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A qualitative study of unaffected *ATM* and *CHEK2* carriers: How participants make meaning of "moderate risk" genetic results in a population breast cancer screening trial

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Abstract

Relatively little is known about experiences of individuals with a pathogenic variant in a moderately penetrant breast cancer gene, particularly those without a personal history of cancer. The WISDOM trial is testing a model of risk-based breast cancer screening that integrates genomic (nine genes and polygenic risk) and other risk factors. In the context of an embedded Ethical, Legal and Social Implications (ELSI) study of WISDOM, we conducted qualitative interviews at two timepoints post-results disclosure with 22 *ATM* and *CHEK2* carriers. Results disclosure and interview recordings were transcribed and analyzed using a grounded theory analysis framework. We found that participants minimized the significance of their results in comparison to *BRCA*; were surprised but not alarmed by the results in the absence of family history; did not fundamentally change their perception of their breast cancer risk despite the new genomic information; exhibited variable responses to WISDOM's screening and risk reduction recommendations; and shared test results with family but did not strongly encourage cascade testing. Participants viewed the results as having limited utility and responded accordingly. Our study offers important insights into how genetic test results for moderate risk genes are received, understood, and acted upon in population screening context.

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Animal Studies: No non-human animal studies were carried out by the authors for this article.

Keywords

ATM; CHEK2; breast cancer; genetic testing; risk perception; population screening; moderate risk genes; ELSI

INTRODUCTION

Breast cancer risk is associated with pathogenic variants in several genes with wide-ranging penetrance (Vysotskaia et al., 2020). With the advent of multigene panel testing for cancer susceptibility genes and sequencing, more people are learning that they have pathogenic variants in "moderate" penetrance genes such as *ATM* and *CHEK2* (Idos et al., 2019). These variants confer a 33% and 28–37% lifetime risk of breast cancer, respectively, compared to 60% and 55% for the highly penetrant *BRCA1* and *BRCA2* gene variants (Reyes et al., 2021) and 13% average lifetime risk for women in the U.S. While *BRCA1* and *BRCA2* have well-established clinical guidelines for risk reduction and surveillance, guidelines for *ATM* and *CHEK2* are not as well established, and less is known about how risk is modulated by other risk factors (Hu et al., 2021; Lumish et al., 2017; Robson, 2018). The current National Comprehensive Cancer Network (NCCN) guidelines for those with a variant in *ATM* or *CHEK2* recommend surveillance with annual mammograms and consideration of tomosynthesis and breast MRI with contrast starting at age 40 (Daly et al., 2020). Regarding risk-reducing surgery, NCCN recommends shared decision making in consultation with a provider that takes into account other risk factors (Apostolou & Papasotiriou, 2017; Daly et al., 2020). Nevertheless, some studies suggest that overtreatment with mastectomy and oophorectomy may be occurring (Cragun et al., 2020; West et al., 2018). Those at increased risk for breast cancer may be candidates for risk reducing medications (such as Tamoxifen or Raloxifene), although data on efficacy in unaffected *ATM* and *CHEK2* carriers is limited, and uptake of these medications remains low among carriers of both high and moderate penetrance genes, especially for women under 50 (Flanagan et al., 2019; Narod, 2021). Risk estimates and clinical guidelines continue to evolve, and uncertainty about appropriate risk management strategies remains for both patients and providers (Reyes et al., 2021; Stolarova et al., 2020).

Relatively little is known about the experience of learning about a pathogenic variant in a moderately penetrant gene, particularly among individuals without a personal history of cancer. Most research on the psychosocial impact of genetic findings related to breast cancer risk has been conducted with *BRCA* carriers. Some quantitative research has indicated that receiving results in moderate-risk genes leads to patient confusion, uncertainty, and psychological distress (Culver et al., 2021; Esteban et al., 2018; McCormick et al., 2022). However, one qualitative study of carriers of moderate risk breast cancer genes found that participants had a range of responses to their results, including overwhelm, concern, relief and acceptance; feelings of calmness or acceptance arose mainly for breast cancer survivors, while unaffected participants expressed fear about getting breast cancer and concern for the health of their relatives. (Stracke et al., 2022). The only study published to date focused exclusively on unaffected carriers of pathogenic *ATM* and/or *CHEK2* variants found that participants experienced persistent uncertainty about cancer risk and management after

receiving their results. Uncertainty was related to participants' perceptions of ambiguous or limited data regarding the effectiveness of cancer risk reduction strategies available for *ATM/CHEK2* (Reyes et al., 2021). It is unclear how findings from studies with clinical populations will apply to population screening studies or direct-to-consumer settings, which are increasingly common (Carey et al., 2016; Neben et al., 2019; The All of Us Program Investigators, 2019).

Here, we report findings from qualitative interviews with women found to have an *ATM* or *CHEK2* pathogenic variant in the context of a population-based breast cancer screening trial called WISDOM (Women Informed to Screen Depending on Measures of Risk).

