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Inaccuracies in Patient Self-Report of Genetic Testing Results for Hereditary Cancer Risks Could Impact Risk-Management Practices

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Inaccuracies in Patient Self-Report of Genetic Testing Results for Hereditary Cancer Risks Could Impact Risk-Management Practices

by

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Dedication

To Lucy, my constant reminder that a rising tide lifts all boats.

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Abstract

Pathogenic variants (PV) or likely pathogenic variants (LPV) in a cancer risk gene increase lifetime risks of developing cancer. National guidelines provide evidence-based recommendations on cancer risk management (CRM) strategies tailored to the cancer risks associated with PV/LPV in different genes. Emotional responses after learning of a PV/LPV have been studied as predictors of patient adherence to CRM, but less attention has been given to whether patients remember their actual genetic test results and the impact this may have on subsequent adherence to CRM. We surveyed a group of 114 participants registered with the Inherited Cancer Registry (ICARE), all of whom have at least one PV/LPV in a cancer risk gene, have provided their laboratory report to the registry, and completed a survey asking them to self-report their cancer risk variants, CRM practices, and emotional experiences stemming from genetic testing. We found that 27% of participants omitted or self-reported at least one result inaccurately; 61% of these errors could potentially result in over- or under-management of their cancer risks. Participants with errors potentially leading to over-management were more likely to be adhering to minimum CRM guidelines than other participants and reported significantly more positive outcomes. We also found that, regardless of self-report accuracy, patients engaged in CRM in excess of national guidelines reported significantly more distress and uncertainty related to their results but also more positive outcomes. In total, 60% of patients were engaged in either less than the minimum recommended CRM or CRM beyond the scope of national guidelines. These findings suggest that interventions to improve patient recall and promote adherence to

evidence-based CRM are needed among a large segment of patients with hereditary cancer predispositions.

Introduction

Genetic testing has become a powerful tool providing insight into the diagnosis and treatment of cancer. For the 5-10% of individuals whose cancer is caused by hereditary cancer syndromes (National Cancer Institute at the National Institutes of Health [NCI], 2017) and their at-risk family members, genetic testing also informs future cancer risk management (CRM) with prevention and cancer screening options (e.g., more frequent colonoscopies to reduce colon cancer risks). These CRM interventions have the ability to reduce the risk of developing cancer (De Felice et al., 2015), extend life expectancy (NCI, 2019a), and improve quality of life (Neal et al., 2015). Given that more than 1.8 million people in the U.S. are diagnosed with cancer annually (NCI, 2020), 90,000 – 180,000 of these people have genetic predispositions for developing cancer, in addition to innumerable family members who would benefit from enhanced CRM.

Germline genetic testing can reveal elevated lifetime risks faced by a person with a pathogenic variant (PV) or likely pathogenic variant (LPV) in a cancer risk gene, with potential ramifications for patients' emotional wellbeing. Extensive research has explored the psychosocial impact of genetic testing by examining emotional outcomes, and most studies have found no long-term psychological harms (Bleiker et al., 2013; Cella et al., 2002; Esteban et al., 2018; O'Neill et al., 2009). Emotional outcomes of genetic testing are related to adherence to CRM in a complex loop (De Leeuw et al., 2008; Miller, 1995), with some studies showing that lower emotional distress increases the likelihood of active participation in risk management

(Yanes et al., 2019), whereas higher distress is predictive of adherence to CRM in others (Buchanan et al., 2017).

Using empiric cancer risks and international research on management outcomes, the National Comprehensive Cancer Network (NCCN) makes recommendations for CRM tailored to the presence of PV/LPV for each of dozens of cancer risk genes based on potential benefits and harms, leaving latitude for joint patient-clinician decision-making based on variables such as timing of childbearing and family history when medical or ethical ambiguity exists (National Comprehensive Cancer Network, 2021a, 2021c). For example, in genes where PV/LPV confer high risks for ovarian cancer, guidelines include clear recommendations for surgical CRM through risk-reducing salpingo-oophorectomy (RRSO) in *BRCA1/2, BRIP1,* and *RAD51C/D*, but, for breast cancer CRM in high-risk genes such as *BRCA1/2* or *PALB2*, where risk-reducing mastectomy does not have superior survival outcomes relative to increased imaging surveillance, guidelines list either approach as acceptable (National Comprehensive Cancer Network, 2021c). Guidelines are even more nuanced in moderate penetrance cancer genes, where recommendations balance the benefits of cancer risk-reduction against the potential harm of frequent, expensive, or invasive CRM. Although a significant amount of attention has understandably been paid to whether patients with PV/LPVs in cancer risk genes adhere to minimum CRM guidelines, especially in high-risk genes such as *BRCA1/2*, there exists a potential for moderate risk genes to be inappropriately *over*-treated (Tung et al., 2016). The potential for overtreatment based on empiric risks has been comparatively under-studied, but the issue has been explicitly raised in a small number of studies (Cragun et al., 2020; Wood et al., 2020).

In general, adherence to CRM is positively associated with cancer knowledge (Buchanan et al., 2017; Lumish et al., 2017). Although the majority of patients (80%) correctly recalled the body systems in which they have elevated risks (e.g., colon cancer) in one study (Kaphingst et al., 2012), recall of general genetics and hereditary cancer knowledge was fairly low in another, with 50% of content accurately recalled after counseling by a genetics professional (Jacobs et al., 2015). However, it is unclear how CRM is related to patients' ability to recall the knowledge of their actual genetic test *result*. Only a few previously published studies appear to have examined whether patients accurately recall these results; Wing et al. (2021) found that 31% (11/36) of patients undergoing germline testing did not recall even receiving testing, and 44% (4/9) of patients with PV/LPV results identified in germline testing did not accurately recall the gene and/or variant type. In their study, patients who accurately recalled results of germline testing had higher genetics knowledge than those who did not, but they did not differ in whether they had positive or negative test results (Wing et al., 2021). Given the small number of PV/LPV-positive participants in their study, their analyses may have been underpowered to detect differences based on result type. In another study limited to individuals with a variant of uncertain significance (VUS) test result in one of the Lynch syndrome genes, 14% did not recall receiving a VUS result (Solomon et al., 2017). Although information is limited, these studies suggest a troublingly low recall of test results that may negatively impact CRM that appropriately balances the emotional, physical, and economic consequences of management.

To our knowledge, no studies have assessed the extent to which self-reported results match test reports among a large cohort of individuals with PV/LPV in hereditary cancer genes. The aim of this study was to characterize recall of test results among individuals with confirmed PV/LPV in hereditary cancer genes and to identify the extent to which inaccurate recall of test

results could impact medical management. These findings can potentially inform efforts to improve appropriate medical management of cancer risks related to germline cancer predispositions.

Methods

This research was part of a larger, multiyear study conducted to develop interventions to improve family communication and personalized medical management among participants with a PV/LPV in at least one cancer predisposition gene. Approval to conduct this human subjects research was obtained by the institutional review board at Vanderbilt University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Email invitations to participate in the study by completing a questionnaire were issued to 774 participants in the Inherited Cancer Registry (ICARE) who had an email address on file, agreed to be contacted about other research opportunities, had a verified PV/LPV in at least one of 23 genes associated with elevated cancer risks, and, based on prior survey responses, were likely to require ongoing cancer screening/surveillance and have at least one at-risk family member who either has not undergone genetic testing of their own or was not aware of the participant's positive genetic test result. Participants were offered a $10 gift card for completing the questionnaire and medical records release form.

