PROTOCOL TITLE:

ENGAGED2: ExperieNces with MammoGrAphy screeninG and brEast Density 2

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1.0 Study Summary

Study Title	ENGAGED2: ExperieNces with MammoGrAphy screeninG and brEast Density 2
Study Design	Randomized Control Trial
Primary Objective	• Phase 1: Refine interventional materials for web-based use. • Phase 2: Test the efficacy of web-based decision support intervention for women at increased risk of breast cancer to consider uptake of MRI and chemoprevention
Secondary Objective(s)	N/A
Research Intervention(s)/ Investigational Agent(s)	Website
IND/IDE #	N/A
Study Population	Patients
Sample Size	1300
Study Duration for individual participants	Phase 1: 2 hours Phase 2: 12 months
Study Specific Abbreviations/ Definitions	

2.0 Objectives*

2.1 Specific Aims.

- Specific Aim 1: Assess intervention effects on uptake and distress
- Specific Aim 2: Identify mediators/moderators of intervention impact on uptake.
- Specific Aim 3: Use trial data in an established CISNET model to extend the time horizon of the trial to estimate the lifetime costs, benefits, and harms of the intervention from different perspectives.

2.2 Hypotheses/Research questions.

- 1a: Compared to UC, women in the PW arm will have higher rates of MRI and chemoprevention uptake at 12-months post-randomization.
- 1b: The intervention will not lead to increased distress compared with UC.
- 1c: Women in the PW arm will have higher rates of follow-up with providers to discuss MRI/chemoprevention.
- 1d: Women in the PW arm will have higher rates of mammography maintenance.
- 2a: Consistent with PMT, higher uptake of risk management in the PW arm will be mediated by increased perceptions of cancer threat (greater awareness of personal risk, higher perceived breast cancer risk, severity and worry) and stronger coping appraisals (higher response efficacy, lower response cost for preventive services; higher self-efficacy).

3.0 Background*

Over 232,000 women developed breast cancer in 2014.[1] Many of these women were unaware of disease risk factors, their personal risk, and available risk management strategies.[2] Along with better-known risk factors such as family history,[3–6] having dense breasts is one of the strongest breast cancer risk factors.[7–11] Extremely dense breast tissue affects about 10% of women, with an additional third having heterogeneously dense breasts. Women in these categories have 3-6x the risk of breast cancer as compared to women with the least density. Although breast density is measured on routine screening mammograms, it has not typically been communicated to patients.[12,13] However, almost half of US states now ***require*** disclosure of density status following routine screening mammography[14–16] and federal legislation is pending. Given these mandates, expert groups are contending with how best to inform patients about their risk.[14,17]

Guidelines have long recommended risk counseling for women with clinically elevated breast cancer risk, including discussion of chemoprevention and additional breast imaging.[18–20] While chemoprevention use is an individual, preference-based decision, population use is low and efforts to improve uptake are limited.[21,22] Three studies have provided decision support for chemoprevention and assessed subsequent uptake,[23] but did not increase use. These studies did not incorporate density, which may be salient for chemoprevention since early, significant reduction in density with tamoxifen use is a marker for greater breast cancer risk reduction.[24–26] Women could find this more tangible given the ability to measure changes.[27] Beyond chemoprevention, recent guidelines recommend annual screening MRI + mammography for women with a lifetime breast cancer risk $\geq$20%.[18,28] Our data suggest low MRI uptake among high risk women.[29] In the present trial, we propose the first study to evaluate a novel approach for density disclosure. We seek to fill the clinical vacuum presented by density disclosure mandates and encourage uptake of risk management without increasing distress.

4.0 Study Endpoints*

4.1 *Primary Endpoint:* 12 month interview and appointment and pharmacy data for endpoints of chemoprevention, screening and physician appointments.

4.2 *Secondary Endpoints:* 12 month cancer-related distress, mammography maintenance, healthcare utilization

4.3 *Safety Endpoints:* Safety endpoints have not been established as this is a minimal risk study.

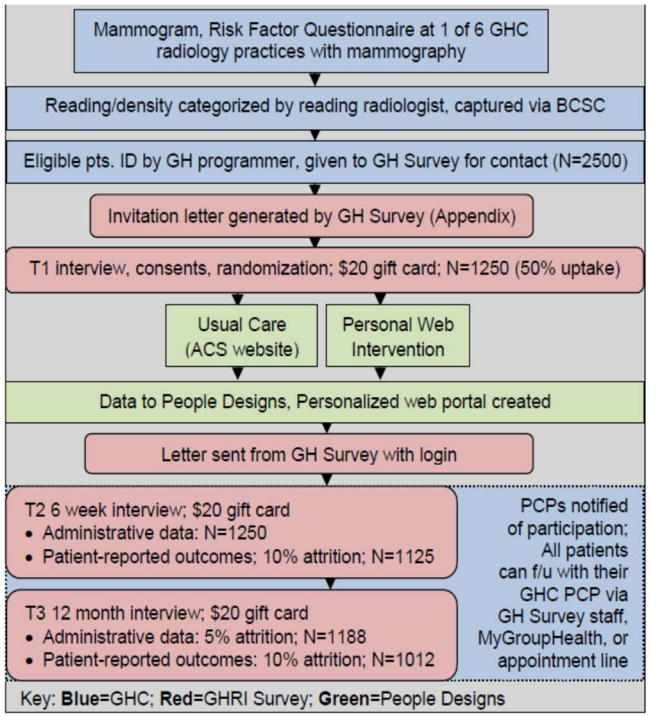
5.0 Study Intervention/Investigational Agent

