Sad” appeared with a 5-point scale (1=*None of the time*, 5=*All of the time*). In Survey 2, emotional reactions to learning the result were captured with the open-ended questions: “In a word or two, how would you describe your feelings now, after hearing these results? What are the first words that come to mind?”

MICRA²⁹ was used in Survey 3 to assess psychological experiences specific to learning genetic results. It consists of 25 items (4-point scale: 0=*Never*, 1=*Rarely*, 3=*Sometimes*, 5=*Often*) with four items assessing two subgroups (i.e., individuals with children and individuals with a cancer history). Six items form the **distress** subscale (e.g., “Feeling upset about my test result”) (Cronbach’s $\alpha=.77$). Nine items form the **uncertainty** subscale (e.g., “Being uncertain about what my test result means about my cancer risk”) (Cronbach’s $\alpha=.82$). Four items form the **positive experiences** subscale, which assesses positive emotional responses toward the result and family support. This subscale had lower reliability compared to the original validation study (Cronbach’s $\alpha=.64$ vs $.75$). Composite subscale scores were computed by summing responses across subscale items. Two additional items assessed regret about learning the result and understanding of cancer prevention options. The two items concerning participants with children assessed worry about one’s children getting cancer and guilt about passing on the disease risk. The two items concerning participants with cancer assessed whether the test result has made it harder or easier to cope with cancer.

Data Analysis

Statistical analyses were performed with SPSS, version 22. Data from participants who completed all three surveys were included in analysis. We first compared carriers and non-carriers who are probands’ blood-relatives and then compared blood-relative non-carriers to spouses who “married in” to these families. Fisher’s exact tests or Welch’s t-tests were used to examine pre-disclosure differences by variant status in sociodemographic and outcome variables. Mixed-design ANOVAs were used to examine changes over time by variant status in GSRH, QoL, and emotional experiences. Welch’s t-tests were used to test differences by variant status in MICRA outcomes 6-months post-disclosure and differences between spouses and blood-relative non-carriers on all outcomes. Statistical significance was declared at $p<.05$. Participants’ qualitative accounts of their emotional reactions immediately

following the disclosure were analyzed by two of the authors (X.Z., C.R.B.) using summative content analysis.³³

Results

Sample Characteristics & Pre-Disclosure Differences by Variant Status

Of the 133 eligible participants, nearly 70% (n=93) chose to learn their result either as part of the LARGO study (n=80) or independent of the study (n=13). Among the 80 participants who returned a signed informed consent and completed Survey 1 (60% study participation rate), 73 (91%) scheduled a disclosure call. One of the participants who began the disclosure call withdrew during Survey 2, and one requested to not receive Survey 3. Of the 71 participants who were mailed Survey 3, 63 completed the survey (Figure 1). The 63 participants who completed all three surveys did not differ statistically significantly from non-participants or those who completed only Survey 1 or Survey 1 and 2 on any sociodemographic characteristics or on cancer history.

Participants were 55 blood-relatives and eight spouses from five families. There were 15 carriers and 48 non-carriers (including the spouses). Sample characteristics are summarized in Table 1. Among blood-relatives, there were no differences by variant status in sociodemographic variables or cancer history. At pre-disclosure, carriers felt sad more often than non-carriers ($t(20.13)=2.94$, $p=.008$). Spouses did not differ from blood-relative non-carriers on any of the variables.

Comparison of Blood-Relative Carriers and Non-Carriers

Self-Assessments of GSRH and QoL—Six months post-disclosure, neither carriers' nor non-carriers' GSRH and QoL differed from pre-disclosure (Table 2).

Immediate and Delayed Emotional Experiences—Among non-carriers, the prominent self-described feelings were relieved and happy; “relief” was mentioned most frequently (56.3%; $n=27$). One participant said, *“Relief. Just that I’m not any more susceptible to get pancreatic cancer than the normal population. With my family history, that’s something I have been worried about. It makes me feel better to know that I don’t have the mutation.”* Also, a few expressed gratitude, such as this participant: *“Thankful, appreciative, and very fortunate they have someone that is working on research on something that is very important to our family.”*

