COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #: 23-0345
Project Title: Understanding and Addressing Rejection of Personalized Cancer Risk Information

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I. Hypotheses and Specific Aims:

Aim 1: Understand the scientific nature of risk rejection. To accomplish this, we propose two sub-aims:

Aim 1a: Identify demographic and psychological factors associated with risk rejection. We will conduct a longitudinal study involving a community sample of women to test a priori theory-derived hypotheses about the precursors of risk rejection. As part of this work, we will determine whether (and if so, why) risk rejection manifests differently among people of different racial backgrounds.

Aim 1b: Identify how risk rejection affects risk-concordant mammography screening behavior. As part of the longitudinal survey, we will identify how risk rejection is associated with (i) screening information-seeking behavior and (ii) receipt of screening up to 1 year after the initial survey. We will also assess exploratory outcomes: (iii) whether risk rejection is associated with talking to their doctor about breast cancer risk and (iv) making a risk-based plan for screening and prevention.

Aim 1a Hypotheses: We will test the following primary hypotheses for Aim 1a (note: these are not necessarily mutually exclusive):
H1: Motivated Reasoning: Participants who feel threatened by their risk estimate will express higher levels of risk rejection (Figure 1, Path 1).
H2: Bayesian Updating: Participants whose risk estimate differs from their prior risk knowledge or is surprising will express higher levels of risk rejection (Figure 1, Path 2).
H3: Trust: Participants who have less trust in science and/or the healthcare system will express higher levels of risk rejection (Figure 1, Path 3).
H4: Perceived personal relevance: Participants who believe that the risk model was developed using data from people unlike them will express higher levels of risk rejection (Figure 1, Path 4).
H5: Black women will express higher levels of risk rejection than White women. H5a: There will be an indirect effect of race on risk rejection through lower trust among Black women (compared to higher trust among white women). H5b: There will be an indirect effect of race on risk rejection through lower perceived personal relevance among Black women (compared to higher trust among white women).
Exploratory Research Question: Lower educational attainment, lower numeracy, and lower health literacy are associated with poorer understanding of health information, and race is associated with education, numeracy and health literacy. (1) We will verify that these socio-demographic variables are associated with risk comprehension and explore whether they are also associated with risk rejection.

Aim 1b Hypotheses: Identify the influence of risk rejection on real-life screening decision making.
H6: Risk-concordant information-seeking behavior at baseline: There will be an interaction between estimated risk and risk rejection on information seeking: Women who accept their BCRAT risk estimate will engage in risk-concordant information-seeking behavior, such that higher-risk women will be more likely to choose to learn about options for high-risk women, and average/low-risk women will be more likely to choose to learn about options for average/low risk women. However, the relationship between BCRAT-estimated risk concordant information will be weaker among women who reject their risk estimate.
H7: Risk-concordant screening intentions and screening behavior at 12-month follow-up: There will be an interaction between estimated risk and risk rejection on screening intentions and receipt of screening: Women who accept their BCRAT risk will have risk-concordant screening intentions and screening behavior, such that higher-risk women are more likely to intend to screen in the next 12 months, and actually

receive screening within 12 months, relative to women at lower risk. However, the relationship between estimated risk and screening intentions/receipt will be weaker among women who reject their risk estimate. Exploratory Research Questions: Do either objective risk or risk rejection correlate with women's report of talking to their doctor about their risk? Do women receive additional health services that are concordant with their risk level (e.g., high-risk women receiving consultation about BRCA1/2 gene mutations), MRI screening, and does this depend on risk rejection?

Aim 2: Identify ways of presenting risk information that minimizes risk rejection.
In Aim 2, our goal is to identify communication strategies that reduce risk rejection. To do this we will conduct semi-structured interviews with a subset of participants who enroll in the longitudinal study. The interview guide will probe theoretical perspectives related to the causes of risk rejection, including feelings of threat (i.e. motivated reasoning), distrust, or thinking that the calculator did not ask about important risk factors. Questions will attempt to identify people's rationales for rejecting their risk to deepen our understanding of this phenomenon. Interviews will also ask women how we could communicate more effectively to help them understand and accept their risk estimate.

II. Background and Significance:
Cancer risk prediction models are a cornerstone of precision medicine and public health efforts to improve population health outcomes. (2–4) We are entering an era of precision medicine for cancer screening in which screening initiation and maintenance is based on personal risk estimates that incorporate multiple risk factors, with the goal of maximizing screening benefits and minimizing the harms.(5) One increasingly common clinical application involves using cancer risk prediction models to inform which patients are screened, how often they are screened, and at which ages screening occurs.(5,6) Sometimes referred to as risk-stratified screening, this practice echoes the basic premise of precision medicine and public health, which is to support shared and informed decision making and to improve outcomes and reduce harm by providing patients, caregivers, and clinicians with personalized health information.(7–10) To facilitate this process, researchers have translated risk prediction models into tools that clinicians or patients can use to calculate the probability that a patient will develop a disease in the future.(11,12) However, many lay people do not accept that their personalized risk information is accurate, and little is known about why, or the consequences for their medical decisions. The proposed research will fill that critical knowledge gap and identify methods for communicating personalized risk information that patients can both understand and accept.