5.1 Phase 1: Refine interventional materials for web-based use

Focus Group: For the initial phase of translation, we propose to conduct one 2-hour patient focus groups, with 8-12 women participating. The purpose of the focus group is to get input from a panel of patients to inform website development.

Beta Testing: After the focus group has been completed, this feedback will be used to develop a functional beta version of the website. We will recruit 20 eligible women to test the intervention procedures, including providing feedback on navigating the intervention website. Beta testing intervention procedures include: 1. Baseline phone interview, 2. Intervention website navigation, and 3. Semi-structured feedback interview and survey after 2 weeks of beta testing.

5.2 Phase 2: Randomized Control Trial



Potentially eligible patients will be identified, recruited, and enrolled following a negative screening mammogram and review of a routine risk factor questionnaire administered at the time of the mammogram.

At the conclusion of consent, a baseline survey (T1) will be administered. At the conclusion of the baseline interview, participants will be randomized in equal numbers to personalized web site (PW) or usual care (UC; ACS website) via computer-generated random numbers.

Participants will be notified after randomization that they will receive instructions in approximately two weeks for them to log into the website. Women will receive login information that will take them to UC or PW. Participants will be contacted for follow-up interviews at 6-weeks (T2) and 12-months (T3).

Control (UC) Arm: Participants randomized to UC will receive a login that will allow them to access the UC portal and the American Cancer Society website. Our creation of a login portal to a public site will allow us to track who viewed the website, but will not allow for complete utilization data. Participants will be told that this website covers many topics that are pertinent to their health. While the participants will be able to examine any part of the website, they will be asked to review the following sections: Medicines to Reduce Breast Cancer Risk, Breast Cancer Early Detection, and the Prevention Checklist for Women. Therefore, UC participants will have the opportunity to receive much of the same general information as PW participants.

Intervention (PW) Arm: To enter the intervention, participants will be provided with a URL and user name with a temporary password (changed to a private password on sign-in). The first time a user signs in, she will see a welcome video with instructions and will be directed to complete the intervention in order, though she will be able to navigate at-will. Participants will see an always-present indicator that clearly shows progress. Returning participants will be provided a record and links to return. They will be able to use the intervention as often as they want. However, because we are aware many participants will not return multiple times, it will be designed to communicate key content quickly and to be effective with a single usage. Similar interventions we have designed took ~40 minutes to complete. Didactic

information in text, image, animation, and video formats will be incorporated throughout. Interactive elements will be incorporated throughout (quizzes, opportunities to enter open-ended comments, controllable animation, expansion of content for detailed topics) and most pages will include audio narration of the content. Content and interface will be written and designed to be accessible by individuals with limited computer literacy. A limited set of obvious navigation elements will ensure participants do not need to "learn" how to use the website. Clear written instructions will walk users through a linear trajectory, with more experienced users having access to menus for quicker and/or non-linear usage. Content will be large and cleanly laid out, with use of obvious titles, short sentences, and lists to allow for quick digestion of key information.

Intervention translation will be guided by PMT and International Patient Decision Aid Standards (IPDAS). IPDAS guidelines suggest that the intervention should provide: 1) factual information about the condition (breast cancer risk, risk management), including severity and likelihood of possible harms; 2) options for risk management; 3) explanation of risks/benefits of each option, 4) clarification of individual preferences about options (value clarification), and 5) guidance in using information to reach decisions. With the exception of values clarification, all components were included in our print intervention; all will be in our PW arm.

6.0 Procedures Involved

6.1 Study design

The grant to fund this research is awarded to Georgetown, with Dr. O'Neill as the Principal Investigator (PI), with Kaiser Permanente Washington being the recruitment site. O'Neill will have ultimate responsibility for all aspects of this study. This is a decision support intervention for women at increased risk for breast cancer due to breast density and other risk factors to consider MRI and/or chemoprevention to manage their breast cancer risk. We will test the efficacy of this web intervention vs. usual care, comparing uptake of MRI and chemoprevention. All patients will be recruited at Kaiser Permanente Washington in Seattle. Phase I will consist of conducting focus groups and beta and usability testing of intervention procedures. Phase II will conduct the randomized control trial to evaluate the efficacy of web-based breast cancer risk communication vs. usual care.