Measures

The survey asked participants to self-report their genetic test results along with information about their cancer counseling experiences, personal and family histories of cancer, and psychological outcomes of receiving results. The questionnaire also included 50 questions about participants' demographics, personal and family histories of cancer, clinicians involved in

their decision to pursue genetic testing, attitudes about genetic testing, and psychological outcomes of their genetic test results, including the multidimensional impact of cancer risk assessment (MICRA) (Cella et al., 2002). The MICRA is a validated, 21-item assessment of four emotional impacts of genetic testing: six items evaluate distress, four items evaluate positive experiences, nine items evaluate uncertainty (Cronbach's α=.86, .75, .77, respectively), and one item evaluates regret. Our questionnaire included 20 of the original 21 MICRA questions plus a re-wording of the original "understanding clearly my choices for cancer prevention or early detection" to a reverse-coded "feeling consumed or uncertain about what cancer prevention guidelines are best for me." With the exception of regret, responses were compiled across each domain and averaged by the total number of questions in order to create a composite response that reflected the original questionnaire scale of 0-3 for "never," "rarely," "sometimes," and "often."

Data Analysis

Self-reported information about genetic variants identified on testing was compared to each participant's actual test results, and discrepancies between self-report versus laboratory report were assessed for the potential to impact medical management based on NCCN guidelines for each gene (National Comprehensive Cancer Network, 2021a, 2021c, 2022, 2022b). Using NCCN guidelines for specific genes, the first author categorized participants into one of four groups: 1) accurate reporters, 2) inaccurate reporters with potential for under-management (i.e., management for the result they reported would not meet NCCN guidelines for their actual test results), 3) inaccurate reporters with potential for over-management (i.e., following guidelines for the gene/variant reported would result in screening, surveillance, or surgery in excess of the guidelines for their actual test result), and 4) inaccurate reporters where the inaccurate recall

should not result in a change to management. Specifically, errors in recall were categorized as potential for under-management if a PV or LPV was 1) not reported, 2) reported without a gene name, or 3) reported as a VUS. Errors were coded as having the potential to result in over-management if a VUS was reported as PV/LPV or a PV/LPV was self-reported but absent from their laboratory result(s). Self-report errors were coded as not expected to affect medical management in cases where a participant 1) did not report a VUS that was on the lab report, 2) reported they had a VUS but could not remember or failed to report the gene name, 3) reported a VUS with the wrong gene name; or 4) they reported more than one PV/LPV in the same gene when only one was noted in the test report. Finally, we noted that a PV or LPV reported with the wrong gene name could result in under- or over-management, depending on the recall error (e.g., *ATM* v. *BRCA2*, which differ in the age at which breast surveillance should begin as well as the strength of oophorectomy recommendation). Each of these errors were examined individually to determine if the inaccuracy had the potential to result in over-management or under-management.

Additionally, participants were classified as concordant with minimum CRM guidelines if they were participating in screening or had completed risk-reducing surgeries listed as "recommended" by NCCN guidelines. We also noted which participants' management was in excess of the guidelines, such as screening or risk-reducing surgery in an organ system without elevated cancer risks or more frequent screening intervals than recommended by NCCN guidelines. Because NCCN guidelines for clinical decision-making for oophorectomy and pancreatic screening in moderate-risk genes are impacted by family history, we did not consider those modes of CRM excessive when oophorectomy occurred in patients with PV/LPV in *ATM* or *PALB2*, nor when individuals engaged in pancreatic screening if they had a PV/LPV in *ATM,*

BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, or *TP53* (National Comprehensive Cancer Network, 2021c). A full list of criteria used as the minimum for guideline-concordant risk management and criteria which is considered in excess of recommendations are listed in Appendix A. Some participants had PV/LPV results for multiple genes; for these participants, we assessed whether medical management met or exceeded recommendations for all PV/LPVs indicated by their laboratory report(s).

Descriptive statistics were conducted to characterize those participants who recalled their genetic test results accurately and those who made an error in self-report of results. ANOVA was used to compare composite MICRA responses between participants who correctly recalled results and those whose errors could result in under-management, over-management, or have no effect on management. Chi-square test was used to assess whether adherence to minimum NCCN guidelines or management in excess of NCCN guidelines differed among participants who accurately recalled their results, and those whose errors could result in under-management, over-management, or have no effect on management. Independent t-test was used to assess whether emotional outcomes differed significantly among 1) all participants engaged in minimum management versus those who were not and 2) all participants receiving management outside the scope of NCCN guidelines versus those who remained within scope. The adherence of two participants was unclear because the frequency of their colonoscopies was marked “other”; these patients were excluded from analyses. Statistical analyses were conducted in SPSS (version 27, IBM), and tests were considered statistically significant at a p value ≤ 0.05.

Results

Participant demographics

One hundred fourteen respondents completed the questionnaire. Respondents were mostly female, White, married, college- or graduate school-educated, had an annual household income over $100,000, and were privately insured (Table 1). Approximately half of respondents reported a personal history of cancer, predominantly breast cancer. Of the 114 participants, 84 (73%) correctly recalled their genetic test results, and 31 (27%) made an error in the gene name or variant classification type (Figure 1). The accurate recall group consisted of a higher proportion of participants who report Ashkenazi Jewish descent (24% v. 10%), were married (75% v. 65%), had at least some college education (98% v. 87%), and had private insurance (78% v. 68%). The accurate recall group had fewer male participants (7.2% v. 16.1%), with only 45% of the 11 male participants self-reporting their results accurately.

The 114 participants had 126 PV/LPV, two cases of the I1307K *APC* increased risk allele, and 26 VUS results. Among the 31 participants in the inaccurate recall group, 36 PV/LPVs, one case of *APC* I1307K, and 18 VUS were present. Self-report inaccuracies could result in under-management of cancer risks in 42% (13/31), over-management in 19% (6/31), and should have no effect on management in 39% (12/31; Figure 2).

Differences in CRM management among test result recall discrepancies

Across all participants, 80% were following the minimum NCCN recommended CRM practices. Among those participants who correctly reported their results (68/83), 82% were participating in the minimum recommended management, while only 67% of the potentially

under-treated group (8/12) were doing so. Conversely, 100% of the potentially over-treated group (6/6) were following minimum cancer risk management guidelines. Chi square tests comparing minimum guideline adherence across reporter types was not statistically significant, X^2 (3, N=112)=3.95, p=0.267).

Among all participants, 46/114 (40%) were receiving care that appeared to be in excess of NCCN CRM recommendations. The percentage of participants receiving excess CRM ranged from 30-39% for accurate reporters and those inaccurate reporters with potential for over- and under-treatment, but excess CRM occurred in 58% of participants with errors that should have no effect on treatment (Figure 3). Despite these descriptive differences, chi square tests comparing groups' overtreatment across reporter types was not statistically significant, X^2 (3, N=112)=1.45, p=0.695).

