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A web-based personalized risk communication and decision-making tool for women with dense breasts: design and methods of a randomized controlled trial within an integrated health care system

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Abstract

Background—Mammographic breast density is one of the strongest risk factors for breast cancer after age and family history. Mandatory breast density disclosure policies are increasing nationally without clear guidance on how to communicate density status to women. Coupling density disclosure with personalized risk counseling and decision support through a web-based tool may be an effective way to allow women to make informed, values-consistent risk management decisions without increasing distress.

Methods/design—This paper describes the design and methods of Engaged, a prospective, randomized controlled trial examining the effect of online personalized risk counseling and decision support on risk management decisions in women with dense breasts and increased breast cancer risk. The trial is embedded in a large integrated health care system in the Pacific Northwest. A total of 1,250 female health plan members aged 40–69 with a recent negative screening

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mammogram who are at increased risk for interval cancer based on their 5-year breast cancer risk and BI-RADS® breast density will be randomly assigned to access either a personalized web-based counseling and decision support tool or standard educational content. Primary outcomes will be assessed using electronic health record data (i.e., chemoprevention and breast MRI utilization) and telephone surveys (i.e., distress) at baseline, six weeks, and twelve months.

Discussion—Engaged will provide evidence about whether a web-based personalized risk counseling and decision support tool is an effective method for communicating with women about breast density and risk management. An effective intervention could be disseminated with minimal clinical burden to align with density disclosure mandates.

Keywords

breast density; risk communication; breast cancer; chemoprevention; breast MRI; prevention

1. Introduction

Almost 247,00 women developed invasive breast cancer in 2016 [1]. Many were unaware of their breast density status even though having dense breast tissue is one of the strongest breast cancer risk factors after age and family history [2, 3]. Recent patient advocacy efforts and legislative initiatives are changing the disclosure of breast density [4], and as of June 2016, 28 US states require notification of breast density status following a routine screening mammogram. More than 68% of the US population resides in breast density notification states, which include California, Texas, and New York [4]. Given these mandates, researchers, radiologists, primary care physicians, and policy experts must learn how to communicate about breast density in a way that informs and empowers women without alarming them [5–7].

Breast density is measured clinically through a mammogram. Density is typically reported using a four-point Breast Imaging-Reporting and Data System (BI-RADS®) scale, which measures from fatty (1) and scattered density (2) to heterogeneously dense (3) or extremely dense (4) breast tissue. Together, the two upper density categories comprise almost half of US women [8]. Women with extremely dense breast tissue have three to six times the risk of breast cancer compared to women with fatty breast tissue [9–11]. Additionally, women with dense breasts are more likely to be diagnosed with interval cancers (i.e., breast cancer diagnosed in the interval between scheduled screening episodes) compared to women with similar 5- and 10-year cancer risk estimates, but less dense breasts [12].

Evidence-based standards for breast density disclosure are lacking. Previously, providers rarely communicated breast density information to patients in part because whether breast density information should change women's clinical management is unclear [13, 14]. Density measurement can be imprecise and changes as a woman ages [15–17]. The lack of guidance about breast density disclosure creates a vacuum that must be filled to support women in the face of these new regulatory mandates.

Coupling breast density disclosure with personalized risk counseling and decision support in a web-based tool is one approach to filling this evidence gap. While there currently are no

density-specific clinical guidelines, clinical practice guidelines have long recommended risk counseling for women at clinically elevated breast cancer risk [18–21]. We, and others, have developed and evaluated a number of individually-tailored online cancer risk communication interventions serving this purpose [22–24]. Linking density disclosure with risk assessment and counseling for women at clinically elevated risk has a number of advantages. This approach allows breast density to be contextualized in light of women's other breast cancer risk factors and overall cancer risk [25]. It also enables intervention content to be tailored to women's preferences and unique benefit/risk profiles. Finally, it helps align risk management recommendations with clinical guidelines, which are largely based on numeric risk estimates [18, 26].

It is possible that the addition of breast density information to standard risk counseling and decision support could also enhance guideline-informed uptake of chemoprevention and breast MRI, which has proved challenging [27–29]. Specifically, density disclosure may motivate risk management by influencing women's risk perceptions [30]. An effective web-based tool could be easily disseminated online to align with density disclosure mandates. Communicating with women about their density status and risk management options through the internet may lower the clinical burden associated with density disclosure. This paper describes the design, methods, and rationale for the Engaged trial, an ongoing randomized controlled trial of an innovative web-based breast cancer risk communication and decision-making tool intended to address the limitations of current breast density disclosure approaches.