The WISDOM Trial

WISDOM is a precision population-based breast cancer screening trial designed to test the hypothesis that risk-based screening will be as safe, less morbid, and have greater healthcare value than annual mammography (Shieh et al., 2017). WISDOM is an online study; participants are largely recruited via email and direct message from electronic health records and communicate with the study through a web-based portal. They are randomized to or self-select (according to the preference tolerant design) the annual screening arm or the risk-based screening (RBS) arm. Those in the RBS arm screen for nine high and moderately penetrant breast cancer genes and a polygenic risk score (PRS). Those who test positive for a variant, including *ATM* or *CHEK2*, receive a phone consultation, including return of pathogenic results (variants of uncertain significance are not reported to participants), from a Breast Health Specialist (BHS) who is a nurse, physician, or genetic counselor, and are recommended to have an annual mammogram or annual mammogram plus annual MRI depending on their family history of breast cancer, breast health, and PRS (Shieh et al., 2017), which aligns with NCCN guidelines. Because WISDOM is a pragmatic trial, these screening regimens are just recommendations; participants are expected to confer with their healthcare providers, and any screening or preventive services must be paid for by the participant or covered by her insurance. Participants are also informed if they may be at increased risk of other cancers and encouraged to consult with their primary care provider or a genetic counselor. (See Supplementary materials.)

METHODS

Study Design

This report is based on data collected as part of a multimethod embedded Ethical, Legal, and Social Implications (ELSI) study of WISDOM. The purpose of our embedded ELSI study is to understand the social and ethical implications of population-based genetic testing and risk-stratified breast cancer screening. Since 2016, our team of ethnographers has observed thousands of meetings of more than 20 ongoing WISDOM working groups which meet regularly to implement various aspects of the study (e.g., risk thresholds, statistical methods, return of results). We conducted semi-structured qualitative interviews with WISDOM participants across risk levels (n=87) as well as key informant interviews with WISDOM BHS, clinicians, and investigators (n=34), which are reported elsewhere. Interviews were conducted by four members of our team (JJ, LR, MC, GJ), two of whom have PhDs in social

sciences and two others who have master's degrees and have been trained in qualitative research. Together, these observations and interviews provide multifaceted context for our interpretation, presented here, of interview data with 22 participants identified as *ATM* (n=5) or *CHEK2* (n=17) carriers.

For the participants who were designated at moderate or elevated risk for breast cancer due to genomic and/or other risk factors, we audio recorded telephone results disclosure sessions and then conducted semi-structured interviews 2–4 weeks later and again after approximately six months to explore how participants understood their risk and subsequently made screening decisions. We invited 32 participants with an *ATM* or *CHEK2* variant to participate in an interview. We began by inviting all participants identified as having a variant and then attempted to sample to ensure greater racial/ethnic and geographic diversity. Eight participants did not respond to the invitation; two participants agreed to participate but canceled the interview. Interviews were conducted by phone between July 2017 and January 2021 until data saturation was reached; demographic data were collected at the end of each initial interview. This paper focuses on findings from first and second interviews with the 22 *ATM* and *CHEK2* carriers as well as recorded BHS sessions (n=17). (BHS session recordings are not available for all interviews as recording technology was not available for all sites at the start of the trial). BHS sessions were 34 minutes long on average. The average length of the initial and follow-up interviews were 52 minutes and 41 minutes, respectively.

Data Analysis

Recordings of results disclosure sessions and interviews were transcribed and analyzed using standard techniques based on a grounded theory coding framework (Strauss & Corbin, 1997). Our research team worked collectively to code initial interview transcripts using open-coding and develop a codebook using ATLAS.ti qualitative data analysis software. Subsequently, each transcript was coded by one member of the team and then reviewed by another to ensure consistent application of the codes; discrepancies were resolved through consensus. Coded transcripts were then discussed with the full research team to explore emerging themes and interpret the data in context (Dossett et al., 2021; Strauss & Corbin, 1997).

The study design was approved by the UCSF IRB (16–20352).

RESULTS

Study Participants

Characteristics of interview participants are described in Table 1 and largely reflect the overall WISDOM study population. Participants ranged in age from 41–73. 86% were white and 86% had a college degree or higher.

Results framed in comparison to BRCA

WISDOM participants sign a detailed online consent form, which lists the genes included in the panel, but do not undergo pretest genetic counseling. We found that participants,

both with and without a pathogenic variant, were often unable to describe the WISDOM genetic test. Many participants were unaware of the existence of breast cancer genes other than *BRCA*, which several were familiar with due to the highly publicized experience of Angelina Jolie.