Reactions to personalized risk estimates are particularly important for mammography screening decision making. There has been controversy in the US for decades about whether women in their 40s should receive annual mammography screening for breast cancer.(13–15) Current data indicate that in 1,000 women screened every year in their 40s, 1 breast cancer death is prevented, 240 women experience a false positive result, and 1-3 women are over diagnosed (i.e. they are diagnosed and treated for a cancer that would never cause them harm).(16) As a result, the chance of screening benefit may not outweigh the chance of harm for some women in their 40s, particularly those at lower cancer risk. At the same time, research has shown that women at higher cancer risk are less likely to start screening in their 40s compared to women at lower risk, indicating that we are screening individuals who are least likely to benefit and failing to screen individuals most likely to benefit.(17) Communicating to women about their personal risk could help to solve this problem.(18) Consistent with that idea, the United States Preventive Services Task Force (USPSTF) guidelines recommend that women age 40-49 make an informed choice with their doctor about when to start regular screening.(19) Making an informed choice means determining whether, for an individual woman, the likelihood of benefits of mammography screening outweighs the likelihood of harms such as false positive results and overdiagnosis.(5,6,20,21) Hence, a critical component of informed choice is a woman's personal cancer risk, because the expected benefit of screening depends on a woman's risk level. Incorporating informed choice into the mammography screening decision-making process means that women are increasingly asked to make critical decisions about screening based on their personalized breast cancer risk estimates.

However, there is considerable evidence that people often do not accept their personalized risk estimates. Even when people appear to understand and correctly recall their personalized cancer risk estimate, many

people nonetheless *reject* their risk number; that is, they believe that their risk estimate is inaccurate, and that their actual risk is different from the result of the risk calculator. Evidence for *risk rejection* spans many disease contexts, from cancer to heart disease to genetic risk of Alzheimer's. (22–25) In one study of high-risk women eligible to take a medication to reduce their risk of breast cancer, women were asked to recall their calculated breast cancer risk. Many women recalled a number that was substantially different from their calculated risk estimate, and follow-up questioning revealed that while some women simply forgot their risk number, 19% of the total sample reported a different number because they thought their personalized risk estimate was inaccurate.(26) Another recent study found that while personalized breast cancer risk motivated women's intentions to engage in physical activity, 25% of women continued to over- or underestimate their risk after receiving personalized risk information (the majority of those women underestimated their risk).(27) In recent pilot data that we collected as part of a national survey of women in their 40s, we similarly found that 24% of women thought that their risk estimate was not accurate for them. Studies in other disease contexts (e.g., lung and colon cancer, diabetes, heart disease) have also demonstrated that large proportions of participants (in some cases half of a sample or more) reject personalized risk estimates. (22,28–31) Hence, existing evidence clearly indicates that risk rejection is common. However, this phenomenon is usually an incidental observation and rarely the primary focus of research. As a result, our understanding of the causes of the phenomenon and its influence on decision making is limited. Our research will take a systematic, theory-driven approach to understanding risk rejection. We will study risk rejection in the context of breast cancer risk, a disease that is particularly likely to have implications for decision-making about risk-stratified screening.

The tendency for some people to reject risk information may be a key reason why people's risk perceptions (i.e., their feeling of being at higher or lower risk) often do not become completely congruent with the information a risk calculator provides, even among people who accurately recall and appear to understand the risk estimate.(22,23,26,27) Existing risk communication literature has often attributed this risk perception gap to poor comprehension and limited numeracy.(32) However, focusing on comprehension and numeracy overlooks other important information processing stages, occurring after risk comprehension, including risk rejection due to denigration of the accuracy or personal relevance of the information.

The proposed research will focus on breast cancer risk but is relevant for many health conditions. In many areas of medicine, risk assessment tools are being developed for use by doctors, patients, or both. This includes tools for breast and lung cancer screening, (5,6,33) breast cancer chemoprevention, (20) and treatments for heart disease, osteoporosis, and atrial fibrillation.(34–36) In addition, many risk assessment tools are available online and are accessible to the public outside of clinical settings.(12,37,37–39) By gaining scientific understanding of how women come to accept or reject their personalized breast cancer risk, the proposed research will shape the success of the broader shift toward risk-based precision medicine in many disease contexts.

Risk comprehension has been previously identified as a high-impact target for improving medical decisions. (40,41) However, risk rejection has been studied far less systematically. Risk rejection is a high impact target for improving health decision making because people who reject their risk are unlikely to make decisions based on that risk estimate, even when they comprehend the estimate. Current mammography screening guidelines from the USPSTF recommend that a woman's decision to receive screening in her 40s should be an informed choice. If a woman rejects her risk estimate, relying instead on uninformed intuitions or misinformation about her risk, then by definition she is making an uninformed choice. For example, a woman who is told her risk is high, but believes instead that her risk is average or low, may dismiss preventive measures like mammography screening, which could put her at increased risk for a late-stage diagnosis, or even death. Conversely, a woman who is told her risk is low, but believes instead that her risk is high, might opt to receive screening that is unlikely to benefit her, and underestimate the potential for harms from screening such as false positive results, overdiagnosis and overtreatment. By identifying the impact of risk rejection on real-life screening decision making, the proposed research will make strides toward understanding how to increase guideline-recommended informed choice about breast cancer screening.

Many questions about the psychology underlying risk rejection remain unanswered. We know that people often reject their risk estimates in many disease contexts including breast cancer, but we do not know: (1) why some people reject their personal risk estimate, (2) who is most likely to reject their personal risk estimate (e.g., whether people from marginalized racial groups might show different levels of risk rejection), 3) what risk communication methods minimize risk rejection while maximizing comprehension, or (4) how risk rejection shapes screening decision making. The proposed research will fill these knowledge gaps, and will result in practical, evidence-informed guidance on how to improve personalized risk communication to optimize both risk comprehension and informed choice.