Emotional outcomes among self-report discrepancies

Across participants, reliability of the MICRA subscales of distress, positive outcomes, uncertainty were high (α=.92, .79, .88, respectively). No significant differences in distress, positive outcomes, uncertainty, or regret was present between participants who accurately versus inaccurately self-reported their results of genetic testing t(112)=1.43, p=.077, t(112)=-.50, p=.31 t(112)=.46, p=.32 t(112)=-.11, p=.46, respectively. When comparing the four groups of participants based on accurate recall of results and their potential to impact CRM, ANOVA found statistically significant differences on the positive outcomes scale, F(3,100)=2.63, p=0.05 (Figure 4). Bonferroni-adjusted post hoc analyses indicated that those with errors that could potentially lead to over-management reported significantly more positive outcomes (M=2.00, SD=1.14) than those whose errors should have no effect (M=0.85, SD=.92), but they did not differ from either accurate reporters (M=1.21, SD=.79) or those whose errors could potentially

result in under-management (M=1.42, SD=1.02). Although distress scores were somewhat lower among those with inaccurately self-reported results that had the potential to lead to over-treatment (M=.36, SD=.65) compared to accurate reporters (M=.70, SD=.76), potential under-treatment (M=.50, SD=.63), or no-effect discrepant reporters (M=.51, SD=.69), differences were not statistically significant, $F(3,110)=.74$, $p=0.53$. Uncertainty and decisional regret did not differ significantly between the four groups of participants, $F(3,110)=.30$, p=.83 and $F(3,110)=.10$, p=.96, respectively.

Emotional outcomes and reported adherence to CRM management

Regardless of whether they accurately recalled their test result, participants who were engaged in CRM practices that appeared excessive based on NCCN guidelines reported significantly more distress (M=.86, SD=.82) and uncertainty (M=.87, SD=.43) relative to participants whose CRM fell within the scope of NCCN guidelines, $t(112)=-2.62$, $p=.003$ and $t(112)=-1.98$, $p=.025$, respectively; they also reported significantly more positive outcomes (M=1.41, SD=.82), $t(112)=-1.71$, $p=.045$ (Figure 5b). Decisional regret did not differ among participants who did and did not appear to be receiving excess management (M=.15, SD=.062 vs. M=.10, SD=.043), $t(112)=-.68$, $p=.25$.

No emotional outcomes assessed by MICRA differed based on whether participants were or were not minimally adherent to guidelines: distress (M=.63, SD=.08 vs. M=.68, SD=.15; $t(110)=.285$, $p=.388$), positive outcomes (M=1.25, SD=87 vs. M=1.22, SD=.19; $t(110)=-.10$, $p=.462$), uncertainty (M=.76, SD=.042 vs. M=.86, SD=.10; $t(110)=.934$, $p=.18$), regret (M=.10, SD=0.39 vs. M=.18, SD=.084; $t(110)=.92$, $p=.18$) (Figure 5a).

Discussion

The long-term goal of genetic testing is to help provide evidence-based CRM that balances reducing cancer incidence (De Felice et al., 2015), increasing survival (NCI, 2019a), and improving quality of life (Neal et al., 2015) against potential complications and comorbidities of excessive medical care (Cragun et al., 2020; Wood et al., 2020). Many studies have assessed psychological outcomes, risk perception, and/or cancer genetics knowledge after results disclosure as a potential proxy for CRM (Jacobs et al., 2015; Lumish et al., 2017; Schwartz et al., 2014; Smerecnik et al., 2009; Yanes et al., 2019). However, we are aware of only one previous study that assessed whether patients correctly recall their germline genetic test results. That prior study found that only 44% of participants with PV/LPV accurately recalled their results of genetic testing, but that study included mostly people with negative germline test results or somatic tumor testing, with only nine patients possessing pathogenic variants in hereditary cancer genes (Wing et al., 2021). Furthermore, Wing et al. did not assess participants' engagement in CRM.

We found that among 114 participants with PV/LPV, 27% incorrectly reported their genetic test results and demonstrated that although the inaccurate recall had the potential to lead to higher rates of over- or under-management, CRM practices were not significantly different among groups with accurate recall of their genetic test results and those with errors in self-report of results. Overall, a majority of participants were following NCCN screening and risk management guidelines, with 81% following minimum recommendations and 60% within the scope of the guidelines' recommendations.

Although our study had a much larger sample size than Wing et al. (2021), there is limited statistical power necessary to detect differences in CRM practices based on accuracy of test result recall. However, we revealed interesting descriptive results that may inform future investigations. Adherence was high overall, peaking at 100% among patients whose self-report could result in over-management. This pattern may suggest higher levels of concern about cancer and, subsequently, more vigilance in monitoring for cancer or higher uptake of surgical prevention options among these participants. Indeed, "monitoring" is a coping style exhibited by patients who seek out information and find management to be a self-efficacious way to control the threat of cancer (Miller, 1995). Similarly, worry has been suggested to be what drives some patients to pursue aggressive cancer risk management (De Leeuw et al., 2008). Our results suggest that those for whom misremembering their result could have led to excess care did have a non-significant tendency to report more distress and had higher adherence to minimum CRM, but they were not ultimately engaging in excessive care more often than other participants. Furthermore, they reported significantly more positive outcomes resulting from genetic testing. One possible explanation for these findings is that self-report errors may be driven by higher perceived risks, but the efficacy provided by participation in CRM may mitigate negative emotional impacts.

Paradoxically, the participants whose management should remain unaffected by their self-report errors were more likely to be receiving CRM that is possibly excessive. The reporting error made by 11 of the 12 participants in this category involved failure to report or recall the name of a VUS. Indeed, recall of VUS results is poor relative to negative and positive results, and patients receiving VUS results often interpret them to be indicative of elevated risk rather than inconclusive or non-contributory to cancer risks (Hirschberg et al., 2015; Richter et al.,

2013; Solomon et al., 2017; Vos et al., 2008). In one study, one-third of patients with no personal history of cancer underwent additional screening after receiving a VUS result (but no PV/LPV) in a gene associated with breast or ovarian cancer risks (Lumish et al., 2017). Unlike much of the previous research on patient perceptions of risk from VUS results, our study includes participants who *also* have at least one confirmed PV/LPV in a cancer risk gene; perhaps the additional presence of a VUS in another gene for some of these participants, however misremembered, may cause them to engage in excess CRM. Recipients of VUS results have often reported elevated distress and uncertainty relative to recipients of negative results (Lumish et al., 2017; O'Neill et al., 2009; Solomon et al., 2017) and cited a desire to have a management plan in place to reduce ambiguity (Bartley et al., 2020). If the excess management that VUS mis-reporters tend to undertake feels empowering, this may explain why, in our study, these participants did not report higher distress and uncertainty than other participants.

Because NCCN guidelines shift as more evidence becomes available, some studies that assess CRM are difficult to compare retrospectively, such as those that assess adherence to "healthcare professionals' advice" that varied across providers (den Elzen et al., 2021) or having ever vs. never engaged in CRM but lack information on frequency of cancer screenings (Pal et al., 2014). A strength of our study is that we provide an explicit framework for assessment of CRM, including modality and frequency, both of which are key components to determining adherence to national CRM guidelines. However, a limitation of our questionnaire design was the inclusion of an option to report a frequency of "other" without an additional free response to clarify the frequency. An additional limitation is the difficulty in defining minimum and excessive care where NCCN guidelines is unclear or provides clinical latitude that we did not assess. For example, in the absence of clinical information, we found it difficult to assess

frequency of prostate CRM in males with *BRCA2* PV/LPVs; although prostate screening beginning at age 40 is listed as a recommendation (National Comprehensive Cancer Network, 2021c), an appropriate follow-up frequency is dependent on the results of each screening, but should not exceed 4 years (National Comprehensive Cancer Network, 2022b). Our assessments of what constitutes under- or over-management of cancer risks are therefore conservative, with participants having to fall completely outside the range of appropriate CRM to be labeled as such (e.g., 5 years or more between PSA screenings for male *BRCA2* PV/LPV). Finally, because we are capturing a self-reported summary of current and past behaviors, it is subject to the typical limitations of self-report. Because we are not verifying these self-reports of CRM with medical records, they may be inaccurately reported or shift in the future, such as becoming less adherent to CRM over time (Rauscher & Dean, 2018).