2. Trial objectives

The primary objective of the Engaged trial is to determine the effect of a web-based breast cancer risk communication and decision-making tool on guideline-informed uptake of risk management and self-reported distress compared to a control group among women with dense breasts and elevated five-year breast cancer risk. The secondary objective is to determine theoretically-informed mediators and moderators of intervention effects on risk management decisions.

3. Methods

3.1 Study design

This randomized controlled trial (RCT) aims to recruit women aged 40–69 with dense breast who are also at increased five-year risk of breast cancer from a large integrated health care system in the Pacific Northwest. Eligible women, who agree to participate complete a baseline interview and provide written informed consent, are randomized to condition and given log-on credentials to access a web-portal. Following the welcome page, women receive an interactive personalized risk counseling and decision-support tool (intervention arm) or are redirected to the American Cancer Society (ACS) website (usual care arm) [31]. With the participants' permission, their primary care providers (PCPs) are also notified of their study participation, including that women are eligible due to an increased five-year risk of breast cancer based on risk factors reported at the time of their most recent negative mammogram. PCPs are not told whether their patient was assigned to the intervention or

control arm, but are not otherwise blinded to study arm. Primary study outcomes are assessed at baseline, 6-weeks, and 12-months using electronic health record (EHR) data and telephone surveys. A study flow diagram is given in Figure 1. This study was approved by the Georgetown University Institutional Review Board.

3.2 Setting

The RCT is embedded in an integrated health care delivery system serving over 600,000 people in the Pacific Northwest. The health system has a fully integrated EHR, including linkages to pharmacy and claims data as well as radiology data, including mammography and tumor registries. Self-reported breast cancer risk factors and BI-RADS® density measurements are systematically collected by radiologists at all screening mammogram appointments at health plan breast imaging facilities for the Breast Cancer Surveillance Consortium (BCSC) [32].

3.3 Theoretical framework

The content and design of the personalized web intervention is guided by Protection Motivation Theory (PMT) [30, 33]. PMT addresses the process of whether a person will respond to a health threat, such as breast cancer risk, by adopting specific behaviors [34, 35]. PMT describes processes of coping with a health threat that incorporate aspects of the disease threat (e.g., breast cancer) and the potential means to cope with this risk (e.g., chemoprevention or MRI). Women are likely to adopt risk management behaviors when their perceived cancer threat is high (e.g., high perceived breast cancer risk, severity, and worry) and their coping appraisal is high (e.g., high response efficacy, low response cost for risk management, high self-efficacy) [36]. Distress can result if perceived threat is prompted, but coping appraisals remain low [37]. We selected this theoretical framework because PMT-based interventions have been applied to numerous health behaviors and have some of the strongest correlations between behavioral intentions and behavior [38, 39]. The study will not include the use of fear appeals, as women at increased breast cancer risk have a variety of risk management options.

3.4 Eligibility criteria

The criteria for eligibility in this study include the following: (1) female health plan member; (2) negative screening mammogram in prior six months; (3) between the ages of 40–69; (4) a Breast Cancer Surveillance Consortium (BCSC) 5-year invasive breast cancer risk 1.67% and BI-RADS® breast density score of 3 (heterogeneously dense) or 4 (extremely dense). Risk factors within the BCSC risk model include age, race/ethnicity, family history, prior breast biopsy, and BI-RADS® breast density score. The model is one of the few risk algorithms to include breast density and was developed and validated in 1.1 million women undergoing mammography across the United States. The BCSC model has been externally validated in the Mayo Mammography Health Study with a discriminatory accuracy, i.e. area under the curve (AUC), of 0.66 [40]. The model performs reasonably well across risk factor subgroups, although slightly underestimates breast cancer rates in young, Asian, and Hispanic women, respectively [41]. Following work by Kerlikowske et al. [12], the sample is further restricted to women at greatest risk of interval cancer, which includes those with either (a) an intermediate 5-year risk (1.67%–2.49%) and extremely dense breasts