Theory suggests reasons why people reject personalized risk information. These reasons have not been systematically tested but will be tested in the proposed research. Figure 1 draws on a stages of processing conceptual model which emphasizes initial attention to a health message (not pictured), followed by comprehension of the message, and then evaluation of the message. (43)

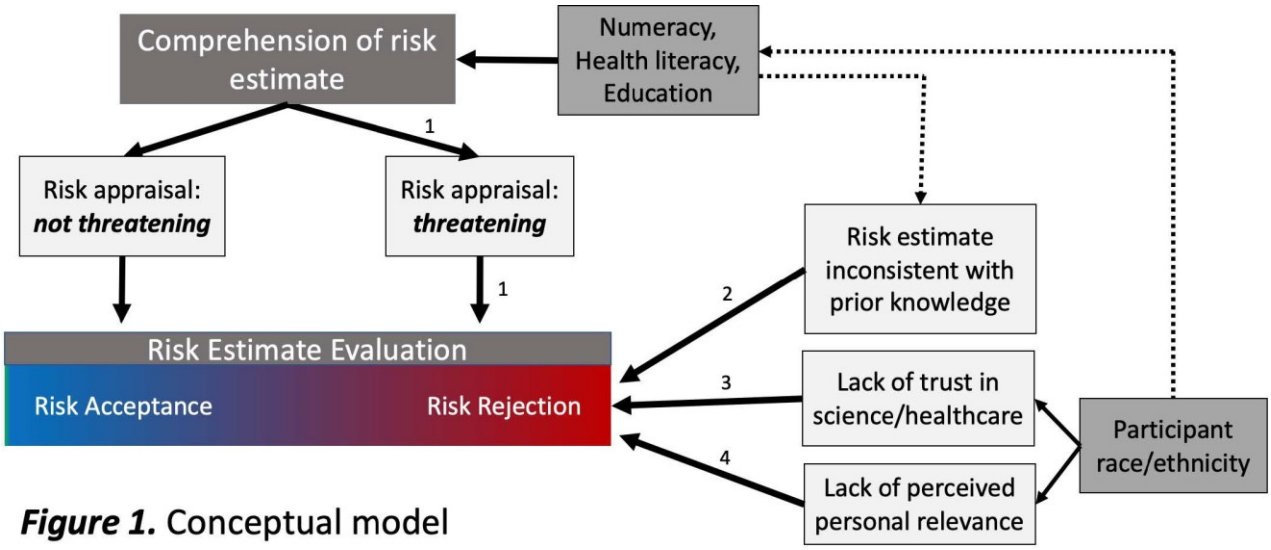


Figure 1. Conceptual model

Rejection or acceptance of health information is thought to occur primarily during the evaluation stage of processing. (43) Figure 1 displays factors that are hypothesized to explain why some people reject personalized risk information. These hypotheses, which we describe in a recent article, (44) will be tested in the proposed research:

1. The Theory of Motivated Reasoning. The Theory of Motivated Reasoning proposes that when people are confronted by unwanted, threatening information they will disregard it or downplay its importance.(45–48) For example, a woman might find her personalized risk estimate to be threatening if it indicates her breast cancer risk is high.(49) She might then choose to believe that the risk estimate is incorrect or unreliable, and conclude that her risk is lower, in order to protect herself from negative feelings or unwanted consequences of the information at hand. Figure 1 illustrates a hypothesized pathway (Path 1) to risk rejection based on the Theory of Motivated Reasoning: If a woman feels threatened by the risk estimate (e.g., because it says she is at high risk of breast cancer), then she may be particularly likely to reject the risk information (whereas if the risk estimate is not threatening, it will be accepted). In the present research, we will test the prediction that feelings of threat in response to the risk estimate will result in risk rejection.

2. Bayesian Updating: A Bayesian Updating perspective offers a more cognitive explanation of risk rejection (Figure 1, Path 2). In particular, it assumes that people will be more likely to reject their risk estimate when it violates their prior knowledge about their cancer risk. (50) When people receive information that conflicts with what they believe to be true, or what they were previously told, they may reject the information because they do not understand how the information could be true, given their prior knowledge. (50) Several studies appear to support this mechanism of risk rejection, showing that people are influenced by their preexisting beliefs about their risk, (26,30,51) and that risk calculator results are more often disregarded when the

results appear contradictory (e.g., when people are told they have old heart age but low risk). (29) A Bayesian Updating perspective allows for risk rejection that is based on accurate or inaccurate beliefs.

The Bayesian Updating and Theory of Motivated Reasoning accounts of risk rejection are not mutually exclusive. It is likely that some individuals reject their risk estimate because they find it threatening, and others reject their risk because it conflicts with their prior knowledge. It is also possible for an individual to reject their risk estimate because they find it threatening and because it conflicts with their prior knowledge. (45,50) However, the key distinction is that the Theory of Motivated Reasoning predicts that risk rejection is driven primarily by feeling of threat, and Bayesian Updating predicts that risk rejection is driven primarily by prior knowledge.

3. Trust: People might reject their risk estimate because of distrust (Figure 1, Path 3) of science, or the healthcare system in general, and this distrust might underlie their rejection of the risk calculator result. While distrust could occur in anyone, it is particularly relevant to perspectives of people from historically marginalized groups. Due to longstanding structural inequities that lead to health disparities by reducing access to quality health care among marginalized racial and ethnic groups, and the influence of these circumstances on trust, (51-53) people from historically marginalized groups, like Black women, may be more likely than White people to reject their personal risk estimates. While some risk calculators incorporate race as a risk factor because of its predictive significance (usually as a proxy measure for the impact of social determinants of health), this may add to distrust if an individual suspects that their race could be used as a factor that either intentionally or unintentionally reduces their access to care. (54-55) Unfortunately, such concerns are not unwarranted. (53-55) Moreover, while communications from trusted sources—e.g., a trusted doctor—can enhance acceptance of persuasive messages, (56) maltreatment of marginalized groups by the medical profession means these patients are often less likely to trust their doctors than White patients. (51-52) Distrust may underlie risk rejection, an issue that affects many marginalized groups in the US. but may be particularly relevant for individuals identifying as Black, due to maltreatment from the medical and scientific fields.