6.2 Procedures

Phase I: Formative Data Collection

1. Focus Group: For the initial phase of translation, we propose to conduct one 2-hour patient focus groups, with 8 – 12 women participating. The purpose of the focus group is to get input from a panel of patients to inform website development. Women for the focus group will be recruited from Kaiser Permanente Washington in Seattle, WA. The Kaiser Permanente Washington programmer will identify patients using Kaiser Permanente Washington administrative data, who are age 40 – 69, receive care in the greater Seattle area and have had a negative screening mammogram as part of their routine care within the past 6 months. From this pool

we will select a sample for outreach, oversampling to include diversity in race, ethnicity, and education level.

Participants will attend an evening focus group which will last approximately 2 hours. The focus groups will be moderated by an experienced facilitator (Wernli) using a semi-structured guide. The group will be audio-recorded and a court reporter will be present to transcribe the discussion in real-time. The local Group Health Research Institute Investigator will also attend the focus group discussions. At least one assistant, and possibly two will attend the group to aid the Facilitator, completing informed consent, manage the audio recorder, manage refreshments, and distribution of remuneration. The Facilitator will answer any questions and the Facilitator or one of the assistants will complete an informed written consent with each participant before beginning the discussion. Participants will also be asked to complete a brief demographic questionnaire (attached). The study will provide receive free parking or transport and light refreshments (sandwiches, salads, cookies) for focus group participants. The Facilitator will give each participant $50 renumeration at the end of the group as a thank you for participating.

2. Usability testing: This Phase will consist of 10 women to visually demonstrate usability testing and initial response to content of the final beta version of the website. The Kaiser programmer will identify patients with Kaiser Permanente Washington administrative data using the following criteria: females aged 40-69 who have received a routine mammogram and are at-risk for breast cancer. Breast cancer risk will be assessed using a risk factor questionnaire provided routinely in mammography visits. This scantron-based patient risk factor questionnaire is part of Kaiser's obligation as a member in the Breast Cancer Surveillance Consortium (BCSC). Based on this questionnaire, women with high 5-year (>1.66%) risk for breast cancer, and high breast density (heterogeneously or extremely dense), will be eligible for recruitment.

From this pool, we will select a sample for outreach, oversampling to include diversity in race, ethnicity, and education level. Kaiser study staff will mail potential participants a letter that invites them to participate in the study. The letter will give a telephone number to call if the woman wants to participate or does not want to be contacted further. Kaiser study staff will follow-up with a telephone call to individuals who have not actively declined to confirm interest and eligibility and give more information about the study. The study staff will mail a confirmation letter to participants who are confirmed, along with a copy of the consent form to review prior to attending usability testing session. With the participant's permission, study staff will also send a letter to her Kaiser primary care provider to alert them to the participant's risk status and let them know that she may be following up.

Usability testing will take place at Kaiser offices in Seattle WA and will last approximately 2 hours. Participants will complete a brief demographic survey before usability testing. During testing, participants will be asked to navigate

through a draft version of the website very much as a typical participant, but not tailored to their specific breast cancer risk, from the point of login forward. Participants will be asked to "think aloud" as they navigate the website, sharing their thought process as they work, so that Kaiser staff can gain better insight into the navigation process. They will be asked to note any feature or content that confuses them or leads to specific questions. Staff will respond in open-ended neutral ways ("What do you mean by that? Tell me more about that.") so as not to lead the participant. If problems are identified, potential solutions or adaptations will be discussed with the participant. Usability guide is attached. Staff also will observe body language and facial expressions as additional sources of information. The goal of these sessions is to ensure that the website is functioning properly and that navigation elements are properly aligned for the participants' experience. Participants will receive $50 for their time. All in-person meetings will be audio recorded and reviewed to inform finalized intervention development for Phase II. We will complete testing and make changes to the intervention.

3. Beta Testing: After the focus group has been completed, this feedback will be used to develop a functional beta version of the website.

We will recruit 20 eligible women to test the intervention procedures, including providing feedback on navigating the intervention website. Women will be recruited from the Kaiser Permanente Washington in Seattle, WA, using the same means as the usability testing.

Kaiser study staff will mail eligible patients a letter inviting them to participate in the beta testing of intervention procedures. Beta testing intervention procedures include: 1. Baseline phone interview, 2. Intervention website navigation, and 3. Semi-structured feedback interview and survey after 2 weeks of beta testing. The invitation letter will provide a telephone number for Group Health to call if participants would like to first ask questions about the study, call to consent and schedule their participation, and/or who do not want to be contacted further. The baseline phone interview will last about 30 minutes.