Other limitations include that this population is unlikely to be representative of all patients with hereditary cancers because our participant population was disproportionately White, high-income, highly-educated, and female relative to the general population. However, given their higher education and income and their engagement in research, we might expect their self-reporting to be among the most reliable; the fact that 27% of participants nonetheless demonstrated discrepancies between their laboratory results of genetic testing indicates the limitations of self-report that are likely even larger in samples more representative of the general population. Furthermore, even in this cohort, adherence to minimum management is not universal, despite the tendency for White race, high income, and/or high education levels to be socioeconomic predictors of interest and engagement in CRM (Buchanan et al., 2017; Hinchcliff et al., 2019; Plamann et al., 2021).

This study makes a novel contribution to cancer risk management and patient education literature by assessing self-report and its potential impact on management. We found that participants with errors that could lead to potential over-treatment are more likely to conform to minimum guidelines, report significantly more positive psychological outcomes, and tend to experience less distress about GT than other participants. Although we did not find significant differences in management practices among our participants based on recall of test results, future research will include a larger sample size to sufficiently power analyses and apply family history to resolve appropriateness of ovarian and pancreatic risk management.

In summary, given that 60% of our sample may be over or under-managed relative to national guidelines, this research highlights that interventions are needed to improve adherence to minimum guidelines and to prevent unnecessary CRM. Finally, this research underscores the necessity of verifying patients' reports of genetic test results and continually revisiting the most current national guidelines to confirm CRM maximizes benefits relative to potential harms of medical management.

References

Bartley, N., Napier, C., Best, M., & Butow, P. (2020). Patient experience of uncertainty in cancer genomics: A systematic review. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, *22*(9), 1450–1460. https://doi.org/10.1038/s41436-020-0829-y

Bleiker, E. M. A., Esplen, M. J., Meiser, B., Petersen, H. V., & Patenaude, A. F. (2013). 100 years Lynch syndrome: What have we learned about psychosocial issues? *Familial Cancer*, *12*(2), 325–339. https://doi.org/10.1007/s10689-013-9653-8

Buchanan, A. H., Voils, C. I., Schildkraut, J. M., Fine, C., Horick, N. K., Marcom, P. K., Wiggins, K., & Skinner, C. S. (2017). Adherence to Recommended Risk Management among Unaffected Women with a BRCA Mutation. *Journal of Genetic Counseling*, *26*(1), 79–92. https://doi.org/10.1007/s10897-016-9981-6

Cella, D., Hughes, C., Peterman, A., Chang, C.-H., Peshkin, B. N., Schwartz, M. D., Wenzel, L., Lemke, A., Marcus, A. C., & Lerman, C. (2002). A brief assessment of concerns associated with genetic testing for cancer: The multidimensional impact of cancer risk assessment (MICRA) questionnaire. *Health Psychology*, *21*(6), 564–572. https://doi.org/10.1037/0278-6133.21.6.564

Cragun, D., Weidner, A., Tezak, A., Clouse, K., & Pal, T. (2020). Cancer risk management among female BRCA1/2, PALB2, CHEK2, and ATM carriers. *Breast Cancer Research and Treatment*, *182*(2), 421–428. https://doi.org/10.1007/s10549-020-05699-y

De Felice, F., Marchetti, C., Musella, A., Palaia, I., Perniola, G., Musio, D., Muzii, L., Tombolini, V., & Benedetti Panici, P. (2015). Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: A meta-analysis. *Annals of Surgical Oncology*, *22*(9), 2876–2880. https://doi.org/10.1245/s10434-015-4532-1

De Leeuw, J. R. J., van Vliet, M. J., & Ausems, M. G. E. M. (2008). Predictors of choosing life-long screening or prophylactic surgery in women at high and moderate risk for breast and ovarian cancer. *Familial Cancer*, *7*(4), 347–359. https://doi.org/10.1007/s10689-008-9189-5

den Elzen, N., Joseland, S. L., Saya, S., Jonnagadla, S., Isbister, J., Winship, I., & Buchanan, D. D. (2021). "Left in limbo": Exploring how patients with colorectal cancer interpret and respond to a suspected Lynch syndrome diagnosis. *Hereditary Cancer in Clinical Practice*, *19*(1), 43. https://doi.org/10.1186/s13053-021-00201-1

Esteban, I., Vilaró, M., Adrover, E., Angulo, A., Carrasco, E., Gadea, N., Sánchez, A., Ocaña, T., Llort, G., Jover, R., Cubiella, J., Servitja, S., Herráiz, M., Cid, L., Martínez, S., Oruezábal-Moreno, M. J., Garau, I., Khorrami, S., Herreros-de-Tejada, A., … Balmaña, J. (2018). Psychological impact of multigene cancer panel testing in patients with a clinical suspicion of hereditary cancer across Spain. *Psycho-Oncology*, *27*(6), 1530–1537. https://doi.org/10.1002/pon.4686

Hinchcliff, E. M., Bednar, E. M., Lu, K. H., & Rauh-Hain, J. A. (2019). Disparities in gynecologic cancer genetics evaluation. *Gynecologic Oncology*, *153*(1), 184–191. https://doi.org/10.1016/j.ygyno.2019.01.024

Hirschberg, A. M., Chan-Smutko, G., & Pirl, W. F. (2015). Psychiatric implications of cancer genetic testing: Implications of Cancer Genetic Testing. *Cancer*, *121*(3), 341–360. https://doi.org/10.1002/cncr.28879

Jacobs, C., Dancyger, C., Smith, J. A., & Michie, S. (2015). Accuracy of recall of information about a cancer-predisposing BRCA1/2 gene mutation among patients and relatives. *European Journal of Human Genetics*, *23*(2), 147–151. https://doi.org/10.1038/ejhg.2014.84

Kaphingst, K. A., McBride, C. M., Wade, C., Alford, S. H., Reid, R., Larson, E., Baxevanis, A. D., & Brody, L. C. (2012). Patients' understanding of and responses to multiplex genetic susceptibility test results. *Genetics in Medicine*, *14*(7), 681–687. https://doi.org/10.1038/gim.2012.22

Lumish, H. S., Steinfeld, H., Koval, C., Russo, D., Levinson, E., Wynn, J., Duong, J., & Chung, W. K. (2017). Impact of Panel Gene Testing for Hereditary Breast and Ovarian Cancer on Patients. *Journal of Genetic Counseling*, *26*(5), 1116–1129. https://doi.org/10.1007/s10897-017-0090-y

Miller, S. M. (1995). Monitoring versus blunting styles of coping with cancer influence the information patients want and need about their disease. Implications for cancer screening and management. *Cancer*, *76*(2), 167–177. https://doi.org/10.1002/1097-0142(19950715)76:2<167::aid-cncr2820760203>3.0.co;2-k