4. Personal relevance: Finally, people may reject their risk estimate because they believe that the risk model was created using data from people who are unlike them or who do not represent them (Figure 1, Path 4). This issue is also particularly relevant to the perspectives of people from marginalized racial groups (54) who have been – and continue to be – under-represented in research that establishes standards of care. (57,58) Thus, for example, a Black woman might reasonably conclude that the risk calculator is less accurate for her than it is for a White woman (even if, as in the case of breast cancer risk, there have been efforts to make risk estimates more accurate for minority population (59). Indeed, there is controversy about the accuracy of health algorithms for predicting health outcomes in marginalized populations. (54,60,61) Hence, people's reasonable concerns about the relevance of the studied populations to themselves could influence whether they accept or reject their personalized risk estimate. However, little research has explored the implications of perceived personal relevance of data for rejection of risk information among Black women

III. Preliminary Studies/Progress Report:

Data informing prevalence estimates of risk rejection and the conceptual model: Data informing prevalence estimates of risk rejection and the conceptual model. We draw on 2 large studies involving different populations of women to estimate the prevalence of breast cancer risk rejection as approximately 25%, or 1-in-4 women. Scherer conducted a national survey that tested a breast cancer screening decision aid for women in their 40s. One component of that decision aid was a breast cancer risk calculator which displayed women's 10-year risk. Of 515 women, 24% believed their breast cancer risk was either higher or lower than the risk calculator estimate, with most overestimating their risk. A study by MPI Waters assessed women's reactions to their lifetime breast cancer risk from the Your Disease Risk website, and found that 25% of women continued to under- or over-estimate their risk after receiving the risk calculator result, and the majority underestimated their risk. (27) Moreover, Scherer's research involving a population of high-risk women provided results from qualitative data that informed our conceptual model explaining why women rejected their breast cancer risk. (26) Waters has made significant contributions to the literature on risk rejection in the context of breast cancer (27,62,63) and the literature on unrealistic risk perceptions. (64,65) Waters, Scherer, and Taber also recently submitted a manuscript that tested and found evidence for some

of the key paths of the proposed conceptual model (Figure 1), in the context of personalized diabetes risk estimates. (31)

Risk communication: Waters has key experience translating risk models into patient-facing tools through the development of the Siteman Cancer Center's Your Disease Risk website. She has shown that the quality of personalized risk communication in online risk calculators is often suboptimal. (37) Waters led the present research team (MPIs and Co-Is) in publishing an article describing the considerations and potential pitfalls of communicating personalized risk to patients and the lay public. (44) Together, we have also published a manuscript that evaluates the quality of risk communication in cancer risk calculators that are found online. (66)

Programming risk calculator and graphic displays: As part of (R37 CA254926), Scherer's team programmed the Breast Cancer Risk Assessment Tool (BCRAT) risk calculator in a Qualtrics survey platform, allowing seamless integration of risk calculation, presentation of personal risk estimates, and survey data collection. The program currently calculates and presents a 10-year cancer risk estimate for participants, and displays the result as a numeric value and as an icon array figure. The program can be easily modified to display lifetime risk estimates, as planned in the present research. The program additionally calculates and displays risk results for an average-risk woman who is the participants' own age. This programming work took nearly a year to accomplish, and the proposed research will be able to utilize that programming, saving considerable time and effort.

Breast cancer screening and screening decision making: Co-I Housten has expertise communicating about many aspects of mammography screening, particularly among racially and ethnically diverse women as they assess the potential benefits and risks of screening guidelines. (67-69) Scherer has current NIH funding to examine how people evaluate and use information about overdiagnosis and screening benefits in the context of mammography (R37 CA254926), research that complements the proposed studies. Lewis brings clinical expertise to this project, and has expertise developing decision aids and informational tools for patients about colorectal cancer screening, prostate cancer screening, and breast cancer screening. (71-73)

Motivated reasoning: Basic theory and health applications: Consultant Taber has examined risk rejection/acceptance in the context of genetic risk using a motivated reasoning framework, (74-78) and has implemented interventions to reduce motivated reasoning. (79,80) Taber and Waters coauthored a paper describing the adaptation of a conventional self-affirmation intervention for use on mobile devices to reduce motivated reasoning-based resistance to anti-smoking messages. (79)

Health disparities: Co-I Tate provides key expertise in health equity and disparities. She spent 9 years at Denver Health Hospital Authority (the safety net hospital system in the Denver Metro area) conducting health disparities and equity research. She is an expert in stereotype threat, perceived discrimination, trust, and implicit bias. (80-82) Her prior work, funded by an NIH R36, explored how perceived discrimination and mistrust in healthcare moderated how older Black patients made decisions about hospice care.

IV. Research Methods

A. Outcome Measure(s):

List of measures, Aim 1.