Participants will be notified at the end of the baseline interview that they will receive a letter and if requested email with information in order for them to log into the intervention site. With the participant's permission, study staff will also send a letter to her Kaiser primary care provider to alert them to the participant's risk status and let them know that she may be following up. Before sending the letter/email to the participant, Kaiser study team staff members will organize the following data to be sent via secure data transfer for People Designs to tailor the intervention: 1. Participant study ID number, 2. Assigned username and temporary password, 3. BCSC 5 and 10 year risk estimates. The intervention will be designed to monitor utilization through website metrics (e.g., page views, feature utilization, time on site, repeat logins). All of these data points will be aggregated by People Designs and sent securely back to Kaiser to update tracking in Kaiser's database system and for future trial analytics. After a two-week beta testing period,

participants will complete a follow-up interview and provide feedback to evaluate the relevance, acceptability, credibility, and comprehensibility of the information and interface. We will gather their feedback with a semi-structured phone interview to inform the intervention site. Feedback interviews will last about 30 minutes and be scheduled at participants' convenience with Kaiser staff. Participants will receive $20 for completion of the first interview, and $30 for the second interview, up to $50 total for their participation.

4. RCT Trial: Kaiser will recruit women as they receive a negative screening mammogram. Patients routinely complete a scantron patient risk factor questionnaire at the time of the mammogram as part of Kaiser's membership in the BCSC. A Kaiser study programmer who works with the BCSC will use these risk factor data and density readings to identify eligible patients. Women will have either (a) an intermediate 5-year risk (>1.67%-2.49%) and extremely dense breasts or (b) a high 5-year risk (≥2.50%) and either heterogeneously dense or extremely dense breasts. Women must also have a valid email address. Patients will be recruited via an introductory letter from the study team. This letter will notify them of their density status and introduce them to the study. Kaiser Survey Research Program will use standardized methodology for proactive telephone contact, verbal consent and to conduct baseline interviews. At the conclusion of the baseline interview, participants will be randomized in equal numbers to personalized web site (PW) or usual care (UC; ACS website) via computer-generated random numbers. Participants will be notified at the end of the call that they will receive a letter from Group Health in approximately two weeks in order for them to log into the website. During this time, personalized risk information will be sent to People Designs via secure data transfer to tailor the intervention. Women will receive login information that will take them to UC or PW. Logins will be tracked and follow-up will be made as needed to prompt uptake. Consent will be done online after website login. Patients will have the option to print a copy of the consent for them to keep. For participants that don't login to the website and give consent, they will be sent a paper consent form to sign and return. Patients that don't complete consent will not be contacted for the 12 month follow up survey and will be purged from the database. Patients will have several ways to make appointments at Kaiser and their primary care provider will be notified of their participation. We will conduct follow-up interviews at 6 weeks and 12 months. We chose 6 weeks to gather data as close in time to baseline and their initial mammogram as possible, but allow for women to receive their login and view materials. Use of Kaiser Survey Research Program ensures internal validity of data collection, diminishes missing data and allows seamless integration of survey data with clinical and pharmacy records that will serve as our primary outcome measures and inputs to our cost model. Women will receive a $20 gift card for each interview.

6.3 Risk minimization

The risks of participation are minimal. The primary risk is breach of confidentiality. The PI and all key personnel participating as research study staff in the proposed project have completed and will continually maintain requirements for certification

in Human Subject Research Protection. Research team conference meetings/calls will be conducted to discuss the course of the research and provide a forum for identifying and discussing any adverse events. A specific protocol will be in place to provide study participants experiencing distress with appropriate referrals for psychological counseling, whether or not this distress is connected with their research participation.

6.4 Measures are summarized in Table 1:

Study Measures			
Variable	Timepoint		
	Baseline	6-wk.	12-mo.
Sociodemographics	X		
Medical/Screening Variables	X		X
Plan coverage	X		X
Health-system level variables	X		X
Outcomes			
Healthcare utilization			
Chemoprevention uptake	X		X
MRI uptake	X		X
Mammography uptake	X		X
Healthcare utilization	X		X
Patient-reported outcomes			
Distress (IES)	X	X	X
Patient-provider discussion	X		X
Mediators			
Mammography/CBE intentions	X	X	X
Chemoprevention intentions		X	X
MRI intentions		X	X
Awareness of breast cancer risk	X	X	X
Perceived breast cancer severity	X	X	X
Perceived breast cancer risk	X	X	X
Breast cancer worry	X	X	X
Self-efficacy: Chemoprevention, MRI		X	X
Response cost: Chemoprevention, MRI		X	X
Response efficacy: Chemoprevention, MRI		X	X
Moderators			
Health literacy (Chew et al.)	X		
eHealth literacy (eHEALS)	X		
Numeracy (SNS)	X		

7.0 Data and Specimen Banking*

7.1 Data will only be shared as requested through the NIH Resource Sharing Plan Requirement.
We will make de-identified data available by request to investigators not associated with the study. Priority for sharing of data will be given to junior faculty and/or faculty interested in questions related to translational science. We see this study as an important resource for examining issues related to clinical integration of breast density. Any requests for data from non-study investigators will be reviewed

by the investigative team to ensure that it does not conflict with planned analyses, is otherwise respectful of the study participants, and complies with all relevant IRB and HIPAA regulations.