Among carriers, the most frequent initial reaction was that the positive result was expected; they were not surprised. One participant said, *“I guess I expected to hear it, so I don’t really have a strong feeling one way or the other, I’m just glad to know that a test has come through and that I know it now.”* However, some carriers felt disappointed, anxious, and worried. A few others expressed relief, as the disclosure removed the ambiguity of their high-risk status. One participant said, *“It sounds weird, but, I mean, it’s a relief to me to know that I’m not in limbo any more, like, do I, don’t I? I dealt with this for six years, so, I can keep dealing with it.”*

Both carriers and non-carriers reported feeling hopeful more often 6-months post-disclosure than pre-disclosure ($F(1, 49)=5.39, p=.024, \eta_p^2=.099$). At both pre-disclosure and 6-months post-disclosure, carriers reported feeling sad more often than non-carriers ($F(1, 48)=10.96, p=.002, \eta_p^2=.186$). Neither carriers nor non-carriers' sadness levels at 6-months post-disclosure differed from pre-disclosure. There was no change in happiness, anger, or anxiety (Table 2).

MICRA Outcomes 6-Months Post-Disclosure—Carriers reported higher distress ($t(20.72)=3.03, p=.006$), higher uncertainty ($t(24.77)=2.59, p=.016$), and lower positive experiences ($t(45.61)=5.04, p<.001$) than non-carriers. Regarding positive experiences, carriers and non-carriers differed on “feeling relieved about my test result” ($t(51.57)=-12.59, p<.001$) and “feeling happy about my test result” ($t(39)=-15.60, p<.001$). Consistent with the qualitative emotional reactions reported immediately post-disclosure, non-carriers felt happier and more relieved about their test results. Carriers and non-carriers did not differ in positive experiences regarding family support and communication. Both carriers and non-carriers reported having a relatively clear understanding of their choices for cancer prevention and showed little regret about choosing to learn their result (Table 3).

Among participants with children, carriers were not more worried than non-carriers about the possibility of their children getting cancer and did not feel guiltier about the possibility of passing on the disease risk. Among participants with a cancer history, carriers and non-carriers did not differ on whether the test result made it harder or easier to cope with cancer.

Comparison of Spouse and Blood-Relative Non-Carriers

At 6 months post-disclosure, spouse and blood-relative non-carriers did not differ on GSRH, QoL, or on feelings of happiness, anger, anxiety, or sadness. However, spouses felt more hopeful than blood-relative non-carriers ($t(14.06)=2.78, p=.015$) (Table 2). Regarding MICRA outcomes, spouses reported lower distress ($t(39)=-3.93, p<.001$) and uncertainty ($t(31.46)=-3.51, p=.001$) than blood-relative non-carriers (Table 3). No other difference was found. When asked about their feelings immediately post-disclosure, spouses frequently mentioned “happy,” such as this participant, *“Happy to hear it, didn’t expect to have it because not a blood-relative, would’ve been surprised if I did.”*

Discussion

To our knowledge, this is the first study to examine the impact of returning the *L16R* variant status of the *CDKN2A* gene as an IRR to high-risk PC kindreds. Relative to pre-disclosure, there was no evidence of adverse effects on GSRH, QoL, or emotional experiences, among either carriers or non-carriers at 6-months post-disclosure, suggesting that receiving genetic information about PC and melanoma risk in conjunction with cancer prevention counselling did not have a long-lasting negative impact on how participants evaluate their health and well-being.

Although some carriers expressed disappointment, worry, and anxiety immediately after learning their result, their level of anxiety at 6-months post-disclosure was not different relative to pre-disclosure. Moreover, there was no change in the levels of happiness or anger.

Overall, these findings suggest that returning IRR related to hereditary cancer risk does not have long-lasting adverse emotional impact, although short-lived negative emotions may occur immediately following disclosure, as observed in the clinical genetic testing setting^{34–38}.

Unlike studies in the clinical genetic testing setting^{34,35,38}, this study found no decrease among non-carriers in negative emotional experiences, such as anxiety and anger. It is unlikely that this was due to skepticism about the validity of the non-CLIA-certified research result because blood-relative non-carriers' levels were not different from spouses'. Instead, the uniform levels may have reflected a floor effect as the average anxiety and anger levels were very low at pre-disclosure and 6-months post-disclosure among all participant groups. The difference in sadness levels between carriers and non-carriers at pre-disclosure is puzzling (participants had not learned their variant status yet). Carriers and non-carriers did not differ on variables that may contribute to differences in sadness such as whether they expected to carry the variant or not, personal cancer history, and demographics. Also, sadness level at pre-disclosure was not associated with any of these variables.

