Official Title: The Mathematics of Breast Cancer Overtreatment: Improving Treatment Choice Through Effective Communication of Personalized Cancer Risk

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Randomized clinical trial of a DCIS decision support tool (DCIS App)

Design & Analysis Plan: Aim R3

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Principal Investigator: Marc D. Ryser
Co-Investigators: Ilona Fridman, Lok Chan, Kevin Weinfurt, E. Shelley Hwang, Kathryn Pollak, Nicole Hunter
Biostatisticians: Cassie Ford, Kelley Jones
Project Managers: Amy Clark, Jennifer Thomas

A. Background

Every year, close to 50,000 women in the US undergo radical surgery after diagnosis with screen-detected ductal carcinoma in situ (DCIS), yet as many as 45,000 of these are treated for benign lesions that would not progress to invasive breast cancer in their lifetime. The resulting overtreatment of non-progressive DCIS lesions can cause substantial harms and significantly reduce the patient's quality of life without reducing breast cancer mortality.

Although the widespread overtreatment of women with DCIS is well documented at the population level, its prevention at the patient level is hindered by the current treatment paradigm, which dictates that virtually all patients undergo immediate treatment. This in turn perpetuates the lack of data needed for the evaluation of alternative management strategies, such as active surveillance. To resolve this conundrum, randomized controlled trials (RCTs) on active surveillance have recently been initiated, two in Europe and one in the US. Because low-risk DCIS is slow-progressing, it will take a long time until US-relevant evidence will be available.

At the same time, however, there is a wealth of existing clinical and biological data on DCIS that is dispersed across a large number of data and knowledge sources. In the absence of quantitative models that enable the integration of these dispersed data sources, the bulk of the existing data remains inaccessible to patients. Thus, to enable informed decision making among patients with DCIS, there is a critical need (i) to develop predictive models that integrate available patient- and tumor-specific data to generate personalized risk and uncertainty projections for different management strategies, and (ii) to effectively communicate these personalized projections to patients. In the absence of tools for the quantification and communication of personalized risk and uncertainty projections, it remains difficult for patients and physicians to weigh the tradeoffs associated with different management strategies and to make an informed, evidence-based decision that reduces the risk of potentially harmful overtreatment of DCIS.

The long-term goal is to develop personalized decision aids that maximize informed decision-making and minimize overtreatment in patients with DCIS. The overall objective of this proposal comprises the first three steps towards this goal: (i) to develop personalized risk projection models for different management strategies of DCIS, (ii) to use these projections to develop a personalized decision aid, and (iii) to evaluate its impact in a test cohort of women without a history of breast cancer. Our central hypothesis is that communication of model-based personalized risk projections leads to an improved understanding of the trade-offs associated with different management strategies for DCIS. The rationale for the proposed research is that, thanks to personalized decision aids, women gain access to the information needed for an evidence-based decision that is understandable and aligned with their personal risk tolerance

B. Aims

Aim R1: Perform model validation and uncertainty quantification to maximize model confidence.
Aim R2: Stage 1: Conduct cognitive interviews to develop and refine an interactive decision aid for the effective communication of personalized risk projections in DCIS patients.
Aim R3: Stage 2: Implement an RCT to test the main hypothesis that the use of personalized decision aids leads to (i) an increase in the proportion of women who would consider active surveillance as a viable management strategy for DCIS, and (ii) an increase in knowledge of the associated risk trade-offs.