	Measure description	Source
Primary DVs	Aim 1a: Risk rejection	Waters et al., 2020; Weinstein et al., 2004
	Aim 1b: Risk-concordant information seeking, Screening intentions, Receipt of screening	Schapira et al., 2019, obtained from survey question
Primary IVs	Motivated reasoning measure	

	Emotional response to risk, e.g., upset, anxious, relieved etc. (modified PANAS)	Watson & Clark, 1999
	Bayesian updating measures	
	Perceived conflict with previous knowledge	Scherer et al., in prep
	Belief that calculator does not include import and risk factors or includes unimportant risk factors	Ad hoc; will be pilot tested in Aim 1
	Trust measures	
	Trust in science	Farias et al., 2013
	Trust in healthcare system	Egede et al., 2008
	Trust in developers of the risk model	Scherer et al., in prep
	Personal Relevance measure	
	Belief that the model was developed using people like you; Is accurate for people of your racial/ethnic background	Ad hoc; will be pilot tested in Aim 1
Secondary IVs and control variables	Risk comprehension	Reyna et al., 2009; Aspinwall et al. 2014
	Subjective numeracy	Fagerlin et al., 2007
	Objective numeracy	Weller et al. 2013
	Health Literacy	Chew et al. 2008
	Breast density (if known)	Harvey et al. 2004
	Assessment of more extensive family history of cancer (FHS-7)	Ashton-Prolla et al., 2009
	Prior use of hormone replacement therapy	Yes/no self-report
	Friends/family experience with cancer	Petrova et al. 2015
	Past screening experience	Petrova et al. 2015
	Standard demographics (race, ethnicity, education, income, etc.)	
Exploratory outcomes (Aim 1b)	Whether women talked to a health provider about their breast cancer risk	Scherer et al., in prep
	Receipt of additional breast health services: BRCA1/2 gene consultation MRI screening	Yes/no self-report

Non-Interventional IIT (No Additional Risk) At Multiple institutions

The principal investigator will be responsible for the conduct of this study at all participating institutions, overseeing participant safety, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all trials at the CU Cancer Center. A summary of the DSMC's relevant activities is as follows:

- Conduct of internal audits
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

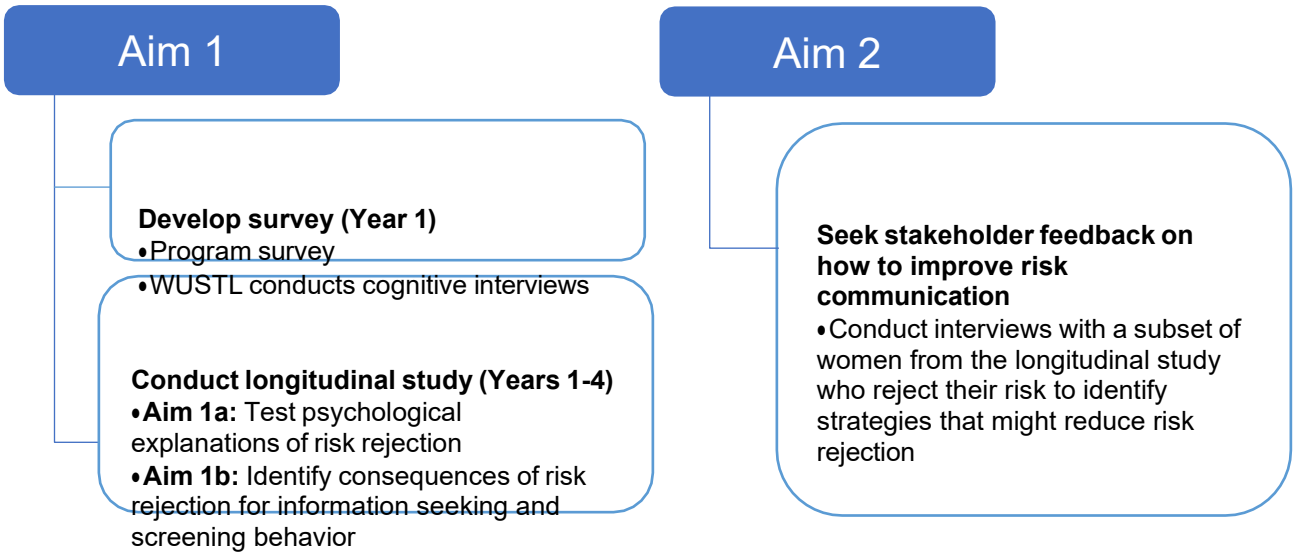
Study audits conducted by the DSMC will consist of a review of the regulatory documents, consent forms, and source data verification. Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial (if applicable).

B. Description of Population to be Enrolled:

For all studies described in this proposal, inclusion criteria are female sex, age 39-74 (i.e., people who are eligible for routine breast cancer screening), and being able to read English. Exclusion criteria are prior

diagnosis of breast cancer, DCIS, LCIS, known BRCA1/2 gene mutation, Cowan syndrome, Li-Fraumeni syndrome, and having received previous chest radiation for treatment of Hodgkin's lymphoma. The reason for these exclusion criteria is that the BCRAT risk model is not designed to assess risk in women with a prior diagnosis of breast cancer or in women with these additional rare risk factors. Women with these characteristics have such different risk profiles and corresponding screening recommendations compared to women without these characteristics that a separate study focusing only on them would be required to study their acceptance or rejection of personalized risk information.

C. Study Design and Research Methods



Aim 1 longitudinal study recruitment: We will test the conceptual model in a longitudinal study. Participants will be asked to complete a baseline and a 12-month follow-up survey.

Prior to conducting this longitudinal survey, the team at Washington University in St. Louis (WUSTL) will conduct cognitive interviews (N=10) to ensure the survey items are of an appropriate literacy level and are interpreted by participants as intended.