National Cancer Institute at the National Institutes of Health. (2017, October 12). *The Genetics of Cancer*. https://www.cancer.gov/about-cancer/causes-prevention/genetics

National Cancer Institute at the National Institutes of Health. (2019, January 16). *Screening tests*. https://www.cancer.gov/about-cancer/screening/screening-tests

National Cancer Institute at the National Institutes of Health. (2020, September 25). *Cancer statistics*. https://www.cancer.gov/about-cancer/understanding/statistics

National Comprehensive Cancer Network. (2021a, May 11). *Genetic/Familial High-Risk Assessment: Colorectal (version 1.2021)*. https://www.nccn.org/professionals/physician_gls/default.aspx#detection

National Comprehensive Cancer Network. (2021b, August 11). *Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic (version 1.2022)*. https://www.nccn.org/professionals/physician_gls/default.aspx#detection

National Comprehensive Cancer Network. (2022a, January 11). *Gastric Cancer (version 2.2022)*. https://www.nccn.org/professionals/physician_gls/default.aspx#detection

National Comprehensive Cancer Network. (2022b, February 16). *Prostate Cancer Early Detection (version 1.2022)*. https://www.nccn.org/professionals/physician_gls/default.aspx#detection

Neal, R. D., Tharmanathan, P., France, B., Din, N. U., Cotton, S., Fallon-Ferguson, J., Hamilton, W., Hendry, A., Hendry, M., Lewis, R., Macleod, U., Mitchell, E. D., Pickett, M., Rai, T., Shaw, K., Stuart, N., Tørring, M. L., Wilkinson, C., Williams, B., … Emery, J. (2015). Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *British Journal of Cancer*, *112*(S1), S92–S107. https://doi.org/10.1038/bjc.2015.48

O'Neill, S. C., Rini, C., Goldsmith, R. E., Valdimarsdottir, H., Cohen, L. H., & Schwartz, M. D. (2009). Distress among women receiving uninformative BRCA1/2 results: 12-month outcomes. *Psycho-Oncology*, *18*(10), 1088–1096. https://doi.org/10.1002/pon.1467

Plamann, K., McCarthy Veach, P., LeRoy, B. S., MacFarlane, I. M., Petzel, S. V., & Zierhut, H. A. (2021). Effects of monitoring versus blunting on the public's preferences for information in a hypothetical cancer diagnosis scenario. *Journal of Genetic Counseling*, *30*(1), 132–143. https://doi.org/10.1002/jgc4.1302

Rauscher, E. A., & Dean, M. (2018). "I've just never gotten around to doing it": Men's approaches to managing BRCA -related cancer risks. *Patient Education and Counseling*, *101*(2), 340–345. https://doi.org/10.1016/j.pec.2017.07.015

Richter, S., Haroun, I., Graham, T. C., Eisen, A., Kiss, A., & Warner, E. (2013). Variants of unknown significance in BRCA testing: Impact on risk perception, worry, prevention and counseling. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, *24 Suppl 8*, viii69–viii74. https://doi.org/10.1093/annonc/mdt312

Schwartz, M. D., Valdimarsdottir, H. B., Peshkin, B. N., Mandelblatt, J., Nusbaum, R., Huang, A.-T., Chang, Y., Graves, K., Isaacs, C., Wood, M., McKinnon, W., Garber, J., McCormick, S., Kinney, A. Y., Luta, G., Kelleher, S., Leventhal, K.-G., Vegella, P., Tong, A., & King, L. (2014). Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. *Journal of Clinical Oncology*, *32*(7), 618–626. https://doi.org/10.1200/JCO.2013.51.3226

Smerecnik, C. M. R., Mesters, I., Verweij, E., de Vries, N. K., & de Vries, H. (2009). A systematic review of the impact of genetic counseling on risk perception accuracy. *Journal of Genetic Counseling*, *18*(3), 217–228. https://doi.org/10.1007/s10897-008-9210-z

Solomon, I., Harrington, E., Hooker, G., Erby, L., Axilbund, J., Hampel, H., Semotiuk, K., Blanco, A., Klein, W. M. P., Giardiello, F., & Leonard, L. (2017). Lynch Syndrome

Limbo: Patient Understanding of Variants of Uncertain Significance. *Journal of Genetic Counseling*, *26*(4), 866–877. https://doi.org/10.1007/s10897-017-0066-y

Tung, N., Domchek, S. M., Stadler, Z., Nathanson, K. L., Couch, F., Garber, J. E., Offit, K., & Robson, M. E. (2016). Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nature Reviews Clinical Oncology*, *13*(9), 581–588. https://doi.org/10.1038/nrclinonc.2016.90

Vos, J., Otten, W., van Asperen, C., Jansen, A., Menko, F., & Tibben, A. (2008). The counsellees' view of an unclassified variant in BRCA1/2: Recall, interpretation, and impact on life. *Psycho-Oncology*, *17*(8), 822–830. https://doi.org/10.1002/pon.1311

Wing, S. E., Hu, H., Lopez, L., Solomon, I., Shen, J., Raquel, C., Sur, M., Chao, J., Cristea, M., Fakih, M., Mortimer, J., Pal, S., Reckamp, K., Yuan, Y., & Gray, S. W. (2021). Recall of Genomic Testing Results Among Patients with Cancer. *The Oncologist*, *26*(12), e2302–e2305. https://doi.org/10.1002/onco.13928

Wood, M. E., McKinnon, W., & Garber, J. (2020). Risk for breast cancer and management of unaffected individuals with non-BRCA hereditary breast cancer. *The Breast Journal*, *26*(8), 1528–1534. https://doi.org/10.1111/tbj.13969

Yanes, T., Willis, A. M., Meiser, B., Tucker, K. M., & Best, M. (2019). Psychosocial and behavioral outcomes of genomic testing in cancer: A systematic review. *European Journal of Human Genetics: EJHG*, *27*(1), 28–35. https://doi.org/10.1038/s41431-018-0257-5

Appendix A: Supplemental Tables

Table 1. Demographic characteristics of study participants.

	Correct recall of test result (n=83)		Discrepant recall of test result (n=31)		All participants (n=114)	
	n	**%**	**n**	**%**	**n**	**%**
Gender						
Male	6	7.2	5	16.1	11	9.7
Female	77	92.8	26	83.9	103	90.4
Ancestry						
Ashkenazi Jewish	20	24.1	3	9.7	23	20.2
Hispanic or Latino	4	4.8	2	6.5	6	5.3
Race						
American Indian or Alaskan Native	1	1.2	0	0	1	0.9
Asian-South	0	0	1	3.2	1	0.9
Black, African, African-American	2	2.4	1	3.2	3	2.6
Hispanic or Latin American	4	4.8	2	6.5	6	5.3
White	80	96.4	28	90.3	108	94.7

Table 1. (Continued)