C. Research Questions

Primary

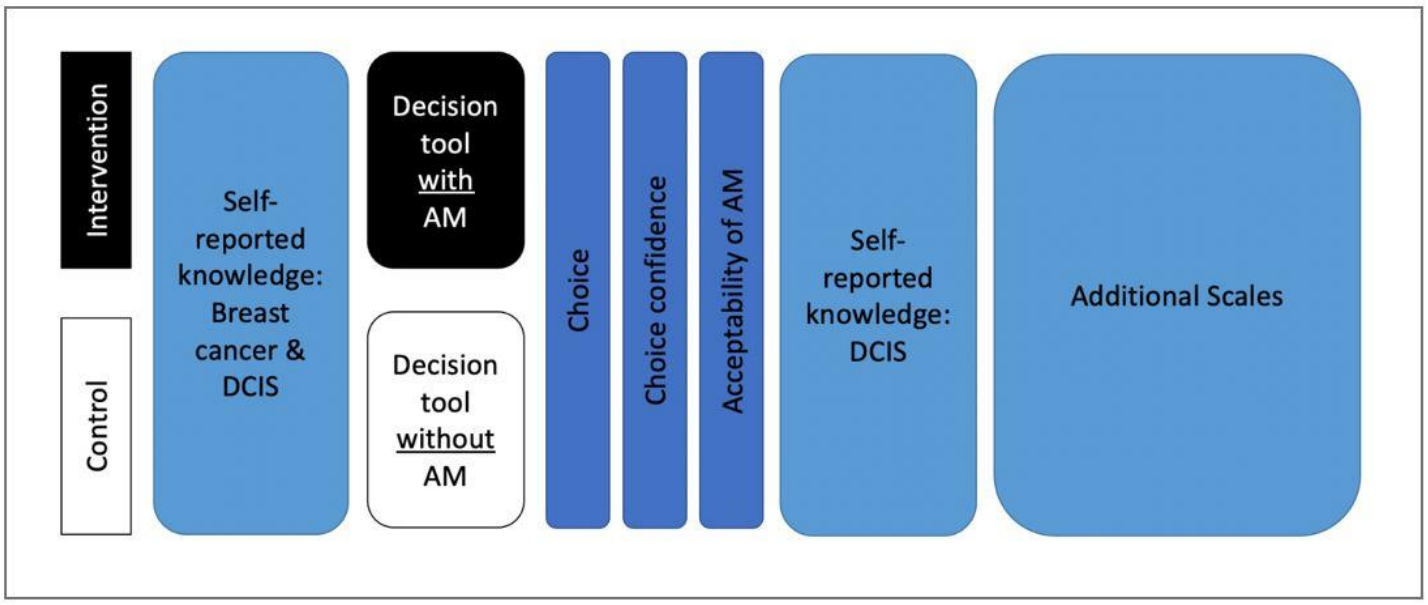
Compared to presenting active monitoring (AM) as an experimental option, does presenting AM as a guideline-concordant care option increase its uptake as treatment choice?

Secondary

Compared to presenting active monitoring (AM) as an experimental option, does presenting active monitoring as a guideline-concordant care option increase AM acceptability, decrease perceived AM riskiness, and decrease uptake of mastectomy as treatment choice?

D. Study Design

Two-arm parallel randomized controlled clinical trial stratified by age (<65 vs. ≥ 65). Block-randomized in both age strata, with block sizes of n=6.



Control: Decision tool with AM:

- AM portrayed as experimental approach currently evaluated in clinical trials
- Contains in-depth information about the 3 surgical options only

Intervention: Decision tool with AM:

- AM offered as standard of care alongside lumpectomy, lumpectomy with radiation, and mastectomy
- Contains in-depth information about all 4 options

Primary data collection with healthy trial participants. All measures, except for participant age, are self-reported. Participants complete a baseline survey prior to randomization (Decision tool with or without AM), use the Decision tool, and then complete a post survey immediately after. The entire session is expected to take less than 1 hour to complete.