For the longitudinal survey, we will recruit a community sample from UCHealth's metro system and WUSTL Barnes Jewish Healthcare system (BJC) and the greater St. Louis metropolitan region. We will recruit N=750 participants split approximately evenly (+/- 5%) between WUSTL and UCHealth (n≈375 per site). Due to the high proportion of African Americans in St. Louis (i.e., 45.3% in St Louis City and 25.0% in St. Louis County), recruitment at WUSTL will enhance the sample's racial diversity relative to what could be obtained at UCHealth. Due to key hypotheses involving perspectives from Black women, we will aim for 40% (n=300) of the sample identifying as Black. WUSTL will also use purposive sampling to enrich the sample for participants with lower educational attainment.

Sites will recruit through the community and our respective healthcare systems. The WU site will use the support of the WU ICTS Recruitment Enhancement Core (REC). The WU site will additionally engage in a variety of practices referred to as "community-based recruitment." These activities include: (a) posting flyers, (b) distributing flyers directly to potential participants, and (c) supporting potential participants in accessing the technology needed to screen participants for eligibility. When staff engage in community-based recruitment activities, they will provide basic study information about the study purpose, eligibility

criteria, study activities, time commitment, and incentive structure. When providing information, staff will use a conversational style and tone and be responsive to the potential participants' verbal and nonverbal cues of interest.

(a) Posting flyers: Staff will post recruitment flyers in locations where people gather such as community centers, libraries, restaurants, bars, laundromats, gyms, beauty parlors, non-governmental social service organizations, grocery stores, corner stores, and shops that sell miscellaneous merchandise. When possible, staff will post the flyers on bulletin boards. In locations where a physical bulletin board is not available but other organizations have posted flyers on a wall, staff will post our recruitment flyer on the wall alongside the other flyers. Staff may also tape the flyer to a table or counter or leave a small number of flyers on a table or counter, depending on the shop's preference. In all cases, staff will ask permission to post the flyer from the manager on duty.

(b) Direct distribution: Staff will attend public events where large numbers of people gather (e.g., charity races, festivals, etc.) and hand out flyers to individuals. In some cases, we will arrange to set up a table or booth where study staff can sit and distribute flyers to individuals who pass by the booth. We may also hand out flyers and/or have booths set up in strategic public locations from section (a) above such as, community centers, non-governmental social service organizations, and libraries.

(c) Support accessing eligibility screener: Study staff can provide potential participants with support in accessing the RedCap survey used to screen for eligibility if needed. In these situations, once an individual expresses interest in completing the study, study staff will show the individual how to access the eligibility screener in REDCap using the link on the flyer. If the participant is eligible for the study, as determined by branching logic, they will provide their contact information and answer questions for purposive sampling. If they are ineligible, no identifiers will be collected. Once this is complete, REDCap will automatically send an email to a different study team member, who will review the eligibility screener results and, if appropriate, call the participants to go through the consent form and answer questions, and then email the potential participant a link containing the postcard consent and survey.

(d) Some potential participants may choose to contact the research team directly using contact information provided on the flyer rather than use the REDCap link. In those instances, a member of the research team will perform the screening over the phone verbally with the potential participant then, if appropriate, email the potential participant a link containing the consent and survey.

CU will recruit through UChealth's RECRUIT program. This will allow for no need to view electronic health records or need for clinical relationship. Potential participants will be sent a virtual flyer and notify interest. Study team personnel will contact potential participants who express interest via RECRUIT using an approved script and eligibility screening will be conducted over the phone with data stored using a secure REDCap database. Participants who are unable to be screened by phone, or who prefer to not screen over the phone, will have the option of completing screening questions via email using a REDCap survey linkt.

All participants will be given a postcard consent at the start of the survey, which will end by stating "By taking this survey, you are agreeing to participate in this research study."

To retain participants for 12 months, we will text message or email them quarterly for the purpose of keeping up to date with their contact information, using approved communication materials designed to keep participants engaged.

Participant Compensation:

Baseline Survey Gift card	12-month Follow-up Survey Gift card
$ 60.00	$ 60.00

Administrative supplement study and recruitment: We received an administrative supplement to recruit an additional N=750 exclusively black female participants through Dynata, an online survey panel company. This administrative supplement study will include a survey that is nearly identical to the Aim 1 longitudinal baseline survey, and is designed to test the same hypotheses as Aim 1a. This is a one-time survey and therefore we do not plan for retention beyond this single contact. A vendor agreement will be set up to recruit participants through Dynata's online survey panel. Dynata is an opt-in national panel of over 7 million US adults and a trusted source for online data collection and will allow us to collect large samples stratified by race, education, and ethnicity. Dynata will send targeted invitations based on age, race, and sex, and then participants will be screened at the start of the survey based on the aforementioned inclusion/exclusion criteria. Participants who do not meet the criteria will be redirected back to Dynata. All incentives will also be handled by Dynata. No personally identifiable information will be collected as part of this online survey and no study team member will have direct contact with any participant. All participants will be consented using a postcard consent that will appear at the beginning of the survey.

Aim 2 interviews: We will purposively sample women whose responses in the Aim 1 baseline survey indicate they rejected their risk estimate. Women identified using purposive sampling will be recontacted and invited to participate in the interview. We will stratify recruitment so approximately 40% of interviewees are Black women. We will interview up to N=40 women (approximately n=20 from Colorado; n=20 from Missouri).