We will make study data available to other investigators under data sharing agreements that ensure that (1) the data will be used only for research purposes, (2) no individual participant's de-identified data will be disseminated, (3) the data will not be used to identify an individual participant, (4) data will be protected under appropriate security measures including encryption and password protection, and (5) the data will be destroyed or returned to us upon completion of relevant analyses. If appropriate, we will also determine whether at least one study investigator should be involved scientifically in any projects that result from data sharing requests.

8.0 Sharing of Results with Subjects*

8.1 Study results will be shared with participants at the end of the study.

9.0 Study Timelines*

9.1 Phase 1: Participants will be enrolled in the study for a single interview or focus group, approximately 2 hours once.

9.2 Phase 2: Participants will be enrolled in the study for 12 months, with 3 distinct events: baseline survey, 6-week follow-up survey, 12-month follow-up survey. Total combined time commitment is approximately 3 hours or less over the course of the year.

9.3 Total anticipated study duration is 4 years, including subject follow-up and data analysis.

10.0 Inclusion and Exclusion Criteria*

10.1 Study staff will screen eligibility prior to recruitment.

10.2 Inclusionary Criteria:

Focus Group: Women, aged 40-69, who are enrolled at Kaiser Permanente Washington at least one year prior to mammogram, receive care in the greater Seattle area and have had a negative mammogram (BIRADS 1 or 2 assessment) as part of their routine care within the past 6 months, no prior breast cancer, invasive or DCIS (ever), no prior LCIS diagnosis, no BRCA mutation carriers or genetic counseling visits.

Beta/Usability testing: Women, aged 40-69, who are enrolled at Kaiser Permanente Washington, receive care in the greater Seattle area and have had a negative mammogram (BIRADS assessment of 1 or 2) as part of their routine care. Utilizing the Breast Cancer Surveillance Consortium Risk Calculator (http://tools.bcsc-

scc.org/BC5yearRisk/), women will have high 5-year (>1.66%) risk for breast cancer and high breast density (heterogeneously or extremely dense). Women will have been enrolled for year prior to the mammogram at Group Health.

Randomized Controlled Trial: Women, aged 40-69, who are enrolled at Kaiser Permanente Washington, and have had a negative mammogram as part of their routine care. Utilizing the Breast Cancer Surveillance Consortium Risk Calculator (http://tools.bcsc-scc.org/BC5yearRisk/), women will have either (a) an intermediate 5-year risk (>1.67%-2.49%) and extremely dense breasts or (b) a high 5-year risk (≥2.50%) and either heterogeneously dense or extremely dense breasts. Women must also have a valid email address.

Exclusionary Critera:

Exclusion criteria include not able to speak and read English; not able to physically attend the focus group location and time. Exclusion criteria for beta/usability testing and the trial include not able to speak and read English; history of LCIS, prior cancer diagnosis (including DCIS), known BRCA1/2 family mutation, or previous receipt of cancer genetic counseling. While usability testing participants will need to attend in person, beta testing and trial participants will not be required to physically attend to participate. They will also be excluded if they have indicated they do not want to be contacted for research, if they participated in our previous intervention development activities, or if they died or dis-enrolled from health plan between mammogram and start of recruitment.

11.0 Vulnerable Populations*

11.1 Pregnant women will not be excluded from this study if they are otherwise eligible to participate. We will ensure that all participants are able to provide meaningful informed consent such that they will be asked to repeat back the purpose of the study after a member of the study team has explained the study verbally and gone over the written informed consent.

Students will not be excluded from this study if they are otherwise eligible to participate. We will ensure that all participants are able to provide meaningful informed consent such that they will be asked to repeat back the purpose of the study after a member of the study team has explained the study verbally and gone over the written informed consent.

Women who are economically or educationally disadvantaged will not be excluded from this study if they are otherwise eligible to participate. We will ensure that all participants are able to provide meaningful informed consent such that they will be asked to repeat

back the purpose of the study after a member of the study team has explained the study verbally and gone over the written informed consent.

In addition, although we will be providing incentives for participation in the form of a gift card, the amount of the incentives are not so large as to be coercive. Study related materials will be written at an 8th grade level.

12.0 Local Number of Subjects

12.1 Total number of subjects to be accrued locally: 10

12.2 Total number of subject to be accrued nationally: 1300

13.0 Recruitment Methods

13.1 Recruitment Procedures

Focus Group: The Kaiser Permanente Washington programmer will identify patients using Kaiser Permanente Washington administrative data, who are age 40 – 69, receive care in the greater Seattle area and have had a negative screening mammogram as part of their routine care within the past 6 months. From this pool we will select a sample for outreach, oversampling to include diversity in race, ethnicity, and education level. Kaiser study staff will mail potential participants a letter that invites them to participate in a 2-hour group discussion. The letter will give a telephone number to call if the person wants to participate or does not want to be contacted further. Kaiser study staff will follow-up with a telephone call to individuals who call to say they are interested to confirm eligibility and give more information about the study. The study staff will mail a confirmation letter to participants who are confirmed, along with a copy of the consent form to review prior to attending the focus group.