Marital status						
Single or never married	9	10.8	2	6.5	11	9.7
Married	62	74.7	20	64.5	82	71.9
Living together	4	4.8	3	9.7	7	6.1
Divorced or separated	7	8.4	4	12.9	11	9.7
Widowed	1	1.2	2	6.5	3	2.6
Education						
11th-12th grade	2	2.4	2	6.5	4	3.5
GED or equivalent	0	0	2	6.5	2	1.8
Some college	9	10.8	3	9.7	12	10.5
Graduated college	43	51.8	10	32.3	53	46.5
Postgraduate or professional school	29	34.9	14	45.2	43	37.7
Household income						
<$25,000	2	2.4	1	3.2	3	2.6
$25,000-49,999	3	3.6	2	6.5	5	4.4
$50,000-74,999	9	10.8	7	22.6	16	14.0
$75,000-99,999	12	14.5	4	12.9	16	14.0
$100,000-$124,999	15	18.1	2	6.5	17	14.9
$125,000 - $149,999	10	12.1	5	16.1	15	13.2
$150,000 or more	23	27.7	8	25.8	31	27.2
I don't know	8	9.6	2	6.5	10	8.8
Prefer not to answer	1	1.2	0	0	1	0.9

Table 1. (Continued)

Insurance						
Private	65	78.3	21	67.7	86	75.4
Medicare/Medicaid	14	16.9	8	25.8	22	19.3
Military	1	1.2	1	3.2	2	1.8
Other	8	9.6	6	19.4	14	12.3
Ever had cancer						
No	45	54.2	14	45.2	59	51.8
Yes	38	45.8	17	54.8	55	48.3
Basal, squamous cell, or "skin" cancer	*3*	*7.9*	*7*	*41.2*	*10*	*18.2*
Breast	*24*	*63.2*	*11*	*64.7*	*35*	*63.6*
Cervical	*2*	*5.3*		*0*	*2*	*3.6*
Colorectal	*2*	*5.3*	*3*	*17.7*	*5*	*9.1*
Esophageal	*0*	*0*	*1*	*5.9*	*1*	*1.8*
Gastric	*1*	*2.6*	*0*	*0*	*1*	*1.8*
Glioblastoma	*1*	*2.6*	*0*	*0*	*1*	*1.8*
Melanoma	*2*	*5.3*	*0*	*0*	*2*	*3.6*
Oral	*0*	*0*	*2*	*11.8*	*2*	*3.6*
Ovarian	*3*	*7.9*	*0*	*0*	*3*	*5.5*
Thyroid (papillary follicular)	*4*	*10.5*	*0*	*0*	*4*	*7.3*
Prostate	*2*	*5.3*	*0*	*0*	*2*	*3.6*
Rectal neuroendocrine tumor	*1*	*2.6*	*0*	*0*	*1*	*1.8*

Table 1. (Continued)

Renal	*1*	*2.6*	*1*	*5.9*	*2*	*3.6*
Uterine	*3*	*7.9*	*1*	*5.9*	*4*	*7.3*

Appendix B: Supplemental Figures

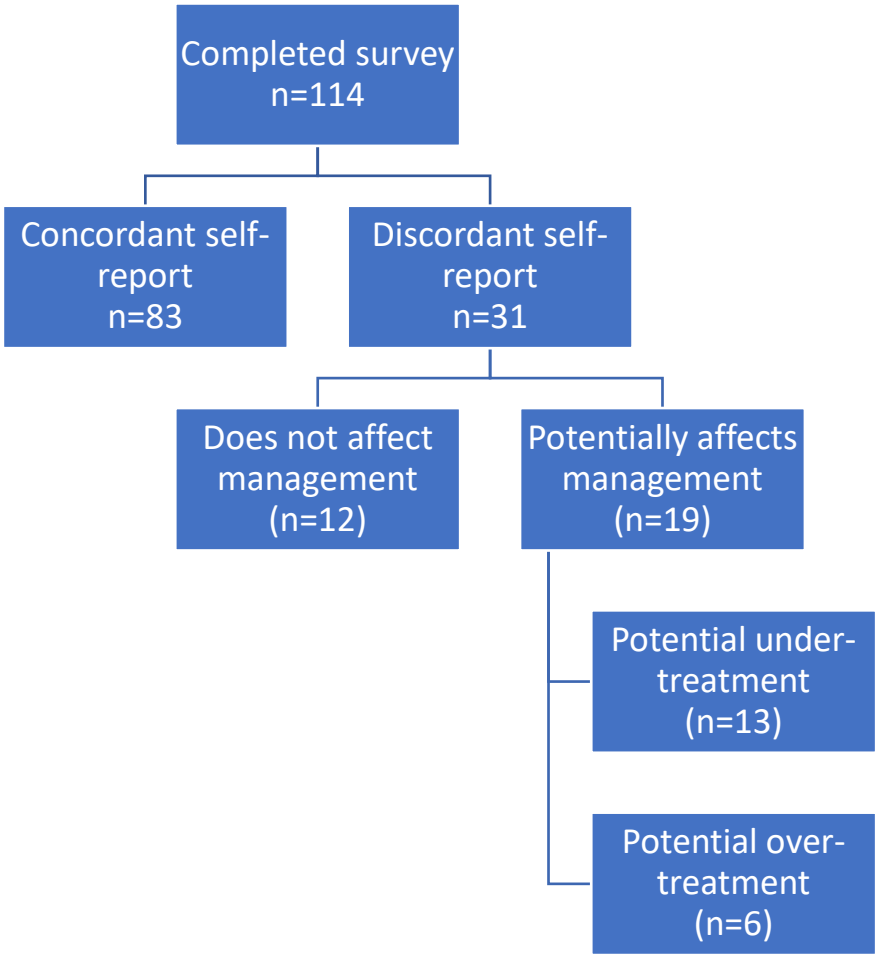


Figure 1. Participants whose lab reports were concordant versus discordant with self-reported recall of genetic testing results for inherited cancer susceptibility and potential effects on medical management.

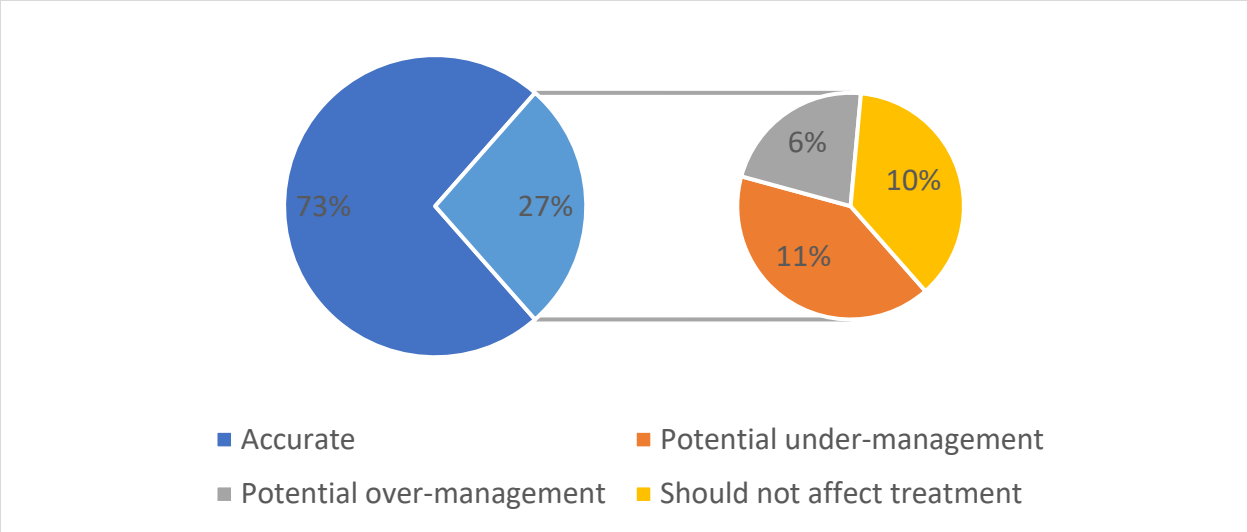


Figure 2. Percentage of patients who accurately self-reported their genetic test results (n=83) or inaccurately report them in a way that could potentially result in under-management (n=13), over-management (n=6), or should have no effect on treatment (n=12).