WUSTL Co-I Housten (the facilitator) and an RA (the note-taker) will conduct the interview. The facilitator will present the participants with their risk estimate as previously presented to them during the survey. The facilitator will ask the woman to reflect on thoughts and reactions to their risk estimate, including an open-ended probe assessing participants' rationales for rejecting their risk, or the reason(s) for their uncertainty. This approach will allow all women the opportunity to react to their risk estimate and the information previously presented to them. Next, the interview will present some proposed modifications to risk communication framing, and probe participants' reactions to those modifications to gain further insight into how to improve the design and message framing. Examples of communication modifications include clarifying the way in which each risk factor measured in the BCRAT changes risk, and providing brief descriptions of what is known about risk factors not assessed by the BCRAT, such as lifestyle factors. These interviews will use an iterative process to improve these communications. The study team will discuss further modifications suggested by interviewees, incorporate modifications as appropriate, and then test the clarity of those modifications with subsequent participants.

The interviews will be audio-recorded, transcribed, and qualitatively analyzed by the WUSTL study team.

D. Description, Risks and Justification of Procedures and Data Collection Tools:
We will use the Breast Cancer Risk Assessment Tool (BCRAT), also known as the Gail model, to assess women's risk.[2,61,90] This model is designed to estimate breast cancer risk in women 35-84, and uses the following predictors: 1) age, 2) age at first menstrual period, 3) age at first live birth, 4) first-degree relatives with breast cancer, 5) previous breast biopsy with atypical hyperplasia, and 6) race/ethnicity. Advantages of the BCRAT are that it is calibrated to breast cancer rates in the US, and has shown good calibration in the general U.S. population and for women who are at elevated or high risk. (3,83) The BCRAT is a good predictor for populations and can be used to evaluate appropriate risk-reduction options, such as screening and chemoprevention, by helping patients to weigh the potential harms and benefits of those interventions against the likelihood of developing cancer. (83) Because the BCRAT only accounts for breast cancers in first degree relatives it may underestimate risk in women with a strong family history. The BCRAT also does not account for prior use of hormone replacement therapy (HRT) or breast density, both of which can affect breast cancer risk. We will account for these features of the BCRAT model in the proposed research by identifying whether an extensive family history, use of HRT and known breast density are reasons that some women reject their risk estimate.

We will leverage Scherer's prior work that programmed an interactive risk calculator as a seamless survey element, and which visually displays the risk information using icon arrays. The IT team at the University of Colorado School of Medicine will support any necessary further modifications to the risk model output and displays, with programmer Kelli Giacomini contributing effort to this project who has worked on several academic risk communication projects and is highly qualified to support this research.

E. Potential risks:
Every possible effort will be made to minimize risks and discomforts to participants. All risk information conveyed to participants will be information that current guidelines recommend that all patients receive. No deception will be used. Nevertheless, remaining risk is expected to consist of feeling uncomfortable as a result of the information conveyed, and the risk of loss of confidentiality, which will be minimized.

Every possible effort will be made to protect subjects from risks and discomfort. All participants will be informed that they may discontinue their participation at any time during the interviews or surveys without penalty. The risk of inadvertent or unauthorized release of confidential participant information will be protected against in a number of ways. All electronic documents will be stored only on IRB-approved computers, which are subject to strict security requirements standard for healthcare institutions. No personal identifying information will be stored.

The data security standards for the ACCORDS server are administratively the same as that for the University of Colorado Hospital's system for patient data. All data, including online samples, will be examined closely for any potentially identifiable information, and such information will be removed prior to sharing any data with individuals outside of the immediate research team. All informed consent documents for the quantitative data will inform participants of our intention to make the de-identified data sets openly available.

It is also possible that after learning about their personalized breast cancer risk some women may require additional support and information and manage their concerns about breast cancer. To address this, in all studies women will be encouraged to talk to their doctor about their cancer risk and their options for screening and prevention. To further support participants, we will provide a phone number and email address dedicated to providing support for women enrolled in this research. This phone number and email will be monitored by the project manager with clinical support from Co-I Lewis (MD), and will serve the purpose of answering additional questions that women might have about their risk and providing resources for continued support of high risk women (e.g., helping women identify their risk of BRCA1/2 gene mutation, and local resources for further clinical consultation).

F. Potential Scientific Problems:
Our team extensively discussed whether to study risk rejection in the context of patient-clinician interactions, on the basis that risk estimates may be more readily believed when coming from a trusted provider. However, we cannot put the burden on doctors to be the sole communicators of personalized cancer risk, and people often receive personalized risk estimates outside the context of a clinical interaction., (66) There are numerous risk calculators widely accessible online through patient-facing websites, such as the popular Susan G. Komen website which links to the NCI BCRAT and encourages women to calculate their risk outside the context of a clinical encounter. Also, patient decision aids—which increasingly include risk calculators—are often designed to be used outside of a clinical encounter. (5,20) Hence, studying risk rejection outside the context of a clinical interaction is both important and representative of how these tools are used in the real world. Nonetheless, in all studies we will provide a downloadable pdf summary of each participant's risk estimate so they can bring this information to their next medical appointment (this functionality is already programmed), and in the longitudinal survey we will ask women if they discussed their risk with their doctor.