Usability Testing: The Kaiser programmer will identify patients with Kaiser Permanente Washington administrative data using the following criteria: females aged 40-69 who have received a routine mammogram and are at-risk for breast cancer. From this pool, we will select a sample for outreach, oversampling to include diversity in race, ethnicity, and education level. Kaiser study staff will mail potential participants a letter that invites them to participate in the study. The letter will give a telephone number to call if the woman wants to participate or does not want to be contacted further. Kaiser study staff will follow-up with a telephone call to individuals who have not actively declined to confirm interest and eligibility and give more information about the study. The study staff will mail a confirmation letter to participants who are confirmed, along with a

copy of the consent form to review prior to attending usability testing session.

Beta Testing: Women will be recruited from the Kaiser Permanente Washington in Seattle, WA, using the same means as the usability testing.

Kaiser study staff will mail eligible patients a letter inviting them to participate in the beta testing of intervention procedures. Beta testing intervention procedures include: 1. Baseline phone interview, 2. Intervention website navigation, and 3. Semi-structured feedback interview and survey after 2 weeks of beta testing. The invitation letter will provide a telephone number for Group Health to call if participants would like to first ask questions about the study, call to consent and schedule their participation, and/or who do not want to be contacted further.

RCT: Kaiser will recruit women as they receive a negative screening mammogram. Patients routinely complete a scantron patient risk factor questionnaire at the time of the mammogram as part of Kaiser's membership in the BCSC. A Kaiser study programmer who works with the BCSC will use these risk factor data and density readings to identify eligible patients. Women will have either (a) an intermediate 5-year risk (>1.67%-2.49%) and extremely dense breasts or (b) a high 5-year risk (≥2.50%) and either heterogeneously dense or extremely dense breasts. Women must also have a valid email address. Patients will be recruited via an introductory letter from the study team. This letter will notify them of their density status and introduce them to the study. Kaiser Survey Research Program will use standardized methodology for proactive telephone contact and verbal consent.

13.2 Recruitment materials are attached with the application.

13.3 Subject compensation

Focus group: $50 cash upon completion of the focus group

Beta and usability testing: $20 cash upon completion of the session

RCT: $20 cash upon completion of each interview

14.0 Withdrawal of Subjects*

Participants will be informed that they can withdraw from the study at any time. We will track the number of eligible participants that withdraw from the study. Reasons participants may withdraw or dropout of the study include lack of time and not being interested in participating in research related to breast density and mammography.

When a participant drops out, if she indicates that we cannot use the data collected thus far, then we will destroy it and not include it in analyses. If the

participant simply no longer wants to participate but does not request that we do not use the existing data, then we will use the data already collected.

15.0 Risks to Subjects*

15.1 The primary sources of risk concerns data privacy, confidentiality, and psychological discomfort. There are few psychological risks to completing cognitive, decision making, and psychological assessments. However, surveys and interviews may contain questions that make participants feel uncomfortable or bring up unwanted thoughts or feelings. All participants will be informed in advance of participation and each data collection opportunity that any questions that make them feel uncomfortable may be skipped or ignored.

The risk of gathering social, behavioral, and medical information is also present.

There is some risk for breach of confidentiality. However, we have taken multiple steps to ensure this risk is very low. Only key staff members will have access to individually identifiable private information about participants, including the principal investigator, the project coordinator, and research assistants. We also developed a rigorous data management plan to reduce this risk.

16.0 Potential Benefits to Subjects*

16.1 There is no direct benefit to subjects. It is possible that participants may derive benefit from taking part in the intervention and surveys. Participants will be informed about the results of the study.

17.0 Data Management* and Confidentiality

17.1 Data Analysis Plan, including statistical procedures and power analysis
Phase 1: Analysis of focus group data and most beta and usability testing will be done using qualitative methods and therefore is not subject to statistical considerations. Quantitative data in the beta and usability testing will use t-tests and Chi-square tests to examine differences, with a p-value of .05.

Phase II: We will calculate descriptive statistics for all variables. We will assess the quality of the data and evaluate the extent of missing data. If needed, we will address missing data issues by using multiple imputation methods203; we will generate 10 multiple imputed datasets, analyze each separately, and then combine results across the 10 datasets. All statistical analyses will be performed as intention-to-treat (ITT) analyses. Given our use of administrative data to measure our primary outcomes, we will retain all women who consented and completed the baseline (N=1250). Assuming a 5% attrition rate from Group Health during the 12 months,19 we will use 1188 participants for our primary analyses (594/arm). For patient reported outcomes, we anticipate 10% attrition at 6 weeks and 10% attrition at 12 months, leaving 506/arm at 12 months.18 We will evaluate the associations

between baseline variables, mediating variables assessed at 6 weeks, and 12 month outcomes. For categorical variables we will use Chi-Square tests or Fisher's exact tests if needed, while for continuous variables we will use Student t-tests or Wilcoxon-Mann-Whitney tests. Any variable that exhibits a $p<.10$ association with outcomes of interest will be subsequently controlled for in analyses. We will assess attrition rates and subgroup effects over the short- and longer-term.