Interestingly, both carriers and non-carriers reported feeling hopeful more often at 6-months post-disclosure than pre-disclosure. We speculate that this resulted from different mechanisms for carriers and non-carriers. For blood-relatives, it is likely that learning they were non-carriers brought relief and reduced worry about the future. To this point, over half of blood-relative non-carriers spontaneously mentioned the words “relief” or “relieved” when asked to describe their initial reactions. For carriers, it is possible that learning variant status removed ambiguity around their suspected predisposition to cancer (given their pedigrees); hence they could start taking steps toward confirmatory testing, prevention, and planning for the future.

Another potential contributor to carriers' elevated hopefulness, we believe, is the context in which they received their result. Specifically, results were delivered by the principal investigator of the genetic research study in which the participants initially enrolled; she is a recognized and trusted scientist by these families. Furthermore, variant status was contextualized as one of several factors contributing to cancer risk. In the disclosure call, elements of standard-practice genetic counseling were present including the opportunity for participants to ask questions. The counseling component of the disclosure call may have helped to build carriers' self-efficacy in controlling their cancer risk, as it offered expert, immediate answers to participant questions and provided recommendations for cancer screening and prevention. Therefore, although carriers were informed that they may have an increased risk of PC and melanoma if their carrier status is confirmed in a CLIA-certified lab (a factor that is outside of their control), they were given information regarding factors they can control to mitigate their risk. This counseling element, in conjunction with contextualized disclosure by a trusted individual, may well have reduced worry.

Compared with blood relative non-carriers, carriers reported higher levels of genetic test-related distress and uncertainty. Nonetheless, carriers' distress, uncertainty, and worry were at low to moderate levels. Although carriers reported feeling less relief and happiness about their test results than non-carriers, they reported equivalently high levels of family support

and satisfaction with family communication about the genetic result. These findings are consistent with those of Aspinwall et al. whereby *CDKN2A/p16* mutation carriers did not report high distress, uncertainty, or cancer-related worry and enjoyed equivalent levels of family support and family communication as non-carriers³⁸. Similar patterns were reported in Halbert et al.³⁹ and Lynch et al.⁴⁰ Akin to our elevated hopefulness finding, the low levels of negative genetic test-specific outcomes may be a result of participants having a clear understanding of the meaning of their IRR with regard to cancer risk and their options for further testing, prevention, and early detection; we surmise these are products of the genetic counseling component of the disclosure call, which occurred regardless of variant status.

Research results in this study were communicated by telephone. To ensure participants had accurate information, a summary letter including the specific variant that was tested and general recommendations for cancer prevention was mailed to them after the phone call. To date, there are no data directly comparing outcomes of telephone and in-person return of positive and negative IRR. However, regarding participant preference, Christensen et al. found that about 2/3 of participants chose telephone as the preferred method to receive IRR and when given the choice of receiving the actual IRR in-person or by telephone, all participants chose telephone¹². In the clinical genetic testing setting, the comparative effectiveness of telephone versus in-person counseling has been examined in a number of studies, many in the context of *BRCA* 1/2 genetic counseling^{41–45}. These studies showed that telephone counseling is comparable to in-person counseling for outcomes such as satisfaction, psychological reactions, and information recall, and is more cost-effective and accessible. As research resources for returning IRR are often constrained, these findings and our own regarding telephone disclosure are reassuring. However, researchers seeking to return IRR need to evaluate different modes of delivery and design a strategy that balances research participant preferences and the availability of resources.

In our study, IRR were delivered under arguably “optimal circumstances,” that is, by a known and trusted investigator who reached out with an offer to disclose results, disclosed only to those who wanted results, and contextualized the genetic information while offering education and counseling about cancer risk reduction. This conversation was reinforced by a mailed letter from the investigator. Although it is impossible to disentangle the effects of each individual element, we believe that the counseling component may be the driving force of psychological benefit for many participants in our study. Future research should examine how each component (content, structure, mode of delivery) of disclosing IRR influences people’s receptivity, perceptions, and understanding of potentially threatening genetic information. A better understanding of the effects of these elements will inform the development of best practices that minimize negative psychological consequences and maximize psychological benefits.