or (b) a high 5-year risk ($\geq 2.50\%$) and either heterogeneously dense or extremely dense breasts. Participants will also: (5) have been enrolled in the health plan for at least one year prior to their negative mammogram; (6) able to speak and read written English; and (7) able to provide informed consent. Personal internet/computer access was not included as a study eligible criterion to improve generalizability. The exclusion criteria include the following: (1) personal history of lobular carcinoma in situ (LCIS); (2) prior cancer diagnosis, including ductal carcinoma in situ (DCIS); (3) previous referral for cancer genetic counseling and/or prior genetic testing; (4) died or dis-enrolled from health plan between mammogram and start of recruitment; (5) indicated they do not want to be contacted for research; or (6) participated in intervention development pilot studies.

3.5 Recruitment

Participants are recruited as they receive a negative screening mammogram at one of six breast imaging facilities. Women routinely complete a risk factor questionnaire at the time of their screening mammogram. An Engaged study programmer uses a combination of selected risk factor and other EHR data to calculate 5-year breast cancer risk using the BCSC risk calculator for the trial. This information is combined with breast density scores to identify a pool of potentially eligible women at increased risk of interval cancer. This pool of women is further refined based on the above criteria using health plan EHR data. Eligible women are mailed an introductory letter informing them of their breast density based on their recent mammogram and inviting them to participate in a study focused on developing new approaches to encourage women to be aware of their breast health. The letter also includes a study information sheet and provides a telephone number for women to call if they either want to participate or do not want to be contacted further. Study staff follow up by telephone with women who have not actively declined participation. After confirming participant eligibility and obtaining verbal consent, trained interviewers administer the baseline questionnaire. If the participant gives permission, study staff also send a letter to her primary care provider alerting her/him of their patient's study participation as well as her five-year risk of breast cancer, potential eligibility for chemoprevention and breast MRI, information about numeric risk calculation and referrals, and study contact information.

3.6 Randomization

Participants are randomly assigned in equal numbers to access an online personalized risk counseling and decision support tool (intervention) or standard breast health information (usual care). A unique username and temporary password is generated for all eligible women by the study programmer. The study programmer also randomizes each participant to one of the study arms using a computer-based randomization sequence. This information (username, password, study arm) is then securely uploaded into the backend of the website interface, enabling women to log on.

After a woman enrolls in the study and completes the baseline interview, they are sent a letter and, if desired, email with their username and temporary password along with instructions for accessing the study website. When logging onto the study website for the first time, women in both arms are asked to complete an online informed consent before reaching a universal landing page. The landing page briefly introduces women to changing

policies around breast density disclosure and explains why they were invited to participate in the study, namely because their most recent mammogram indicated that they had dense breast tissue and that this risk factor, in combination with others they reported at that time, makes their current risk of breast cancer higher than an average women of the same age and race. Interested women are also informed they can make an appointment to talk with their primary care provider for more information. This language is modeled on what is typically found in a breast density disclosure letter. From the landing page, women are sent to either the tailored intervention content (intervention arm) or the ACS website (control arm).

3.7 Intervention

3.7.1 Intervention arm: personalized risk counseling and decision support—

Participants randomized to the intervention arm will be directed to an interactive personalized risk counseling and decision support intervention. We selected an interactive web-based approach due to evidence that this modality can increase engagement and enhance comprehension, particularly in individuals with low health literacy and numeracy, and its broad dissemination potential [42–45]. Women also preferred web-based modalities in pilot work. Didactic information in text, image, and animation formats is incorporated along with interactive elements (controllable animation and open-ended response fields). The web interface is designed to be intuitive and accessible, with use of obvious titles, short sentences, and lists to allow for quick digestion of key information. There is a clear flow to the intervention, though women have the ability to navigate through content at-will. The intervention is designed to take approximately 30 minutes to complete. Participants may log-out and then return to the intervention as often as they desire.

The intervention content and presentation is guided by PMT and International Patient Decision Aid Standards (IPDAS) [46], previous research conducted using a similar print-based intervention [47], and substantial beta and usability testing with our target audience. Following IPDAS recommendations, the intervention provides participants with: 1) factual information about breast cancer including severity and likelihood of possible harms; 2) options for risk management, namely chemoprevention and breast MRI; 3) explanation of risks/benefits of each management option, 4) clarification of individual preferences about the options (i.e., value clarification), and 5) guidance in using this information to make risk management decisions. In addition to providing participants with additional information about breast density as a breast cancer risk factor (see Figure 2), the intervention targets key PMT constructs through personalization.