Power calculations assume a two tailed $\alpha=.05$ and N=1188 at 12 months (594/arm) for primary utilization outcomes of chemoprevention and MRI; calculations for patient-reported outcomes will assume N=1012 at 12 months (506/arm). To account for clustering by provider, we calculated effective sample sizes assuming an average cluster size of 11 patients/provider and intraclass correlation coefficient of 0.02. This reduces the sample size by a factor of 1.2, leaving effective sample sizes of 990 for utilization outcomes and 842 for patient-reported outcomes. We employ generalized estimation equations (GEE) methods with exchangeable working correlation structure to analyze clustered data.

Assess intervention effects on uptake and distress. 1a: Compared to UC, women in the PW arm will have higher rates of MRI and chemoprevention uptake at 12-months post-randomization. We will use logistic regression models with GEE to account for patients' clustered binary outcomes within their providers. We will use 2 separate logistic regression models for each binary outcome: chemoprevention and MRI uptake. These models will include intervention (PW vs. UC) as the main predictor, and baseline covariates as controlling variables. Given the effective sample size of 990, we provide a range of effect sizes that correspond to statistical power ranging from 80% to 99% in Table 5. UC rates are based on published uptake of chemoprevention20 and breast MRI.21 1b: The intervention will not lead to increased distress compared with UC. To demonstrate that the PW arm does not result in greater distress than UC, we will test for noninferiority by constructing a one-sided 97.5% confidence limit for the adjusted (for baseline distress) mean difference between arms. Noninferiority will be demonstrated when the one-sided 97.5% confidence limit does not cross the noninferiority limit of 3 points. We arrived at this noninferiority limit based on outcomes among patients at increased cancer risk.75 Given the effective sample size of 842 we will have 80% power to conclude non-inferiority assuming a SD of 15.3 points. This reflects an extremely small effect size of < 0.20.209 1c: Women in the PW arm will have higher rates of follow-up with providers to discuss MRI/chemoprevention. 1d: Women in the PW arm will have higher rates of mammography maintenance. We will use the approach in 1a for 1c and d.

Identify mediators/moderators of intervention impact on uptake. 2a: Consistent with PMT, higher uptake of risk management in the PW arm will be mediated by increased perceptions of cancer threat (greater awareness of personal risk, higher perceived breast cancer risk, severity and worry) and stronger coping appraisals (higher response efficacy, lower response cost for preventive services; higher self-efficacy). To increase power we will use the product of coefficients method to

evaluate mediation effects. Using logistic regression models with GEE we will estimate the standardized coefficients relating each mediating variable (e.g. worry) to the chemoprevention and MRI uptake outcomes (β), and the standardized coefficients relating the intervention (PW vs. UC) to the mediating variables (α). These models will control for the baseline measurement of the mediator variable and also other baseline covariates. We will then calculate each mediated effect as the corresponding product of these coefficients (αβ) with its standard error and 95% confidence interval estimated as described by MacKinnon. Effect sizes of 0.14, 0.39 and 0.59 for the coefficient parameters are considered "small", "medium" and "large" respectively.211 We will be able to detect a mediation effect (coefficient product) of small size (with coefficient product parameters $\alpha = 0.14$, $\beta = 0.14$) at >95% power for each mediator,210,211 given our total effective sample size of 842.

Given our incorporation of intervention elements supporting patient comprehension, values clarification and communication, we anticipate that PW participants will have similar rates of risk management regardless of literacy/numeracy level. In contrast, we expect lower uptake of risk management options among UC participants with lower literacy/numeracy. However, even with our large sample, we are underpowered to detect this subtle moderation effect. Therefore, we will examine these relationships in exploratory subgroup analyses. We also will assess the robustness of outcomes across patient subgroups using additional, exploratory moderation analyses. Given our individual focus, we will examine adoption by patients, but explore whether effects are moderated by clinical variables (i.e., mammography facilities, primary care clinic home).

17.2 Data Security

Data collected in this study will be used exclusively for research purposes; it will be managed and stored according to our sites' security standards for data that require the highest possible security to ensure there will be no inadvertent disclosure. Any computers storing or accessing data collected for the study will be required to comply with these standards.

During the trial, all study data that will be collected from surveys or gathered from other sources will reside in a HIPAA-compliant study folder. During analysis, all data will be stored in Box. to the study folder is provided based on employee's role, on a 'need to know, least privilege' basis. Georgetown Box is a secure (HIPAA/PHI approved) place to store study files.

No identifying data will be stored on laptop computers or other mobile computing hardware. Computers used to access the data will be protected by a username and password that meet our IT departments' complexity and change requirements to ensure a high degree of security, and they will be protected with anti-virus software and scanned regularly for vulnerabilities.