Limitations

Although our findings show remarkable consistency with research in the clinical genetic context, it is important to note that similar to previous studies^{12,35,38,46,47}, our sample is homogenous. Participants in our study were white, predominantly female, relatively highly educated, mostly married with children, had a family history of PC, and were from families

that have research participation experience through the PC research registry. Our participants were likely more engaged with research and had higher sensitivity surrounding cancer due to their family histories. Additionally, we did not have data on the psychological experiences of those individuals who did not respond to the study invitation or declined learning the result and/or participate in the study. Our findings are limited to individuals who elected to learn IRR and participate in a study surrounding that process, thus, our results may be biased toward those who were more prepared to cope with genetic results. All of the above factors may have served to counter the potential negative psychological consequences of receiving a positive variant result. Moreover, our sample size was small and participants were from five families that may not be representative of the hereditary cancer population, thus limiting our ability to extrapolate our findings to the larger hereditary cancer population or other hereditary disease contexts. More research in larger, diverse populations and participants less experienced with the genetic research context is needed to examine the generalizability of our findings.

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All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study (IRB ID: 14-007845).

Appendices

Figure 1.
Flow of Participants

References

1. O'Daniel J, Haga SB. Public perspectives on returning genetics and genomics research results. *Public Health Genomics*. 2011;14(6):346–355. [PubMed: 21555865]
2. Meulenkamp TM, Gevers SK, Bovenberg JA, Koppelman GH, van Hylckama Vlieg A, Smets EM. Communication of biobanks' research results: what do (potential) participants want? *Am J Med Genet A*. 2010;152A(10):2482–2492. [PubMed: 20799322]

3. Radecki Breitkopf C, Petersen GM, Wolf SM, et al. Preferences Regarding Return of Genomic Results to Relatives of Research Participants, Including after Participant Death: Empirical Results from a Cancer Biobank. *Journal of Law Medicine & Ethics*. 2015;43(3):464–475.
4. Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. *Genet Med*. 2008;10(11):331–339.
5. Burke W, Evans BJ, Jarvik GP. Return of Results: Ethical and Legal Distinctions between Research and Clinical Care. *American journal of medical genetics Part C, Seminars in medical genetics*. 2014;0(1):105–111.
6. Evans BJ. Minimizing liability risks under the ACMG recommendations for reporting incidental findings in clinical exome and genome sequencing. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2013;15(12):915–920. [PubMed: 24030435]
7. Beskow LM, Burke W. Offering Individual Genetic Research Results: Context Matters. *Sci TranslMed*. 2010;2(38):38cm20–38cm20.
8. Lakes KD, Vaughan E, Lemke A, et al. Maternal Perspectives on the Return of Genetic Results: Context Matters. *Am J Med Genet A*. 2013;161(1):38–47.
9. Jarvik GP, Amendola LM, Berg JS, et al. Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between. *Am J Hum Genet*. 2014;94(6):818–826. [PubMed: 24814192]
10. Fabsitz RR, McGuire A, Sharp RR, et al. Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group. *Circ Cardiovasc Genet*. 2010;3(6):574–580. [PubMed: 21156933]
11. Cacioppo CN, Chandler AE, Towne MC, Beggs AH, Holm IA. Expectation versus Reality: The Impact of Utility on Emotional Outcomes after Returning Individualized Genetic Research Results in Pediatric Rare Disease Research, a Qualitative Interview Study. *PLoS One*. 2016;11(4):e0153597.
12. Christensen KD, Roberts JS, Shalowitz DI, et al. Disclosing individual CDKN2A research results to melanoma survivors: interest, impact, and demands on researchers. *Cancer Epidemiol Biomarkers Prev*. 2011;20(3):522–529. [PubMed: 21307304]
13. Klein AP. Genetic susceptibility to pancreatic cancer. *Mol Carcinog*. 2012;51(1):14–24. [PubMed: 22162228]
14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7–30. [PubMed: 26742998]
15. Petersen GM. Familial pancreatic cancer. *Semin Oncol*. 2016;43(5):548–553. [PubMed: 27899186]
16. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339–347. [PubMed: 23135763]
17. National Comprehensive Cancer Network. Pancreatic Adenocarcinoma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network 2017.
18. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110(2):223–262; quiz 263. [PubMed: 25645574]
19. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*. 2018;46(D1):D1062–D1067. [PubMed: 29165669]
20. McWilliams RR, Wieben ED, Rabe KG, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling. *Eur J Hum Genet*. 2011;19(4):472–478. [PubMed: 21150883]
21. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *J Am Med Assoc*. 2018;319(23):2401–2409.
22. NM_000077.4(CDKN2A):c.47T>G (p.Leu16Arg). 2018; <https://www.ncbi.nlm.nih.gov/clinvar/variation/219815/>.
23. Marks D, Horn IP, Hogenson TL, et al. Reducing protein stability underlies the protumoral function of L16R(47T>G) CDKN2A, a mutation associated with familial pancreatic cancer. Paper presented at: American Association for Cancer Research (AACR) Special Conference: Pancreatic Cancer: Advances in Science and Clinical Care; September, 2018; Boston, MA.