Specifically, cancer threat appraisals are targeted by providing women with their current personal 5- and 10-year invasive breast cancer risk estimates from the BCSC risk calculator using interactive graphical displays and text (see Figure 3).

Coping appraisals are targeted through presentation of information on risks and benefits of chemoprevention (tailored based on the woman's menopausal status) and breast MRI, as well as the interactive values clarification exercise (see Figure 4). Finally, self-efficacy for risk management is fostered by encouraging interested women to make an appointment with their provider and allowing them to create a tailored question prompt list (QPL) outlining key questions and concerns to guide discussion. Individual risk estimates and menopausal

status are securely uploaded into the backend of the website interface along with usernames and passwords to enable the personalized components of the intervention.

3.72 Control arm: standard breast health information—Participants randomized to the control arm are redirected to the American Cancer Society website from the universal study landing page. Participants are linked to a specific section of the ACS website that provides general content about breast cancer risk factors, breast density, and risk-management, but they have the ability to navigate the full website at will. Participants can log out and return to the ACS website through the study landing page as often as they desire.

3.8 Study retention and adherence

The following steps are taken to retain participants in the trial and increase adherence to the intervention: (1) after sending participants their unique username and password, study staff send a follow up reminder to encourage prompt uptake; (2) participants in both arms can log in and out of the study website at their convenience on multiple devices (phone, tablet, desktop); (3) follow-up assessments are conducted online or over the phone at flexible hours by highly experienced survey research interviewers affiliated with the health plan; (4) the first follow-up assessment occurs at 6-weeks when breast density disclosure and engagement with the study website is still salient; (5) participants are reminded of upcoming follow-up telephone surveys by email; (6) participants receive a \$20 recognition payment for each assessment (baseline, 6-week, 12-months); and (7) primary outcome data are collected using EHR data and self-report in telephone surveys.

3.9 Assessments and health plan electronic health record data

Three participant assessments are conducted by telephone survey or secure web-based survey: at baseline, 6-weeks, and 12-months after baseline. Telephone surveys are conducted by experienced interviewers using computer-assisted telephone interviewing (CATI) and web-based surveys use a DatStat platform (Illume). We collect patient-reported outcomes (e.g., distress); PMT constructs (e.g. breast cancer worry, self-efficacy for risk management); risk-management intentions; patient-provider discussion of breast density and risk management; health literacy and numeracy; internet use variables; and sociodemographic information. Health plan EHR data is used to collect additional sociodemographic data (at baseline) as well as medical and cancer screening history, health plan coverage, health care utilization, and health-system level factors (at baseline and 12-months).

3.10 Outcomes

3.10.1 Primary outcomes

3.10.1.1 Chemoprevention uptake: Specific drug codes in health plan pharmacy data are used to identify onset of new chemoprevention medication, defined as filling two consecutive prescriptions of tamoxifen or raloxifene within 365 days of study enrollment.

3.10.1.2 MRI uptake: Advanced imaging records in health plan EHR data are used to identify breast MRIs within 365 days of study enrollment.

3.10.1.3 Distress: Distress is measured using a visual analog scale (VAS), i.e. a distress thermometer. Participants report *how much distress they have been experiencing in the past week* on a scale from 0 to 10, where 0 is *totally relaxed* and 10 is *the highest distress, fear, anxiety, or discomfort they have ever felt*.

3.10.2 Secondary outcomes

3.10.2.1 Mammography maintenance: All participants have had a negative screening mammography in the six months prior to enrollment as an eligibility criterion. Imaging records in health plan EHR data are used to identify receipt of a screening mammogram by 12-month post-randomization follow-up.

3.10.2.2 Health care utilization: Counts of in-person visits to primary and specialty care providers (e.g. medical genetics, obstetrician/gynecologist, oncology) and procedures likely associated with breast care (e.g. screening imaging, biopsy) from health plan EHR data are used to measure utilization.

3.10.2.3 Patient-provider discussions: Women self-report talking with their health care provider about breast density, chemoprevention, and/or breast MRI.