E. Sample Size & Randomization

Prior information

- COMET study team poll (n=4): Intervention uptake of AM estimated to be ~15%
- Patient advocate poll (n=10): Intervention uptake of AM estimated to be ~35%

- Currently, <3% of patients do not undergo surgery after diagnosis with DCIS (any type of DCIS)
- Usability testing (much closer to intervention than control version, n=19): uptake ~40%

Targets

- Assume control arm has AM uptake of ~5%
- Difference intervention vs control is thus ~10% (COMET study team) to ~30% (patient advocates)
- Clinically meaningful difference is ~15%
- We want to calculate sample size for Δ=15% (control at 5%, intervention at 20%) at significance level $\alpha = 0.05$ and ≥90% power

Calculations:

- Used Mantel-Haenzel test (note: Table below created with power.prop.test in R)
- Scenario 1: we have 90% power with n=101 in each arm
- Scenario 2: if Δ is still 15% but control/intervention at 10%/25% we still have 80% power
- Scenarios 3-6: if, as estimated in usability testing, uptake of AM is 40%, then for Δ of 15%, 20%, 25% and 30%, we have power of 62%, 88%, 98% and 99%

Scenario	n (per arm)	P1	P2	Δ	Power
1	101	5%	20%	15%	90%
2	101	10%	25%	15%	80%
3	101	10%	40%	30%	99%
4	101	15%	40%	25%	98%
5	101	20%	40%	20%	88%
6	101	25%	40%	15%	62%

Randomization

- We prepare two separate random streams, one for younger (<65 years) and one for older (≥65 years) participant strata.
- Each stream is block randomized, with block size k=6.
- For each consented participant, we check for survey completion. Survey completion is defined as:
    - Reached the end of the survey (and thus were paid); and
    - Answered the treatment choice question (primary outcome); and
    - Answered the treatment acceptability questions (n=4; secondary outcome); and
    - Answered perceived riskiness question (secondary outcome); and
    - Answered both pre- and post-tool self-reported knowledge questions about DCIS (secondary outcome); and
    - Clicked on the Guide and the Decision Support Tool links provided in the survey.
- We continue to randomize until we reach n=101 participants (per arm) who pass the survey completion check.

F. Study Sample

Potential patients will be identified through Duke electronic health record system Epic and invited through the MyChart patient portal. Duke has an "opt-out" system that allows patients to be contacted directly about research studies for which they may be eligible. If a patient agrees to participate in the study by replaying to a MyChart message, the patient will be consented and referred to the survey link.

Inclusion criteria

- Female
- Age 50-79

- No history of DCIS/breast cancer [medical record only]
- Negative mammogram in past 12 months [medical record only]

G. Outcomes & Hypotheses

Primary Outcome: Post-tool choice of active monitoring (AM). Presented to participants as a categorical item: active monitoring, lumpectomy, lumpectomy with radiation, mastectomy. Recorded for analysis as binary: AM vs non-AM.

Q1: If you were a patient diagnosed with DCIS, what treatment option would you choose?

[Order is randomized]

- Active monitoring
- Lumpectomy
- Lumpectomy with radiation
- Mastectomy

H1: Participants who receive in-depth AM information are more likely to choose AM post-tool compared to participants in the control group.

Secondary Outcome 1: Post-tool acceptability of the different treatment options. Measured as categorical 5-point Likert scale from "Not at all comfortable" (1) to "Very comfortable" (5); analyzed as continuous variable. The following question is repeated four times, each time substituting OPTION X for one of the four treatment options:

- *Q2.1:* How comfortable would you be with **OPTION X** as your initial treatment for DCIS?

  H2.1: Participants who receive in-depth AM information report higher AM acceptability compared to participants in the control group.

Secondary Outcome 2: Subjective perception of active monitoring riskiness. Measured as categorical 5-point Likert scale from "Not at all likely" (1) to "Very likely" (5); analyzed as continuous variable.

Q2.2: If you choose active monitoring as your treatment, how likely is it that your DCIS will progress to invasive cancer within 10 years after diagnosis?

- (1) Not at all likely
- (2)
- (3)
- (4)
- (5) Very likely

H2.2: Participants who receive in-depth AM information perceive AM to be subjectively less risky than participants in the control group.