24. Petersen GM, de Andrade M, Goggins M, et al. Pancreatic cancer genetic epidemiology consortium. *Cancer Epidemiol Biomarkers Prev.* 2006;15(4):704–710. [PubMed: 16614112]
25. de Snoo FA, Bishop DT, Bergman W, et al. Increased Risk of Cancer Other Than Melanoma in CDKN2A Founder Mutation (p16-Leiden)-Positive Melanoma Families. *Clin Cancer Res.* 2008;14(21):7151–7157. [PubMed: 18981015]
26. Vaseen H, Ibrahim I, Ponce CG, et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. *J Clin Oncol.* 2016;34(17):2010–2019. [PubMed: 27114589]
27. Begg CB, for the Genes E, Melanoma Study G, et al. Lifetime Risk of Melanoma in CDKN2A Mutation Carriers in a Population-Based Sample. *JNCI: Journal of the National Cancer Institute.* 2005;97(20):1507–1515. [PubMed: 16234564]
28. Bruno MJ. Pancreatic cancer screening in high-risk individuals: Ready for prime time? *GastrointestEndosc.* 2018;87(6):1451–1453.
29. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol.* 2002;21(6):564–572. [PubMed: 12433008]
30. DeSalvo KB, Fan VS, McDonnell MB, Fihn SD. Predicting mortality and healthcare utilization with a single question. *Health Serv Res.* 2005;40(4):1234–1246. [PubMed: 16033502]
31. Locke DE, Decker PA, Sloan JA, et al. Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *J Pain Symptom Manage.* 2007;34(6):628–638. [PubMed: 17703910]
32. National Cancer Institute. Health Information National Trends Survey. 2013; https://hints.cancer.gov/docs/Instruments/HINTS_4_Cycle_3_English_Annotated_508c_3_21_2014.pdf Accessed September 28th, 2017.
33. Hsieh H-F, Shannon SE. Three Approaches to Qualitative Content Analysis. *Qualitative Health Research.* 2005;15(9):1277–1288. [PubMed: 16204405]
34. Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, Kaariainen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. *Int J Cancer.* 2001;93(4):608–611. [PubMed: 11477567]
35. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol.* 2009;28(4):510–518. [PubMed: 19594276]
36. Gritz ER, Peterson SK, Vernon SW, et al. Psychological impact of genetic testing for hereditary nonpolyposis colorectal cancer. *J Clin Oncol.* 2005;23(9):1902–1910. [PubMed: 15774782]
37. Meiser B, Collins V, Warren R, et al. Psychological impact of genetic testing for hereditary non-polyposis colorectal cancer. *Clin Genet.* 2004;66(6):502–511. [PubMed: 15521977]
38. Aspinwall LG, Taber JM, Leaf SL, Kohlmann W, Leachman SA. Genetic testing for hereditary melanoma and pancreatic cancer: a longitudinal study of psychological outcome. *Psychooncology.* 2013;22(2):276–289. [PubMed: 23382133]
39. Halbert CH, Stopfer JE, McDonald J, et al. Long-term reactions to genetic testing for BRCA1 and BRCA2 mutations: does time heal women's concerns? *J Clin Oncol.* 2011;29(32):4302–4306. [PubMed: 21990416]
40. Lynch HT, Snyder C, Lynch JF, et al. Patient responses to the disclosure of BRCA mutation tests in hereditary breast-ovarian cancer families. *Cancer Genet Cytogenet.* 2006;165(2):91–97. [PubMed: 16527602]
41. Jenkins J, Calzone KA, Dimond E, et al. Randomized comparison of phone versus in-person BRCA½ predisposition genetic test result disclosure counseling. *Genet Med.* 2007;9(8):487–495. [PubMed: 17700386]
42. Buchanan AH, Rahm AK, Williams JL. Alternate Service Delivery Models in Cancer Genetic Counseling: A Mini-Review. *Front Oncol.* 2016;6(120).
43. Peshkin BN, Kelly S, Nusbaum RH, et al. Patient Perceptions of Telephone vs. In-Person BRCA1/BRCA2 Genetic Counseling. *Journal of Genetic Counseling.* 2016;25(3):472–482. [PubMed: 26455498]