3.10.4 PMT-based mediating variables

3.10.4.1 Risk-management intentions: Single-items are used to assess intentions for chemoprevention and breast MRI. Women are asked, for example, *how likely or unlikely is it that you will use tamoxifen in the next year*, measured on a 1 (*very unlikely*) to 5 (*very likely*) scale [48, 49].

3.10.4.2 Perceived risk: Five- and ten-year perceived risk for breast cancer is assessed with a Personal Absolute Percentage Risk item. Women are asked what they *think the chance is that they will develop breast cancer in the next five and ten years*, from 0% (*no chance*) to 100% (*definitely will*) [50, 51].

3.10.4.3 Awareness of personal risk: The absolute difference between participants' quantitative perceived risk of breast cancer in the next 5 and 10 years and their calculated risk estimate is used to measure risk awareness. [52].

3.10.4.4 Perceived cancer severity: Three items measured on a 1 (*strongly disagree*) to 5 (*strongly agree*) scale are used to measure perceived breast cancer severity. Women report how strongly they believe that breast cancer is *severe*, *serious*, and *significant* [53].

3.10.4.5 Cancer worry: A modified version of a standard 3-item scale developed by Lerman et al. is used to measure breast cancer worry [52].

3.10.4.6 Self-efficacy: Items adapted from Witte et al. are used to assess self-efficacy, asking women, for example, *how confident are you that you can manage chemoprevention side-effects*, measured on a 1 (*strongly disagree*) to 5 (*strongly agree*) scale [53].

3.10.4.7 Response cost and efficacy: Items asking about the pros/cons of chemoprevention and MRI, measured on a 1 (*strongly disagree*) to 5 (*strongly agree*) scale, are used to assess perceptions of the response cost and response efficacy of these behaviors, e.g., *I am concerned about the side effects of chemoprevention; chemoprevention would reduce my risk of developing breast cancer* [54].

3.10.5 Moderating variables

3.10.5.1 Health literacy: A three-item scale developed by Chew et al. is used to assess health literacy [55]. We ask women to self-report: *How often do you have someone help you read hospital materials? How confident are you filling out medical forms by yourself? How often do you have problems learning about your medical condition because you have difficulty understanding written information?* Items are scored on a 5-point scale (*always-never*). eHealth literacy is measured using the e Health Literacy Scale (eHEALS), a 10-item measure developed to measure knowledge and perceived skills at finding, evaluating, and using eHealth information [56].

3.10.5.2 Numeracy: We use the Subjective Numeracy Scale, an 8-item measure of one's perceived ability to perform mathematical tasks measured on a 1–6 scale, to determine numeracy [57, 58].

3.11 Sample size and power calculations

We based sample size calculations on the effect of personalized risk communication and decision support on uptake of risk management (i.e., chemoprevention and breast MRI) and distress. We employ generalized estimation equations (GEE) methods with exchangeable working correlation structure to analyze clustered data, where study participants are clustered within providers. To have 80% power to detect an increase in chemoprevention uptake from 0.5% to 2.8%, an effective sample size of $N=990$ (495/arm) is needed at a significance level of 0.05. This requires a total sample size of $N=1250$ (625/arm), assuming a 5% health system attrition rate over the 12-months, an average cluster size of 11 patients per provider, and an intraclass correlation coefficient of 0.02 (i.e. a reduction of the sample size by a factor of 1.2) [59–62]. An effective sample size of $N=990$ (495/arm) provides 80% power to detect an increase in MRI uptake from 3% to 6.9% at a significance level of 0.05. Assuming a 10% attrition rate at the 6-week follow-up survey and 10% attrition at the 12-month follow-up survey, we will have a total sample size of $N=1,012$ (506/arm) and an effective sample size of $N=842$ (421/arm) to determine intervention effects on distress. We will have 80% power to conclude non-inferiority, using a non-inferiority limit of 1 point, assuming a mean difference between arms of 0.5 points and a SD of 2.6 points [63] for the distress thermometer. Thus, a target sample size of $N=1250$ (625/arm) provides ample power to detect differences in uptake of risk management and distress between the arms, accounting for attrition, using both health plan EHR and telephone survey data.