The BHS often began the results disclosure calls with participants who tested positive for *ATM* or *CHEK2* by emphasizing that a *BRCA* variant had *not* been identified. For example, in this call with a 56-year-old woman with *CHEK2*, the BHS said,

> I can tell you right off the bat you do not have a *BRCA* variant, so you do not have an abnormality in one of the genes that causes a very high risk for breast cancer...If you had had one of those, you would've been recommended to have a more aggressive prevention plan. But we did find a genetic risk factor in a gene that you've probably never heard of 'cause most people haven't, and it's called *CHEK2*. It's sort of a medium-level genetic risk factor. So I want to talk to you a little bit about that, what it means to you, but I want to say right off the bat that it's not one of the things that causes a high, high genetic risk. It's just something that makes us want to keep a little bit of a closer eye on you than we would for a woman who had no risk factors.

A common reaction among women we interviewed was relief that a *BRCA* variant had not been found; some had joined WISDOM because they had concerns about breast cancer in their family and saw the study as an opportunity to be tested for *BRCA*. One participant described initially feeling "alarmed" when she heard that she had a variant, then comforted upon learning that it was not in *BRCA*. Pam, 61, said, "I was just glad it wasn't the BRCA1 or 2 'cause that's the one you hear about in the news that you know is the bad one." (*ATM*, 1st interview)

While some had thought it was possible they would receive "bad news" in the study (i.e. a *BRCA* variant), most hoped or assumed they would receive "good news" (no variants identified). Few anticipated news that felt somewhere in-between: "I was prepared for, like, good news or really bad news. I wasn't prepared for something that was kind of like, 'oh, okay.' It's something I need to know, but it's not something that's going to keep me awake." (Angela, 51, *ATM*, 1st interview)

Reactions to results evolved over time and were contingent on many factors

By observing results disclosure sessions and then interviewing participants at two time points, we gained an understanding of if and how participants' perceptions of their genetic findings changed over time. A few participants expressed initial surprise or alarm upon learning that they had an *ATM* or *CHEK2* variant. However, they also noted that the BHS's communication style helped them to process their results, and most participants did not convey serious concerns about their genetic findings. Comments included, "it's not keeping me up at night," and "it floats in and floats out."

One participant, Pam, 61, reported not worrying about the *ATM* variant until her sister was diagnosed with ovarian cancer. At that point, she asked herself: "Do I have to do [an] Angelina Jolie and go have a double mastectomy and have my ovaries removed?" She

decided to discuss next steps with her gynecologist. However, overall in both the initial and six-month interviews, participants indicated that they had not spent much time thinking about their results. Participants had chosen not to put undue energy into worrying, given the perception that cancer is largely out of one's control and that they were already paying appropriate attention to their health. Several older participants reflected that this information might have carried more weight if they were younger, but at this point in their lives they felt they had eluded breast cancer or believed that other health risks were more concerning. For example, one participant noted she had more concern about her familial risk of developing Alzheimer disease than her risk for breast cancer (See Table 2).

Prior risk perceptions persisted despite genomic information

Overall, learning they had a pathogenic variant in *ATM* or *CHEK2* did not substantially change most participants' perception of their risk for breast cancer. For those who already viewed themselves as being at increased risk for breast cancer, often due to family history, learning about their variant offered an additional clue to the cancer in their family, but did not dramatically shift their pre-existing risk perception. Similarly, for participants who were less concerned about their breast cancer risk prior to WISDOM, learning about their variant did not translate to feeling at increased risk. Participants understood themselves to be generally healthy (due to factors such as diet and exercise) which led them to believe they were at lower risk for breast cancer. They did not view their genetic result as the most important or relevant risk factor, but rather as one factor among several they used to weigh their risk.

While it is encouraging that most participants did not express anxiety about their breast cancer risk due to their results, our data suggest that a number of participants may have misunderstood the risk information provided by the BHS, believing their risk to be lower than it was. One participant accurately recalled her risk was 3.5%, and was relieved by this perceived "low" number. This participant was given both her 5-year and lifetime risk of breast cancer and the BHS described her risk as being twice that of the average woman. However, in reflecting on her risk during an interview, she misinterpreted the 3.5% risk information as conveying the risk of *ever* being diagnosed with breast cancer rather than her 5-year risk (See Table 3).

Responses to screening and risk reduction recommendations varied

The primary intervention of WISDOM is a breast cancer screening schedule recommendation. For participants assessed as moderate or high risk, this recommendation, as well as follow-up care guidance and risk-reduction strategies, is discussed during the BHS results disclosure consultation. Several participants described how the BHS consultation helped them to recognize that they should pay more attention to lifestyle choices that could improve or preserve their health, such as exercising more, eating healthier foods, drinking less alcohol or doing more frequent self breast exams (See Table 4). However, in both the initial and 6-month interviews, only a few participants told us they had followed recommendations such as scheduling additional genetic counseling or discussing their genetic test results with their providers. While many participants found their results informative, they did not express a sense of urgency about screening or prevention

in response. This was especially true for the 16 (73%) participants who received a recommendation to have annual mammograms. They understood annual mammograms as the standard of care for all women, rather than a tailored recommendation for those at elevated risk, as it is defined in WISDOM. Most had been getting annual mammograms prior to joining the study, and thus did not perceive the study's recommendation to reflect a change in risk status. However, for some, learning their genetic test results affirmed they should continue with an annual screening schedule and not "skip a year" as they had in the past.