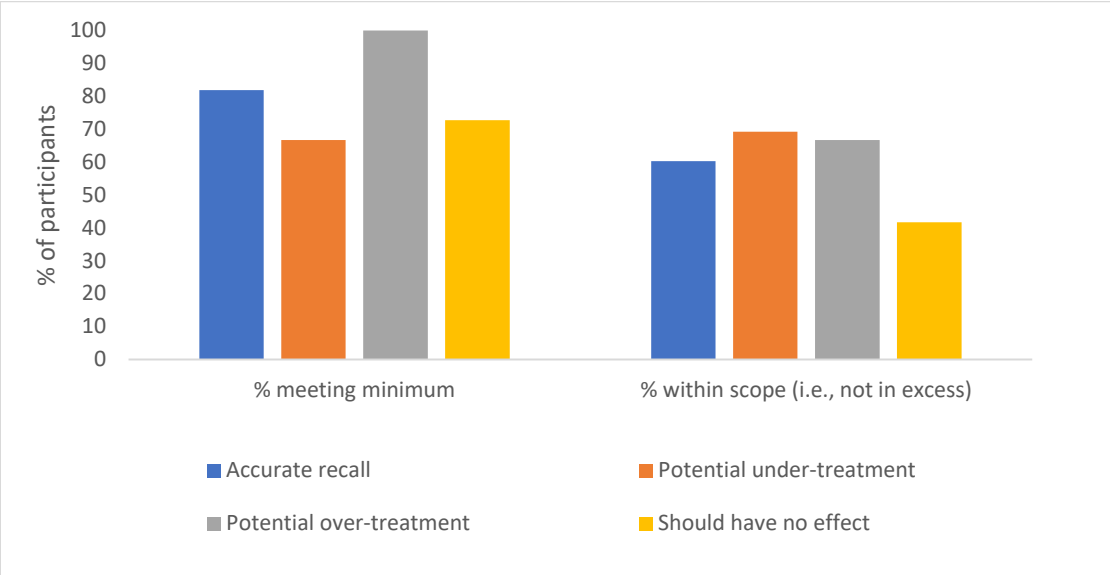


Figure 3. Percentage of patients meeting minimum NCCN guidelines for cancer risk management among patients who accurately self-report their genetic test results (n=83) or inaccurately report their result in a way that could lead to under-management (n=13), over-management (n=6), or no effect on treatment (n=12). Adherence to minimum guidelines was highest in potentially over-treated participants and remaining within scope of guidelines (i.e., not receiving excess management) was lowest in those whose self-report errors should not impact cancer risk management; however, these descriptive differences were not statistically significant (p>.05).

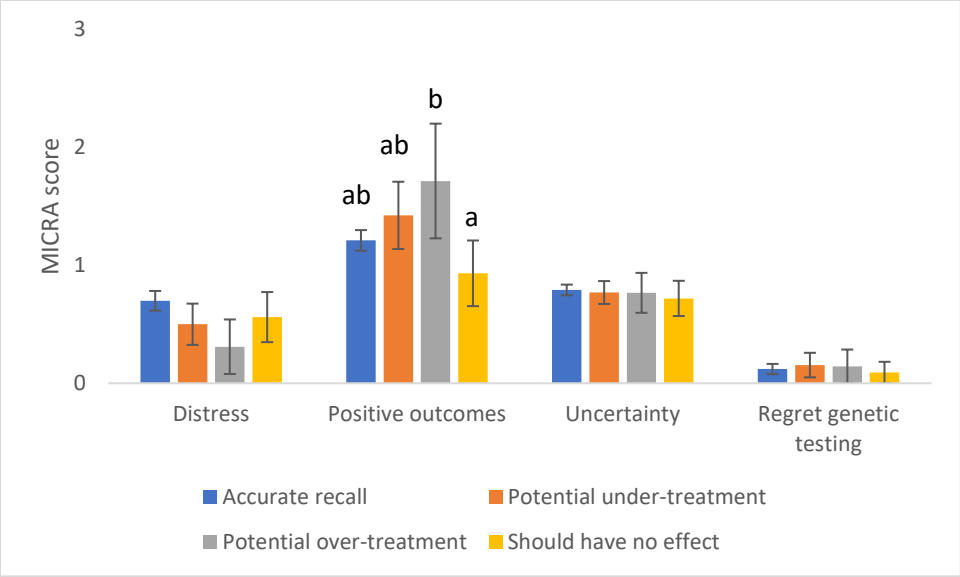
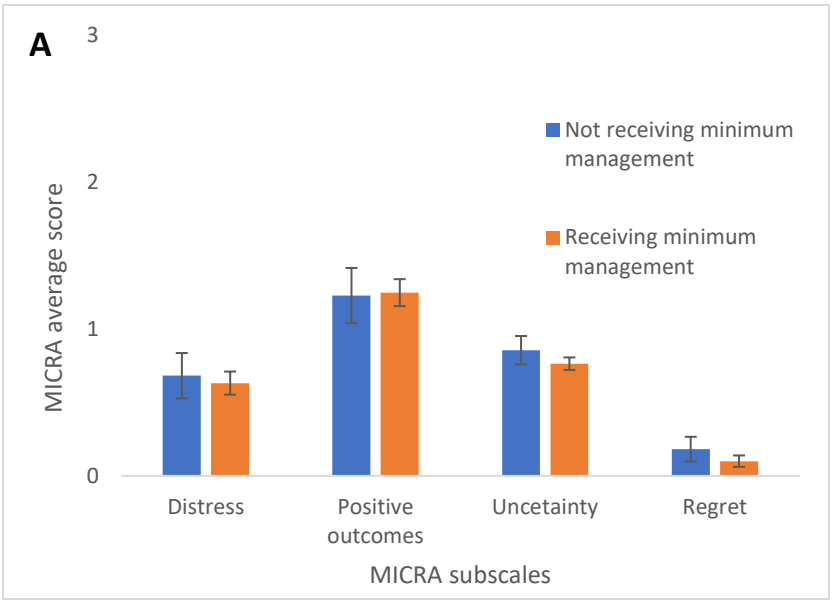


Figure 4. Self-reported frequency (0: never, 1: rarely, 2: sometimes, 3: often) of emotional impacts of genetic testing in participants who correctly reported results versus participants whose self-report discrepancy could potentially affect management. Participants whose self-report errors could potentially result in over-management of their cancer risks reported significantly more positive outcomes of genetic testing than those whose self-report errors should have no effect on their management (Bonferroni post-hoc; groups that do not share a letter are significantly different, $p \leq .05$). Distress also tended to be lower in potentially over-treatment self-report errors, but this difference was not statistically significant. Emotional impact of results did not otherwise significantly differ across groups.