Secondary Outcome 3: Post-tool mastectomy choice. Presented to participants as a categorical item: active monitoring, lumpectomy, lumpectomy with radiation, mastectomy. Recorded for analysis as binary: mastectomy vs non-mastectomy.

Q2.3: see Q1

H2.3: Participants who receive in-depth AM information are less likely to choose a mastectomy compared to participants in the control group.

Secondary Outcome 4: Change in self-perceived knowledge about DCIS. Measured pre- and post-tool as a categorical 5-point Likert scale from "I know very little about DCIS" (1) to "I know a lot about DCIS" (5); analyzed as continuous variable.

Q2.4: How much do you know about ductal carcinoma in situ, abbreviated as DCIS?

- (1) I know very little about DCIS
- (2)
- (3)
- (4)
- (5) I know a lot about DCIS

H2.4: In both groups, self-perceived knowledge about DCIS is higher post-tool compared to pre-tool.

H. Exploratory Aims

See next sections for details about covariates and additional scales used in the explanatory aims.

Exploratory Aim1: Descriptive analyses of the following scales:

a) DCIS knowledge (11 questions), including AM knowledge (2 questions)
b) Choice confidence (1 question)
c) Information needs satisfaction
d) Preparation for decision making
e) Treatment choice reason

Exploratory Aim 2: Does knowledge about AM mediate AM acceptability?

Exploratory Aim 3: Is the score of the minimizer-maximizer scale associated with post-tool treatment choice?

Exploratory Aim 4: Are extreme scores of the minimizer-maximizer scale (1 or 6) associated with less accurate DCIS knowledge?

Exploratory Aim 5: What covariates and personality scales are associated with post-tool treatment choice and AM acceptability?

Exploratory Aim 6: Does subjective perception of AM riskiness mediate choice of AM?

I. Covariates

1) Age: Will be known before participation begins due to the recruitment method; will be used to ensure equal study arm assignment within the two stratification groups. For the analysis we will use self-reported age (years).

2) Race & Ethnicity: Asked as two separate questions

Are you Hispanic or Latina?

- Yes
- No

With which of the following groups do you most closely identify?

- ☐ White (1)
- ☐ Black or African American (2)
- ☐ American Indian or Alaska Native (3)
- ☐ Asian or Pacific Islander (4)
- ☐ Other (5)

3) SES: 4-level categorical variable

How would you describe your household's financial situation right now?

- ☐ After paying the bills, you still have enough money for special things you want
- ☐ You have enough money to pay the bills, but little spare money to buy extra or special things
- ☐ You have money to pay the bills, but only because you have cut back on things
- ☐ You are having difficulty paying the bills, no matter what you do

4) Education: 6-level categorical variable. May be recoded (e.g., college vs no college)

What is your highest level of education?

- ☐ Some high school
- ☐ High school
- ☐ Bachelor's degree
- ☐ Master's degree
- ☐ Professional degree (e.g., MD, JD)
- ☐ Doctorate degree (e.g., PhD)

5) Marital Status: 6-level categorical variable. May be recoded (e.g., married vs not married)

What is your current marital status?

- ☐ In Relationship
- ☐ Married
- ☐ Divorced
- ☐ Separated
- ☐ Single
- ☐ Other

6) Short Graph literacy. Single score derived from 4 items, each scored as correct or incorrect. Correct answers are summed for a total "graph literacy score" (0-4). See "Survey" document for details.

7) Current Health. Self-reported health status (visual analog scale, 0-100%), see "Survey" document for details.