WISDOM recommended a more aggressive screening regimen to the other six women we interviewed: annual mammogram and MRI. One participant, Karen, was already being surveilled via breast MRI. At the time of the initial interview, one participant was undecided and the rest indicated that they were willing to follow WISDOM's recommendation. However, at the time of their six-month interviews, only one, Kathy, had actually scheduled an MRI. Another participant, Andy, explained that neither the WISDOM BHS nor her ob/gyn had strongly encouraged or discouraged the MRI; since her ob/gyn didn't think it would be paid for or "add much," Andy felt "less inclined to try to pursue it too hard." Among those who planned to get an MRI but hadn't scheduled one by the six-month interview, one was inclined towards MRI because of her breast density and another due to her trust in the study.

The few participants who had discussed their genetic findings with their health care providers found clinicians to be unfamiliar with *ATM* and *CHEK2* and relevant management guidelines. Andy, who learned about her *CHEK2* variant before WISDOM, reported her provider "just shrugged his shoulders [and] had no idea what to do" (1st interview). Participants appreciated WISDOM's clear screening recommendations. As Jo, 43, said: "Prior to the study I felt that I had an increased risk but […after BHS consultation] I had a plan moving forward as opposed to a vague sense of unease, and with the options for detection, I was very comfortable." (*ATM*, 1st interview)

The BHS consultation with *ATM* and *CHEK2* carriers typically also included a discussion of risk reducing medication known as "chemoprevention." These drugs, which include both selective estrogen receptor modulators and aromatase inhibitors, can be prescribed for both the treatment and prevention of breast cancer. The majority of participants we interviewed were not interested in taking medication to lower their risk; there were several reasons for their reluctance, but primary among them were concerns about side effects. Many participants felt that the risks of preventive therapies outweighed the risks associated with their variant, and believed taking medication to reduce their risk "seemed excessive" and "not worth it" given their level of risk. One knowledgeable participant noted that she could not know for sure if a potential cancer would be estrogen sensitive and thus responsive to this medication. Another participant's disinterest in the medication was related to her belief that breast cancer is a treatable disease. Lastly, one participant noted that taking medication felt like it crossed a line from preventive care to treatment; many prided themselves on not taking any medications and felt that accepting chemoprevention would indicate a change in their health status.

Results shared but cascade testing not frequently encouraged

Universally, participants reported sharing the news of their genetic finding with a loved one (e.g. spouse, family, or friends). Decisions about what to share were based on both their understanding of each individual's risk (or potential to pass on risk) and their perceptions of the relative's interest in or ability to act on the information (See Table 5). By the second interview, most had shared their findings with at least one blood relative, although one reported she did not have any living blood relatives and another did not speak to her living blood relative. Participants with young children planned to share their results with them when they got older.

Several women believed the results were less relevant for their male relatives, unless they had additional risk factors for other cancers associated with the variant, such as prostate or colon cancer. Some felt that their male relatives would find this information less applicable to their lives and be less motivated to get tested. Participants commonly described any risk for their male relatives as being more about the risk for his (future) daughters, not the male relative himself.

While one participant whose sister had recently been diagnosed with ovarian cancer felt strongly that her own daughter should get tested, a sense of urgency for relatives to be tested was not typical. Some who had told their relatives about the genetic variant did not directly suggest or inquire about the relative's plan for testing. Further, many participants indicated that they did not see value in their relatives being tested; rather the genetic variant became an additional piece of family history that could be shared with a healthcare provider. Participants expressed not wanting to worry older relatives with the information, and those with children in their teens, twenties, or thirties often noted that a more appropriate time for them to get tested would be prior to having children or when they reached breast cancer screening age. For others, they felt that if their relative was already doing routine cancer screening, there was no added value from genetic testing. Six months after receiving their results, only two participants reported that a family member had undergone genetic testing. Participants noted several barriers, or perceived barriers, to cascade testing, including family members residing outside of the United States, lack of interest, and inconvenience, which led some to not mention the possibility of testing to those relatives.

DISCUSSION

For participants in the risk-based screening arm, WISDOM provides a multigene panel test including nine genes which have varied associations of risk for breast cancer. While multigene panel tests are routinely offered in clinical and direct-to-consumer settings, WISDOM raises largely unexamined questions about the experience of unaffected women receiving these results in a population screening context.