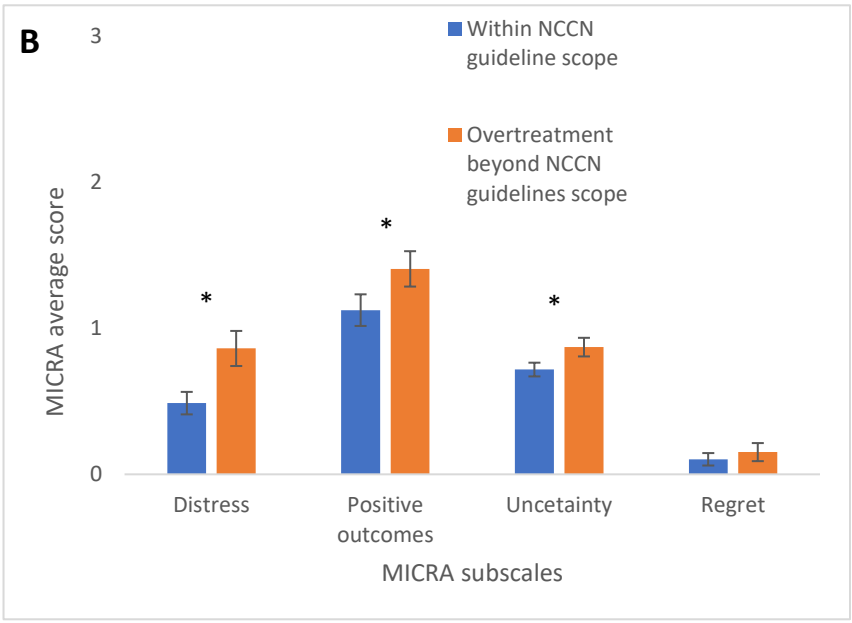


Figure 5. Self-reported frequency (0: never, 1: rarely, 2: sometimes, 3: often) of emotional impacts of genetic testing in participants according to cancer risk management (CRM). A) No significant differences exist among MICRA subscales for participants who were or were not participating in the minimum recommend CRM according to NCCN guidelines. B) Participants who were engaged in CRM in excess of NCCN guideline scope report significantly more distress and uncertainty but also more positive outcomes of genetic testing (*$p \leq 0.05$).

Appendix C: Cancer Risk Management Classification Criteria

- All guidelines originate from the most recent available NCCN high-risk guidelines for breast, ovarian, and pancreatic cancer (National Comprehensive Cancer Network, 2021b) and colorectal cancer (National Comprehensive Cancer Network, 2021a) as well as prostate cancer early detection (National Comprehensive Cancer Network, 2022b) and gastric cancer management (National Comprehensive Cancer Network, 2022a).
- Possible over-treatment for any gene
    - Continued regular breast imaging after RRM
    - both MRI and mammogram *each* every six months
    - Routine breast ultrasound
    - Pancreatic screening in the absence of *ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11,* or *TP53* PV/LPV
    - Oophorectomy in the absence of *ATM, CHEK2, PALB2,* or *BARD1* PV/LPV unless participant had a personal history of breast and/or ovarian cancer
- *APC*
    - Minimum care
        - PV/LPV
            - Colonoscopy at least every 2 years
            - Upper endoscopy beginning age 20-25 at least once (frequency unspecified in guidelines)
            - Thyroid ultrasound at least every 5 years beginning age 20
        - I1307K increased risk allele
            - Colonoscopy at least every 5 years beginning age 40
    - Outside of NCCN scope:
        - Management outside of GI and thyroid risks
- *ATM*
    - Minimum care
        - Annual mammogram beginning age 40
    - Outside of NCCN scope
        - Mammogram every 6 months
- *BARD1*
    - Minimum care
        - Annual mammogram beginning age 40
    - Outside of NCCN scope
        - Management beyond breast cancer risks
- *BRCA1*
    - Minimum care
        - Female
            - RRSO by age 40 unless childbearing incomplete
            - Breast risks

            - RRM or
            - breast screening
                - 25-30 y, annual breast MRI
                - >30 y, annual breast MRI and annual mammogram
        - Male: prostate exam at least every 4 years (National Comprehensive Cancer Network, 2022b)
    - Outside of NCCN scope
        - Management beyond breast, pancreatic, ovarian, melanoma, and prostate cancer risks
- *BRCA2*
    - Minimum care
        - Female
            - RRSO by age 45 unless childbearing incomplete
            - Breast risks
                - RRM or
                - breast screening
                    - 25-30 y, annual breast MRI
                    - >30 y, annual breast MRI and annual mammogram
        - Male: prostate exam at least every 4 years (National Comprehensive Cancer Network, 2022b)
    - Outside of NCCN scope
        - Management beyond breast, pancreatic, ovarian, melanoma, and prostate cancer risks
- *CDH1*
    - Minimum care
        - Annual mammogram beginning age 30
        - Gastrectomy by age 40 (National Comprehensive Cancer Network, 2022a)
    - Outside of NCCN scope
        - Management beyond gastric and breast cancer risks
- *CHEK2*
    - Minimum care
        - Annual mammogram by age 40
        - Colonoscopy at least every 5 years after age 40
    - Outside of NCCN scope
        - Management outside of breast or colon cancer risks
- *RAD50*
    - No NCCN guidelines; not assessed
- *MLH1*
    - Minimum care
        - Colonoscopy at least every 2 years beginning age 25
    - Outside of NCCN scope
        - Upper endoscopy more often than every 3 years
- *MSH2*
    - Minimum care
        - Colonoscopy at least every 2 years beginning age 25
    - Outside of NCCN scope

        - Upper endoscopy more often than every 3 years
- *MSH6*
    - Minimum care
        - Colonoscopy at least every 2 years beginning age 35
    - Outside of NCCN scope
        - Upper endoscopy more often than every 3 years
- *MUTYH* (monoallelic)
    - Minimum care
        - Colonoscopy every 5 years beginning age 40
    - Outside of NCCN scope
        - Pancreatic screening, upper GI endoscopy, any non-GI screening
- *MUTYH* (biallelic)
    - Minimum care
        - Colonoscopy every 1-2 years beginning age 30
    - Outside of NCCN scope
        - Pancreatic screening, any non-GI screening
- *PALB2*
    - Minimum care
        - Annual mammogram and breast MRI beginning age 30
    - Outside of NCCN scope
        - Management outside of breast and ovarian cancer risks
- *PMS2*
    - Minimum care
        - Colonoscopy at least every 2 years beginning age 35
    - Outside of NCCN scope
        - Upper endoscopy more often than every 3 years
- STK11
    - Minimum care
        - Colonoscopy at every 2-3 years, beginning age 20
        - Annual mammogram and annual breast MRI, beginning age 25
        - Upper endoscopy every 2-3 years, beginning by age 20
        - Small bowel visualization (CT, MRI, or video capsule endoscopy) at least every 3 years beginning age 18
        - Pancreatic MRI at least every 2 years beginning age 35
    - Outside of NCCN scope
        - Upper endoscopy or colonoscopy more often than every 2 years, management outside of breast and GI cancer risks
- TP53
    - Minimum care
        - Breast
            - Age 20-29, annual breast MRI
            - Age 30-75, annual breast MRI and mammogram
        - Annual whole-body MRI
        - Annual brain MRI (either separate or as part of whole-body)