J. Additional scales (See "Survey" documents for details about each scale)

- Choice confidence (Chambers et al., 2012) (post-tool)
  - Measured as categorical 5-point Likert scale from "Not at all confident" (1) to "Very confident" (5); analyzed as continuous variable
- Medical Maximizer Minimizer Scale (Scherer et al., 2020) (MM1; post-tool)
  - Measured as categorical 6-point Likert scale from "I strongly lean toward waiting and seeing" (1) to "I strongly lean toward taking action" (6); analyzed as continuous variable
- Self-reported breast cancer knowledge (pre-tool)
  - Measured as 5-point Likert scale from "I know very little about breast cancer" (1) to "I know a lot about breast cancer" (5); analyzed as continuous variable
- Information Needs Satisfaction (Adapted from Hess, 2012) (post-tool)
  - Measured as 4-item scale, each item elicited on a 7-point Likert scale; items analyzed separately as continuous variables
- Knowledge Scale (De novo)
- Knowledge Scale: Decision Quality Instrument (Adapted from Sepucha, et al., 2019)
- Preparation for Decision Making (PDMS) (Bennett, et al., 2010) (post-tool)
  - Measured as 9-item scale, each item elicited on a 5-point Likert scale from "Not at all" (1) to "A great deal" (5); for each participant, the average score across 9 items is recorded and analyzed as a continuous variable.
- Usability Question (open text field)
- Treatment Choice Reason (open text field)
- Aspects of Health Literacy Scale (AAHLS) (Chinn et al., 2013)
- Personality Scales
  - Attitude Toward Risk (Zhang et al., 2019)
  - Pain Tolerance (McCracken et al., 1992; two questions from each subscale)

- Importance of Appearance (Borzekowski et al., 2000)
- Cancer Fear (Lerman Worry Scale, 1991)

K. Statistical Analysis

K.1. Descriptive statistics

We will describe demographic characteristics and pre-tool general knowledge for the full sample, as well as by study arm (Table 1), using proportions for categorical variables and means with standard deviations or medians with quartiles for continuous variables. Group differences will be evaluated using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. We will also describe the proportion of responses on the primary outcome of treatment choice, and the means and proportions for the secondary outcomes by study arm (Table 2).

K.2. Primary outcome analysis

To answer the primary research question, we will use a log-binomial regression model to test the effect of study arm on binary treatment choice (see primary outcome measure), controlling for age group to account for the stratified design:

(1) $$Y_i = \beta_0 + \beta_1 X_i + \beta_2 a_i$$

where

Y_i = subject i's response: Y=1 for AM, Y=0 for non-AM choice
X_i = subject i's study arm: X=0 for control arm, X=1 for intervention arm
a_i = subject i's age group: a=0 for age<65 years, a=1 for age≥65 years

The main effect of interest (1) is represented by β_1 which quantifies the difference in AM uptake between the two arms and will be reported as exp(β_1) with 95% confidence interval [CI].

To follow the CONSORT statement and because the control arm prevalence is expected to be >10% we will report risk ratios as the relative measure, and absolute risks in both arms.

K.3. Secondary outcome analyses

Secondary Outcome 1. Linear regression model, as in (1), reported as β_1 (95% CI).

Secondary Outcome 2. Linear regression model, as in (1), reported as β_1 (95% CI).

Secondary Outcome 3. Same analysis as primary outcome analysis, reported as β_1 (95% CI).

Secondary Outcome 4. Linear regression model, controlling for age group, and with random intercepts to account for within-subject dependence.

Model:

(1) $$Y_{ij} = \beta_0 + \beta_1 X_i + \beta_2 t_j + \beta_3 t_j X_i + \beta_4 a_i$$

where

Y_{ij} = subject i's response at time t_j. (0=surgical; 1=AM)
t_j= time (0=pre-tool; 1=post-tool)
X_i = subject i's study arm (0 = control; 1 = intervention)
a_i = subject i's age group: a=0 for age<65 years, a=1 for age≥65 years

If the models for secondary outcomes 1-4 do not meet the required assumptions for linear models, we will explore using median regression and/or dichotomizing the continuous variable (e.g., top quartile=high, remaining values=normal/low).

K.4. Exploratory aims analyses

Ad hoc statistical analyses will be performed for exploratory aims 1-4. For Exploratory Aim 5 (association of covariates and additional scales with choice), we will extend the model (1) to include covariates and additional scales as outlined sections I and J above. The additional model features will first be assessed for multicollinearity, with features removed if necessary. We will do model building to identify a final model, and present both unadjusted and adjusted parameter estimates for the final model (Table 3).