Our data suggest that the BHS were adept at their roles and successful in assuaging potential panic for participants who may have been unprepared for the results. Contrasting *ATM* or *CHEK2* with *BRCA* served as a powerful rhetorical strategy given many participants' familiarity with it, and allowed the BHS to distinguish the risk associated with *ATM* and *CHEK2* as more moderate in order to reduce fear (Borzekowski et al., 2014; Campbell,

2019; Waltz et al., 2020). However, it is unclear whether this strategy inadvertently diminished the subjective level of risk conferred by these variants (Reyes et al., 2021; Waltz et al., 2020). We did find that participants' understanding of specific risk estimates was imprecise, which is not uncommon. Risk communication is well documented to be a significant challenge in general and specifically in genetic/genomic medicine (Hong, 2020; Lautenbach et al., 2013; Lea et al., 2011), and in distinguishing between lifetime vs. short-term risk (Fagerlin et al., 2011). In the WISDOM study, the BHS provide both lifetime and 5-year risk estimates to participants, resulting in lack of accurate recall for some participants. However, all participants appeared to understand the key "take home message" that they were at increased risk compared to the average woman their age.

Overall, we found that WISDOM participants took their pathogenic *ATM* and *CHEK2* results in stride. The majority of participants we interviewed were recommended to screen with annual mammograms, which they did not perceive as an elevated-risk screening regimen. Those recommended to screen with annual MRI in addition to annual mammogram expressed a willingness to do it, but exhibited a lack of urgency in seeking the MRI or other follow up care.

For most participants, the news of an *ATM* or *CHEK*2 variant did not substantially change their breast cancer risk perception. For those who already believed themselves to be at high risk, primarily due to family history, the identification of a pathogenic variant served to confirm, validate and/or explain their risk. Yet, the genetic component of risk did not overshadow other risk factors with which they were more familiar, such as family history and lifestyle behaviors. In fact, several participants incorporated their already healthy behaviors (such as diet and exercise), as well as their age and other health risks into their own risk calculation, thereby reducing or balancing out their concern about the genetic variant. These data suggest that the genetic information was not understood to be determinant of breast cancer outcomes but rather one factor contributing to overall risk.

In contrast to Reyes, et al.'s study of patient experiences with receipt of moderate risk breast cancer genes (Reyes et al., 2021), uncertainty did not emerge as a major theme in our data. This may be due to our approach which was open-ended and inductive, rather than the deductive approach of applying Han et al's taxonomy of uncertainty (Han et al., 2017) used by Reyes, et al. These disparate outcomes may also reflect the different populations and contexts of our participants. While both were unaffected by cancer, Reyes et al included a cancer genetics clinic population who sought out testing due to family history. Alternatively, our participants were drawn from a population-based screening trial, with a mix of people who did and did not have a family history of breast cancer, only a minority of whom would have been eligible for clinical testing. While some of the issues identified as contributing to uncertainty by Reyes, et al. were present in our data (e.g., lack of familiarity with *ATM/CHEK2*; lack of provider knowledge), our participants minimized uncertainty and did not express urgency to act based on their genetic findings. Participants in WISDOM are given clear screening recommendations which may have reduced uncertainty and, in using the rhetorical strategy of "it's not *BRCA*", the BHS reassured participants that regular screening would suffice.

Implications for Practice

The WISDOM model highlights important considerations for population genetic testing, which is increasingly being offered in both research and clinical contexts. WISDOM participants do not receive pre-test counseling, and the BHS typically do have access to the participant's medical record. The BHS consultations are intended to be an interim step in their risk assessment and surveillance and prevention planning, and the BHS recommend that participants follow up with their primary care provider and/or a genetic counselor for a more complete assessment and plan for next steps. Our findings indicate that this model is acceptable for delivering moderate-risk breast cancer genetic results, especially given the shortage of genetic counselors; however, questions remain about whether those with pathogenic genetic findings ultimately pursue genetic counseling and obtain appropriate screening and preventative care. It was striking but not surprising that participants who took their genetic findings to their primary care providers, found little awareness of *ATM* and *CHEK2* and little understanding of the implications for surveillance and risk reduction. Primary care providers are already overburdened and have cited multiple barriers to integrating genetic testing into routine clinical practice, including lack of time and confidence in the skills needed (Chambers et al., 2015; Hajek et al., 2022).

Many of our interview participants did not pursue genetic counseling as recommended, at least within the six months following results disclosure. Therefore, adjustments to the model, such as providing a referral to a specific genetic counseling practice, or other more direct hand-off may be warranted, though challenging in the fragmented US healthcare context and given the shortage of genetic counselors. In addition, while the WISDOM patient population is highly educated, we still found that some participants misunderstood or misinterpreted their risk estimates, though all understood they were at increased risk. Utilizing known methods of effective communication is critical for ensuring that patients of all health literacy and numeracy levels comprehend the risk information they are given in the population screening context (Fagerlin et al., 2011; Riddle et al., 2021; Yen & Leasure, 2019), but further research is needed to assess the importance of accurate recall of risk estimates for completing appropriate follow up care.