44. Burgess KR, Carmany EP, Trepanier AM. A Comparison of Telephone Genetic Counseling and In-Person Genetic Counseling from the Genetic Counselor's Perspective. *Journal of Genetic Counseling*. 2016;25(1):112–126. [PubMed: 26044544]
45. Schwartz MD, Valdimarsdottir HB, Peshkin BN, et al. Randomized Noninferiority Trial of Telephone Versus In-Person Genetic Counseling for Hereditary Breast and Ovarian Cancer. *J Clin Oncol*. 2014;32(7):618–626. [PubMed: 24449235]
46. Shiloh S, Koehly L, Jenkins J, Martin J, Hadley D. Monitoring coping style moderates emotional reactions to genetic testing for hereditary nonpolyposis colorectal cancer: a longitudinal study. *Psychooncology*. 2008;17(8):746–755. [PubMed: 18615871]
47. de Snoo FA, Riedijk SR, van Mil AM, et al. Genetic testing in familial melanoma: uptake and implications. *Psychooncology*. 2008;17(8):790–796. [PubMed: 18613292]

Table 1.Sample Characteristics: *n*(%)

	All Participants (<i>N</i> =63)	Blood-Relatives		Spouses (<i>n</i> =8)
		Carriers (<i>n</i> =15)	Non-Carriers (<i>n</i> =40)	
Age				
Mean(SD)	58.76(14.9)	54.8(12.2)	57.7(15.8)	71.5(7.0)
Range[Median]	28–90[59]	37–75[57]	28–90[56]	63–83[69.5]
Sex				
Female	41(65.1)	12(80)	24(60)	5(62.5)
Male	22(34.9)	3(20)	16(40)	3(37.5)
Race				
White	61(96.8)	15(100)	38(95)	8(100)
Missing	2(3.2)		2(3.6)	
Ethnicity				
Non-Hispanic	55(87.3)	13(86.7)	34(85)	8(100)
Missing	8(12.7)	2(13.3)	6(15)	
Marital Status				
Married	50(79.4)	11(73.3)	31(77.5)	8(100)
Single/Never married	5(7.9)	1(6.7)	4(10)	
Widowed	2(3.2)		2(5)	
Divorced	1(1.6)	1(6.7)		
Missing	5(7.9)	2(13.3)	3(6.3)	
Education				
High school degree	19(30.2)	3(20)	12(30.0)	4(50)
Some college	10(15.9)	3(20)	4(10)	3(37.5)
College degree	23(36.5)	6(40)	17(42.5)	
Post-graduate degree	8(12.7)	2(13.3)	5(12.5)	1(12.5)
Missing	3(4.8)	1(6.7)	2(5)	
Biological Children				
Yes	52(82.5)	13(86.7)	31(77.5)	8(100)
No	8(12.7)	1(6.7)	7(17.5)	
Missing	3(4.8)	1(6.7)	2(5)	
Personal History of Cancer				
No	44(69.8)	9(60)	30(75)	5(62.5)
Yes	19(30.2)	6(40)	10(25)	3(37.5)
Breast cancer		1 [†]	1	
Colorectal cancer			1	

	All Participants (N=63)	Blood-Relatives		Spouses (n=8)
		Carriers (n=15)	Non-Carriers (n=40)	
Kidney cancer			1	
Lymphoma				1
Melanoma		5	2	
Non-melanoma skin cancer			1	
Pancreatic islet cell tumor			1	
Prostate cancer				1
Testicular cancer			1	
Thyroid cancer		1 [†]		
Cancer type not disclosed		1	2	1

[†]Note: This participant has been diagnosed with breast cancer, melanoma, and thyroid cancer.