G. Data Analysis Plan:

Based on prior research we anticipate that 25% of the sample will reject their risk estimate. The primary risk rejection outcome is a continuous variable representing the difference between the participant's calculated estimate and the number they believe is more accurate. Aim 1a: Our prior work suggests that the mechanisms of risk rejection may differ based on the direction of the rejection (overestimating vs. under-estimating). (31) Therefore, we will test H1-H4 using 2 linear regressions, one using a risk rejection outcome that includes only risk-acceptors and over-estimators, and the other including only risk-acceptors and under-estimators. (31) The predictors for each of the regressions will be the variables representing each hypothesized mechanism (e.g., negative affect for H1 Motivated Reasoning; surprise for H2 Bayesian updating, etc). In the *Statistical Design and Power* attachment, we consider the effect of different outcome distributions on statistical power for these tests. In each regression, we will adjust for recruitment site as a fixed effect to capture mean difference in the outcome by site, and explore race/ethnicity, education, numeracy, and health literacy as potential confounders. We will go through the same process for H5, except we will treat race/ethnicity as a predictor, not a confounder. If a race difference is found, follow-up indirect effects models will test H5a/b. (86.87) Aim 1b: For H6-H7, we expect that the greater risk rejection in either direction (over-estimating and under-estimating), the less likely it is that the BCRAT estimate will predict their behavior. That is, when women think their risk estimate is accurate, their behavior will correspond to that risk estimate, but when they think it is inaccurate, their behavior will not correspond to that risk estimate. Hence, for these analyses we will create a variable that is the absolute value of the risk rejection score; a continuous measure for which higher numbers indicate greater risk rejection, with zero indicating complete agreement with the BCRAT estimate (i.e., participants' recalled risk matches their "believed" risk exactly). For the binary outcomes (i.e. risk-concordant choice of information, risk-concordant receipt of screening), we will use multivariable logistic regression models with each individual's BCRAT risk estimate and the absolute value risk rejection score as predictors. An interaction term between the BCRAT risk estimate and absolute value risk rejection variable will also be included. A linear regression model with the same predictor variables will be used for the outcome screening intentions (Likert scale treated as continuous).

H. Summarize Knowledge to be Gained:

Cancer risk prediction models are increasingly being translated into risk assessment tools that are patient-facing and widely available. These tools must be designed and delivered in a way that is accessible, meaningful, and useful for the public and in clinical practice. Personalized cancer risk prediction is especially critical for breast cancer screening for women in their 40s. Currently, women who are at higher breast cancer risk are among those least likely to initiate screening at 40, suggesting we are screening those least likely to benefit and failing to screen those most likely to benefit.(17) With an estimated 1 out of 4 women rejecting their breast cancer risk estimate, risk rejection stands in the way of implementing USPSTF guideline-recommended informed choice for women in their 40s. This collection of studies will provide critical insight into the scientific nature of rejection of personalized breast cancer risk information. The proposed work will provide insight into who rejects personalized risk information and why (Aim 1a), and the impact of risk rejection on screening decision-making and behaviors (Aim 1b). In total, these studies will provide a comprehensive understanding of a phenomenon – risk rejection – which, if not addressed, will impede the implementation of informed patient choice in breast cancer screening and personalized, risk-based medicine more broadly.

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COMIRB
APPROVED
For Use
16-Apr-2026
15-Apr-2027

Study Title: Understanding and addressing rejection of personalized breast cancer risk information

Principal Investigator: Laura Scherer, PhD

COMIRB No: 23-0345

Version Date: 3.12.25

You are being asked to be in this research study because you are an African American/Black female, between the ages of 39-74, with no prior diagnosis of breast cancer, DCIS, LCIS, known BRCA1/2 gene mutation, Cowden syndrome, Li-Fraumeni syndrome, and are able to read English.

If you join the study, you will complete a 20 min survey on your phone or computer.

This study is designed to learn more about the underlying mechanisms of personal breast cancer risk skepticism.

Possible discomforts or risks are minimal but may include feeling uncomfortable or emotionally distressed as a result of the information conveyed.

This study is not designed to benefit you directly.

Every effort will be made to protect your privacy and confidentiality. Data will be stored on protected computers and access will be limited to the research team. Additionally, no personal identifying information will be linked to you individually.

This research is being paid for by the National Institutes of Health (NIH).

You have a choice about being in this study. You do not have to be in this study if you do not want to be.

The data we collect will be used for this study but may also be important for future research. Your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

If you have questions, you can call Dr. Laura Scherer at 303-724-5749, or the study project coordinator, Emily Vidal, at 303-724-5426. You can call to ask questions at any time.

You may have questions about your rights as someone in this study. If you have questions, you can call COMIRB (the responsible Institutional Review Board) at (303) 724-1055.

Certificate of Confidentiality

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any

identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records.

The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,
- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

A Certificate of Confidentiality does not protect information you or a member of your family voluntarily release.

By completing this survey, you are agreeing to participate in this research study.

COMIRB
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16-Apr-2026
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Study Title: Understanding and addressing rejection of personalized breast cancer risk information

Principal Investigator: Laura Scherer, PhD

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Every effort will be made to protect your privacy and confidentiality. Data will be stored on protected computers and access will be limited to the research team. Additionally, no personal identifying information will be linked to you individually.

This research is being paid for by the National Institutes of Health (NIH).

You have a choice about being in this study. You do not have to be in this study if you do not want to be.

The data we collect will be used for this study but may also be important for future research. Your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

If you have questions, you can call Dr. Laura Scherer at 303-724-5749, or the study project coordinator, Emily Vidal, at 303-724-5426. You can call to ask questions at any time.

You may have questions about your rights as someone in this study. If you have questions, you can call COMIRB (the responsible Institutional Review Board) at (303) 724-1055.

Certificate of Confidentiality

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any

identifiable information, document or biospecimen from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records.

The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,
- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

A Certificate of Confidentiality does not protect information you or a member of your family voluntarily release.

By completing this survey, you are agreeing to participate in this research study.