Our findings indicate that participants understood that variants in *ATM* and *CHEK2* can be inherited and often shared their genetic test results with relatives. However, this rarely translated to an encouragement of cascade testing. The importance and urgency of cascade testing seemed to vary based on factors such as personal and family history and the life stage, sex, and priorities of the relative (Dean et al., 2021). Information on how risk translates to relatives may be difficult to convey in brief results disclosure sessions, an important implication for population screening. However, the expansion of population genetic testing, including models like WISDOM, may alleviate the burden on individuals to convey complex risk information to their family as more individuals are tested regardless of risk or family history (Bowen et al., 2021; Dean et al., 2021; Lieberman et al., 2018).

Limitations

Our study population, drawn from WISDOM participants, was reflective of the WISDOM population but not the diversity of the overall US population. Despite our efforts to

oversample women of color, our participants were often white, as well as highly educated and affluent. Further, those who chose to join WISDOM may have been more likely to have family history or other risk factors, or more knowledge of breast cancer risk factors, and thus not reflect the average screening population. As such, the study population might not be as distinct from a clinical population seeking genetic testing for hereditary breast cancer as might be expected in population screening.

Conclusion

The primary aim of WISDOM is to build the evidence needed to change the paradigm of breast cancer screening to a risk-based model. The trial design offers a potential model for population genomic screening, and our interviews and observations offer critical insights into how genetic testing results for moderate penetrance genes are received, understood, and acted upon in an unaffected screening age population. Our findings suggest that in this population screening context, participants were able to absorb the news that they carry a pathogenic variant in a moderate risk breast cancer gene without undue concern. In contrast to studies that show potential overtreatment of individuals carrying these moderate risk variants, most of our participants viewed the results as having limited utility for themselves and their relatives and responded accordingly. Further research is needed to understand how the perceived value and personal utility of moderately penetrant variants identified in the population context will translate to screening and preventative care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The data are not publicly available due to privacy or ethical restrictions. Further information is available in the supplementary material or by contacting the corresponding author.

Data Availability Statement:

The data for this project is qualitative and potentially identifiable if shared in full. The UCSF IRB has not approved this data to be shared beyond the research team.

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What is known about this topic:

Relatively little is known about experiences of individuals with a pathogenic variant in a moderately penetrant breast cancer gene, particularly those without a personal history of cancer.

What this paper adds to the topic:

Our study offers important insights into how genetic test results for moderate risk genes are received, understood, and acted upon in population screening context.

Table 1.

Demographic and study characteristics of the 22 interview participants

	ATM		CHEK2		Total	
Age	**N**	**%**	**N**	**%**	**N**	**%**
40–49	1	5%	3	14%	4	18%
50–59	2	9%	3	14%	5	23%
60–69	2	9%	6	27%	8	36%
70–79	0	0%	5	23%	5	23%
Total	5	23%	17	77%	22	100%
Self-identified race/ethnicity [from interviews)						
White	4	18%	15	68%	19	86%
Black or African American	1	5%	0	0%	1	5%
Mixed/Multi-racial	0	0%	2	9%	2	9%
Total	5	23%	17	77%	22	100%
Arm selection						
Randomized	2	9%	8	36%	10	45%
Risk-based	3	14%	9	41%	12	55%
Total	5	23%	17	77%	22	100%
Screening assignment						
Annual Mammogram	4	18%	12	55%	16	73%
Annual Mammogram/Annual MRI	1	5%	5	23%	6	27%
Total	5	23%	17	0%	22	100%
Prior knowledge of variant						
Yes	0	0%	1	5%	1	5%
No	5	23%	16	73%	21	95%
Total	5	23%	17	77%	22	100%
Education						
Some college	0	0%	2	100%	2	9%
Associate’s degree	0	0%	1	5%	1	5%
College degree	2	9%	4	18%	6	27%
Advanced degree	3	14%	10	45%	13	59%
Total	5	23%	17	77%	22	100%
Income						
0–25k	0	0%	0	0%	0	0%
25–49k	0	0%	1	5%	1	5%
50–74k	0	0%	0	0%	0	0%
75–99k	0	0%	2	9%	2	9%

	ATM		CHEK2		Total	
Age	**N**	***%***	**N**	***%***	**N**	***%***
>100k	5	23%	13	59%	18	82%
Refused	0	0%	1	5%	1	5%
Total	5	23%	17	77%	22	100%
Health Insurance						
Medicare	0	0%	1	5%	1	5%
Private	3	14%	14	64%	17	77%
Medicare + Private	0	0%	2	9%	2	9%
Health share plan	1	5%	0	0%	1	5%
Missing	1	5%	0	0%	1	5%
Total	5	23%	17	77%	22	100%

Table 2.