3.12 Statistical analysis

The main intervention effects on uptake of risk management (chemoprevention and breast MRI) and distress will be determined based on comparisons of the intervention and control arms at 12-months post-enrollment using intention-to-treat (ITT) analyses. We will evaluate

associations between baseline variables, mediating variables assessed at 6-weeks, and 12-month outcomes in descriptive analyses. For categorical variables, we will use Chi-Square tests or Fisher's exact tests if needed. Student t-tests or Wilcoxon-Mann-Whitney tests will be used for continuous variables. Any variable that exhibits a $p < 0.10$ association with an outcome will be subsequently controlled for in the main analyses. We will use a separate logistic regression model for each binary outcome (chemoprevention and MRI uptake). Generalized estimating equations (GEE) methods will be used to account for patients' clustering within providers. These models will include an indicator for study arm as the main predictor and baseline covariates as controlling variables. We will follow the same analytic approach with the secondary outcomes (mammography maintenance, patient and provider discussions, binary health care utilization outcomes). To demonstrate that the intervention does not result in greater distress than usual care, we will test for non-inferiority by constructing a one-sided 97.5% confidence limit for the adjusted (for baseline distress) mean difference between arms. Non-inferiority will be demonstrated when the one-sided 97.5% confidence limit does not cross the non-inferiority limit of 1 point.

To address the secondary outcomes, we will evaluate mediation effects using the product of coefficients method: We will estimate the standardized coefficients relating each mediating variable (e.g., cancer worry) to the chemoprevention and MRI uptake outcomes (β), and the standardized coefficients relating the indicator variable for study arm to the mediating variables (α), controlling for baseline covariates and baseline values of the mediator of interest. Logistic regression models will be similar to those used in the main analyses. We will calculate each mediated effect as the corresponding product of coefficients ($\alpha\beta$) with its standard error and 95% confidence interval estimated by bootstrapping [64]. Moderating effects of health literacy and numeracy will be assessed in exploratory subgroup analyses.

Given that the GEE methods are valid only under the assumption that the data is missing completely at random, in sensitivity analyses we will use extensions based on inverse probability weighting and multiple imputation, that are valid under the missing at random assumption. For completeness, we will also provide the results of the per-protocol analysis in addition to the ITT analysis.

4. Summary

The Engaged trial will contribute to the literature on risk communication and personalized intervention modalities for breast cancer prevention, specifically in women with dense breasts and increased breast cancer risk. The strengths of the study include its embedded nature, which allows for clinically-integrated implementation within a single health system and facilitates uniform participant access to health care services, including risk-management interventions. Additionally, the study collects both EHR and participant-reported data on primary outcomes. Study limitations include generalizability. Like many RCTs, the women who participate in the Engaged trial will not be representative of all women at increased risk of breast cancer with dense breasts.

A large and increasing proportion of US women are mandated to receive their breast density status following a mammogram, despite limited understanding of how to best communicate

density information [14, 65]. This trial evaluates a novel web-based approach that couples density disclosure with personalized breast cancer risk communication and decision support, which should enable women to make informed, values-consistent risk management decisions without increasing distress. Engaged thus provides important evidence to inform the implementation of national breast density disclosure legislation with a goal of increasing uptake of guideline-informed risk management strategies with minimal clinical burden.

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Figure 1. Study flow diagram

Abbreviations: GHC: Group Health Cooperative (now Kaiser Permanente Washington), BCSC: Breast Cancer Surveillance Consortium; Pts: participants; GHRI: Group Health Research Institute (now Kaiser Permanente Washington Health Research Institute); ACS: American Cancer Society.

Figure 2.
Intervention page: "The Breast Density Risk Factor"

Figure 3.
Intervention page: "Your Personal Risk of Breast Cancer"

ENGAGED - Making Decisions

Sign Out

Your Risk Managing Your Risk Making Decisions

Reviewing Your Options

Medication

Breast MRI

Talking With Your Provider

Your Printout

Deciding About Medication

Here is a simple two-step process for deciding about whether to take medication to reduce your risk of breast cancer.

Your answers on this page will appear on the **personalized printout** at the end of this section.

Step 1: Decide what is most important to you

Below are some of the advantages and disadvantages of taking medications.

Slide the dots to indicate how important each one is to you.

The ability to reduce my risk of getting breast cancer.

Not at all important 6/10 Extremely important

The risk of major side effects.

Not at all important 6/10 Extremely important

The peace of mind that I am doing something to reduce my breast cancer risk.

Not at all important 8/10 Extremely important

Figure 4.
Intervention page: “Deciding about Medication”