Table 2.GSRH, QoL, and Emotional Experiences: *Mean(SD)*

		Blood-Relatives		<i>p^a</i>	<i>p^b</i>	<i>p^c</i>	Spouses	<i>p^d</i>	<i>p^e</i>
		Carriers	Non carriers						
GSRH	Pre-disclosure	3.80(0.56)	3.83(0.68)	.890	.653	.354	4.13(0.64)	.258	.080
	6-months Post-disclosure	3.67(0.90)	3.83(0.71)	.546			3.75(0.46)	.711	
QoL	Pre-disclosure	7.80(1.42)	8.00(1.36)	.643	.301	.427	8.29(1.70)	.686	.695
	6-months Post-disclosure	7.47(1.46)	8.08(1.37)	.174			8.00(2.67)	.937	
Happy	Pre-disclosure	3.87(0.35)	3.98(0.28)	.295	.175	.369	3.75(0.71)	.403	1.00
	6-months Post-disclosure	3.93(0.26)	4.00(0.23)	.388			3.75(0.71)	.354	
Angry	Pre-disclosure	1.93(0.46)	1.84(0.55)	.556	.829	.930	2.00(0.76)	.598	.351
	6-months Post-disclosure	1.87(0.52)	1.89(0.66)	.870			1.75(0.46)	.470	
Anxious	Pre-disclosure	2.27(0.70)	2.24(0.82)	.768	.704	.232	2.25(0.89)	.886	.516
	6-months Post-disclosure	2.47(0.92)	2.32(0.93)	.595			2.50(0.53)	.457	
Hopeful	Pre-disclosure	3.60(0.83)	3.72(0.78)	.659	.905	.024	3.29(1.25)	.415	.111
	6-months Post-disclosure	4.00(0.53)	3.83(0.61)	.206			4.38(0.49)	.015	
Sad	Pre-disclosure	2.43(0.76)	1.78(0.64)	.008	.002	.936	2.43(0.79)	.070	.356
	6-months Post-disclosure	2.36(0.50)	1.83(0.65)	.005			2.00(0.69)	.595	

Note.

^a *p*-values were from Welch's t-tests comparing carriers and blood relative non-carriers;^b *p*-values were from mixed-design ANOVAs testing difference by variant status;^c *p*-values were from mixed-design ANOVAs testing change between pre-disclosure and 6-months post-disclosure;^d *p*-values were from Welch's t-tests comparing blood relative non-carriers and spouses;^e *p*-values were from paired sample t-tests comparing spouses' pre-disclosure and 6-months post-disclosure responses.

Table 3.MICRA: *Mean(SD)*

	Blood-Relatives		<i>p</i> ^a	Spouses	<i>p</i> ^b
	Carriers	Non Carriers			
Distress	6.00(4.44)	2.15(3.46)	.006	0	<.001
Uncertainty	12.87(7.17)	7.28(7.03)	.016	2.25(2.55)	.001
Positive Experiences	8.27(3.06)	14.25(5.61)	<.001	12.75(4.77)	.448
Feeling relieved about my test result	0.29(0.47)	3.73(1.54)	<.001	2.88(1.73)	.227
Feeling happy about my test result	0	3.83(1.55)	<.001	2.88(2.03)	.243
Feeling that my family has been supportive during the process of learning my genetic result	4.13(1.46)	3.38(2.17)	.145	3.75(2.31)	.682
Feeling satisfied with family communication about my genetic test result	3.87(1.64)	3.33(1.91)	.307	3.25(2.19)	.930
Individual Items					
Understanding clearly my choices for cancer prevention or early detection	2.86(1.79)	2.05(1.74)	.158	1.75(1.39)	.604
Feeling regret about getting my test result	0.13(0.35)	0.23(0.92)	.595	0	.130
Worrying about the possibility of my children getting cancer	2.00(1.18)	1.38(1.02)	.061	1.75(1.04)	.424
Feeling guilty about possibly passing on the disease risk to my child(ren)	1.43(1.09)	1.09(1.03)	.284	0.38(0.74)	.046
Feeling that the genetic research result has made it harder to cope with my cancer	0.33(0.82)	0.56(0.88)	.683	0	.111
Feeling that the genetic research result has made it easier to cope with my cancer	1.50(1.38)	2.00(1.12)	.521	0.67(1.15)	.155

Note.

^a*p*-values were from Welch's t-tests comparing carriers and blood relative non-carriers;^b*p*-values were from Welch's t-tests comparing blood relative non-carriers and spouses.