Reactions to results evolved over time and were contingent on many factors

	Quotes
Initial surprise and concern	"Well, it was a surprise that I had that variant. I was surprised that it was linked with colon cancer, which I do have in my family. I was surprised at how much it increased my risk of breast cancer, like 25% more than the average woman." (Katie, 67, CHEK2, 1st interview) "First it was kind of like whoa, okay. A little alarming at first to think that oh, I do have one of these little mutation guys…So at first, it kind of was a little overwhelming, and I did think about it maybe a lot for the first week or two." (Kathy, 60, CHEK2, 1st interview)
Minimal concern; factors mitigating concern	"[I'm] Not overly concerned. You know, there's probably so many people walking around with the same thing and they have no clue. It's just, you know, you think about it a little bit more when you know." (May, 64, ATM, 1st interview) "I feel like I take pretty good care of myself and whatever happens, you know, anything else is out of my control. So I'm not going to worry about it." (Jan, 70, CHEK2, 1st interview)
Perceptions contingent on changing circumstances	"Before [when I first found out about the ATM] I was like eh, no big deal. I always knew I had a possibility of carrying this defective gene. I mean, my maternal grandmother had cancer, my maternal aunt, my mom has had lumpectomies, my sister had lumpectomies, so I always knew that there were, shall we call them 'female issues.' But this one hit close to home. I mean, this is my sister." (Pam, 61, ATM, 2nd interview, reflecting on her sister's recent ovarian cancer diagnosis)
Variable value of information depending on life stage	"It would've caught my attention more, if I had been younger… But at this point, no, it's less risk than probably getting hit by a car in the street. So it's not really concerning." (Sam, 71, CHEK2, 1st interview)

Table 3:

Prior perceptions of risk persisted despite genomic information

	Quotes
Results confirmed prior perception of elevated risk	"I always felt like I had a decent risk, just based on my GAIL score and my family history. So, I don't think that CHEK2 added anything to my feeling of risk." (Karen, 63, CHEK2, 1st interview) "The reason I participated in the WISDOM study is I have a family history of breast cancer, so the results were not surprising to me at all. They just basically told me what gene it was that was defective in my family history." (Pam, 61, CHEK2, 1st interview).
Risk was assessed within the context of (lack of) family history	"I'm kind of conceptualizing [my risk] at around 20%…that's high enough that I do have a concern and I do have a motivation, but at the same time, it's not a keeping-me-up-at-night kind of risk…I think there's also the fact that I have no real family history, makes it feel a little bit less likely to happen, although that's not always a great indicator, especially if you have a small family. So…yeah. I mean I guess it's probably my actions are speaking most loudly here of just well, yes I should take care of that, but I don't feel like it's urgent or pressing." (Andy, 46, CHEK2, 2nd interview)
Risk conferred by variant not determinant but rather interpreted in context of other factors	"I don't feel particularly at any greater risk just because, even though I had the variation, there were several other factors that made it so my chances of getting breast cancer were very low, you know, starting menopause early, some of those things that kind of factor in." (Phyllis, 57, ATM, 2nd interview) "…and actually, what this doctor that I just went to, she pretty much said, 'There's like a 10% -- you know, literally the majority of women who have atypical hyperplasia, if you did nothing, it's going to turn into cancer within four or five years.' She said the studies are all there. She said, 'You know, that makes you a higher risk than what your CHEK2 mutancy does.'" (Erin, 50, CHEK2, 2nd interview) "I feel like it's more additive than on its own actionable…I think combining that with the extremely dense breast tissue that my last mammogram showed, well now that actually starts feeling like a constellation of things that are moving in that direction. So I think that it has more of that kind of additive effect than being enough quite on its own." (Andy, 46, CHEK2, 2nd interview)
Misunderstanding of risk information	"[The BHS said] 'you are more likely to get breast cancer than the average person your age and your health' or whatever. But she said it's like three and a half percent…I'm like that's low to me… When she told me the percentage, it was a big relief for me. I mean, that was a good result." (Meredith, 63, CHEK2, 1st interview)

Table 4:

Responses to Screening and Risk Reduction recommendations varied

	Quotes
Increased awareness of breast health and more mindful of screening and healthy behaviors	"Anything that puts you at elevated risk for an adverse health outcome makes me think about other things that you can do to make your health decisions better. So, I don't know. Did it make me swim more times a week? It may have because frankly before, I probably swam two or three times a week. I don't know whether that's what increased my frequency, but it made me more aware of other health decisions." (Jill, 56, CHEK2, 1st interview) "I probably have done more breast exams than I used to, self-examination. But it has not made me hypervigilant or anything." (Tina, 56, CHEK2, 1st interview) "I don't take for granted my checkups and I don't take for granted, you know, like looking at what you're putting into your body as far as alcohol, drugs, smoking and anything else that would increase the risk…it kind of just makes you realize when you have certain things in your body that are capable of contributing to having cancer, it kind of makes you kind of look at the whole scenario of how there's so many things in our day to day, the things we breathe, the air we breathe, the food we eat with all different types of chemicals and things… It just makes me want to live a healthier life." (Erin, 50, CHEK2, 2nd interview)
Annual mammogram viewed as standard screening, not elevated risk screening	"I guess the thing was that I was already in that regimen, it led to the same recommendation. I haven't had to make a lot of changes. It's all very – it was a very easy flow. You know, there were no shocking revelations, there were no shocking changes. So it's all good." (Karen, 63, CHEK2, 1st interview) "Given that information, my perception is it's in my best interest to make sure that I get an annual check-up. But I didn't feel like that meant I should go more frequently, just meant that I should definitely do it at least as frequently as annually…Maybe if it was 50% I'd be a little more anxious about it. 25 just, I don't know, it just seems like a low enough bar. Even though there is a bar there, it just seemed low enough that I wasn't – I'm not as concerned." (Angela, 51, ATM, 2nd interview)
Intention to follow elevated risk screening recommendation but no action at 6 months	With respect to learning that I had the variant, I made some changes in my daily life. I have not scheduled an MRI yet, which when I got your email [about scheduling an interview] I was shocked by, but I've done little or more personal things. I've been trying to lose a little weight, trying to eat a little bit more clean, drinking less alcohol, more conscientious about specifically exercising and introduced a meditation practice, so some self-care things too. And I think those are the big changes I've made. I have not followed up on the diagnostics, obviously, which horrifies me…because you have information that you could do something with and if you don't go looking for it, you're not going to find it." (Jo, 43, ATM, 2nd interview)
Providers had limited knowledge and understanding of ATM/CHEK2 associated risks and recommended screening	"It's funny, even my primary care doctor at Kaiser was like, 'Oh, CHEK2. The only one I knew about was the BRCA one.'" (Kathy, 60, CHEK2, 1st interview) "I said, 'My test shows I have the CHEK2.' And [the Nurse Practitioner] just went, 'Yeah. Uh-huh.'…She did not emphasize that that was adding a huge amount of concern. You know, it didn't seem like that made her more concerned about me…What she cared more about was what was on the MRI." (Karen, 63, CHEK2, 1st interview)
Negative reactions to recommendation to consider taking risk reducing medications	"I don't want to think of myself as a sick person. I think that would change how I did see myself. Not sick but, you know, a patient…I don't want to be on medication if I don't have to be. The risks and side effects, in my mind, outweigh the potential benefit. I feel like breast cancer is something that's treatable, you know, depending on when you detect it, which is going back to the reason I'm embarrassed I haven't scheduled that MRI." (Jo, 43, ATM, 2nd interview) "You know, I have not followed up on that too much. I did talk to a geneticist friend of mine, who has much more expertise in cancer, and that person really thought that seemed excessive. So it did make me wonder like what was the level of sort of - I mean, how strong is the evidence supporting that and, you know, I'd like to know more about well, what are the sort of side effects and things like that…I mean, I don't like taking medication. Nobody does." (Andy, 46, CHEK2, 2nd interview)

Table 5.

Results shared but cascade testing not frequently or strongly encouraged

	Quote
Reasons for sharing results	"I think it's good to know and I think it's good for me to encourage my sisters. I have a sister who lives here and I had sent her information about the Wisdom Study and I said, you know, 'It's probably really worth you doing it because I have this genetic variation and you should probably know if you have it too.'" (Phyllis, 57, ATM, 1st interview) "It just enhances the ongoing dialogue we've been having for years in my family. So I'm glad to have the information. I'm glad that I have the specifics. So if my daughters decide to get tested or, you know, they can share and say 'hey, my mom had this,' you know, and they can have a fuller discussion with their health care providers." (Pam, 61, ATM, 1st interview)
Information perceived to be less relevant for relatives younger than screening age	"I will encourage my girls down the road when they're -- you know, if and when they decide they want to start a family or even for themselves I think, you know, somewhere in their 30s they should probably get tested. But I wouldn't say start doing mammograms in your 30s. I would, again, like me, wait until your 40s." (Pam, 61, ATM, 1st interview) "They weren't interested…You know, they're at a point in their lives where they're young and it's really not that big of an issue for them… They just really don't see the need, and I understand that." (Leah, 60, CHEK2, 1st interview)
Information perceived to be less relevant for male relatives	"Well each of [my relatives] has a 50% chance of having the same variant. And if they're men, we don't – it's less clear to me and maybe less clear to everyone." (Karen, 63, CHEK2, 1st interview) "I did tell my full brother but he has sons so – but yeah, I did mention it to him. I think he just felt like it didn't concern him really." (Molly, 44, CHEK2, 2nd interview)
Uncertainty about relevance or importance of genetic testing for relatives' health	"I just don't think it will make any difference to them. 'Cause I think right now, you know, this testing is sort of just kind of informational to people studying this but it's not really doing me any good. You know, it wouldn't do them any good, I don't think… What are they going to do differently in their life, I mean?…if you're already kind of aware and getting screened annually, it probably doesn't make all that much difference." (Jan, 70, CHEK2, 1st interview) "I'm an only child and my mom, you know, already had a breast cancer diagnosis and she has one sister, who's already doing routine screenings. So this hasn't changed that." (Jo, 43, ATM, 1st interview)