All study staff members will be trained to use these procedures, which will be detailed in a study manual of operating procedures. We have found that using these procedures provides a high degree of protection with respect to the privacy of individuals and the confidentiality of data.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

18.1 We do not anticipate more than minimal risk to participants. Quality assurance reviews will be conducted throughout the course of the study to ensure data quality and adherence to research protocol.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 No one who is not a part of the study team will have access to the study records or data, unless it is necessary to reveal this information for regulatory or legal reasons.

19.2 Participants will be reminded that they are able to skip any questions they do not wish to answer or withdraw from the study at any time.

20.0 Compensation for Research-Related Injury

20.1 n/a

21.0 Economic Burden to Subjects

21.1 n/a

22.0 Consent Process

22.1 Participants will complete an informed written consent prior to the beginning of the focus group at Group Health in Seattle. Dr. Wernli and Ms. Ehrlich will co-lead the group and will obtain consent. The facilitator (Dr. Wernli) will address all participants at the beginning of the focus group and explain study procedures and benefits/risks. Women will have a few minutes to independently read and sign the consent form prior to the start of the focus group discussions. To allow time for them to fully consider their participation, they will be mailed a copy of the consent in advance so that they can review before attending. This will also minimize undue influence, as they can choose to not attend the group or to call study staff if they have questions prior to attending.

Usability testing: Participants will complete an informed written consent and HIPAA prior to the beginning of testing at Kaiser in Seattle. To allow

time for them to fully consider their participation, they will be mailed a copy of the consent in advance so that they can review before the interview.

Beta testing: Participants will complete consent and HIPAA online thru the intervention website. They will receive the same consent language as in a written consent but in an online format and will be required to agree to the consent and check yes to move forward into the tailored information of the website.

Usability testing: Participants will complete an informed written consent and HIPAA prior to the beginning of testing at Kaiser in Seattle. To allow time for them to fully consider their participation, they will be mailed a copy of the consent in advance so that they can review before the interview.

RCT: Participants will complete consent and HIPAA upon logging into the study website for the first time. We have requested an alteration of consent to allow consent to be completed online. Participants will have the option to print a copy of the consent to keep. For participants that never log into the study website a paper consent will be mailed to them to sign and return.

Non-English Speaking Subjects

- *n/a*

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- We are requesting a limited HIPAA waiver to support recruitment. All information obtained for individuals who are not retained as participants will be destroyed.
- We are opting for an online consent as the primary means of consent for anyone using the website (PW or UC) as we have concerns with potential participants accessing and using the intervention website in advance of returning signed written consent and possibly without ever returning the signed written consent. We want to be sure there is clear communication regarding the elements of consent and have documentation of consent before participants enter into the tailored information of the website. Written paper consent will be used as a back-up for those who do not log on. Those who do not return this paper consent will not be contacted for the 12 month and will be purged from the dataset.

Subjects who are not yet adults (infants, children, teenagers)

- *N/A*

Cognitively Impaired Adults

- *N/A*

Adults Unable to Consent

- *N/A*

23.0 Process to Document Consent in Writing

23.1 Written consent forms document consent in writing. For online consent, a statement of consent will be embedded at the start of the survey. The survey will begin with a statement indicating that by starting the survey, they are consenting to participation. No signature will be obtained. A study coordinator will document in writing that consent has been obtained for verbal or online consent without signature.

24.0 Setting

24.1 We will implement this study within the women enrolled at of Kaiser Permanente Washington, an integrated care delivery system in the Pacific Northwest.

25.0 Resources Available

25.1 The study will be conducted within the context of a funded research program and supported by trained research staff. All staff will be trained to support this protocol and methods.

26.0 Multi-Site Research*

26.1 Study-Wide Number of Subjects: 1300

26.2 Study-Wide Recruitment Methods

Recruitment at all sites will follow procedures above. Data management at all sites will follow procedures above. Site PIs will meet regularly to discuss study procedures and track progress.

26.3 Site Activities

	Research Activities
Principal Investigator:	
Suzanne O'Neill: Sco4@georgetown.edu	A, B, C, D, E, F, G

Kaiser Personnel:	*Research Activities*
Karen Wernli (Site PI)	E, F, G

Kathy Leppig (co-PI)	E, F, G
Sarah Knerr	A, B, C, D, E, F, G
Kelly Hansen	A, B, C, D, E, F, G
Hongyuan Gao	A, B, C, D, E, F, G
Erin Bowles	A, B, C, D, E, F, G

Georgetown Personnel:	*Research Activities*
Katherine Lopez (Study Coordinator)	A, B, C, D, E, F
Jeanne Mandelblatt (co-PI)	E, F
Young Chandler (co-PI)	E, F
Marc Schwartz (co-PI)	E, F
George Luta (Biostat)	E, F

**For each person listed above, identify their ROLES with the appropriate letter:*
A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing coded (linked) data or specimens for research purposes
G. Some/all research activities performed outside GU

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