Finally, we will perform exploratory attrition analyses. First, we will compare the number of participants who expressed interest, consented, started the experiment, finished the experiment, and were included in final analysis. Second, if there are 20 or more participants who started the experiment but did not finish it, we will compare any completed baseline items

K.5. Missing Data

During data checks, we will determine the degree to which variables of interest are going unanswered. Depending on the type of variable and the amount of missingness across all subjects, as well as the balance across study arms, we will consider different imputation methods, or removal of the covariate from the models. For variables with a low degree of missing values (<=5%), we will use simple imputation methods, substituting in the median or modal response. For variables with a higher degree of missing values (>5%) we may perform multiple imputation with 25 imputations.

K.6. Subgroup Analysis

Stratification by age group (<65 vs. ≥ 65 years) will occur during study arm assignment to ensure equal age group representation in each study arm. Further, we plan to analyze the effect of study arm on treatment choice separately within each of the two major age groups, while still including age in years as a continuous covariate. If there is a very marked difference in the stratified analysis, we could consider only including the stratified analysis (i.e. if the overall model is a poor indication of treatment effects because of the subgroup differences).

K.7 Sensitivity Analyses

Intent-to-treat vs. per Protocol analysis: Run both Table 1 and primary outcome model for the final sample with all exclusion criteria applied, as well as for the larger sample of all participants who were randomized and completed the post-survey. This comparison will only be necessary if >5% of those randomized, who completed the post-survey, were excluded due to not clicking through the guide and tool (new criteria).

Anticipated tables and figures

Table 1. Participant characteristics (demographic, pre-knowledge), overall and by treatment arm
Table 2. Primary and secondary outcomes at each time point, and change, by treatment arm
Table 3. Intervention effects on primary outcome
Figure 1: Proportion of treatment choice selections post-tool by study arm (*format TBD)*

Table 1. Patient characteristics, overall and by arm (demographics by age group included as a supplemental table)

	Overall	Intervention	Control	p-value
Demographics				
Age (mean, SD)				
Age group				
<65				
≥ 65				
Sex (Female, N (%))				
Age (mean, SD)				
Race/Ethnicity				
African-American / Black				
American Indian or Alaska Native				
Asian or Pacific Islander				
Hispanic				
White				
Marital Status				
In a relationship				
Married				
Divorced				
Separated				
Single				
Other				
Education				
High school or less				
Some college				
College graduate				
Post-graduate degree				
Rural (N, %)				
Cancer History				
Maximizer Minimizer Scale (mean, SD)				
General pre-tool Knowledge (mean, SD)				
Breast Cancer				
DCIS				
Additional Scales (TBD)				

Table 2. Primary and secondary outcomes at each time point, by treatment arm

	Control	Intervention
Primary Outcome		
Treatment Choice (AM, N, %)		
Secondary Outcomes		
AM Acceptability (mean, SD)		
AM Perceived Risk (mean, SD)		
Mastectomy uptake (N, %)		
Change in self-perceived DCIS knowledge (post-pre, mean, SD)		

Table 3. Intervention Effects on primary and secondary outcomes

	Intervention Effect Overall		**Intervention effect: <65 years**		**Intervention effect: ≥65 years**	
Primary Outcome	**RR (95%*C*)**	**ARR (95% CI)**	**RR (95%*C*)**	**ARR (95% CI)**	**RR (95%*C*)**	**ARR (95% CI)**
Choose AM at post-tool						
Risk ratio (95% CI)						
Absolute risk (95% CI)						
	Intervention Effect		**Intervention effect: <65 years**		**Intervention effect: ≥65 years**	
Secondary Outcomes	β (95% CI)	aβ (95% CI)	β (95% CI)	aβ (95% CI)	β (95% CI)	aβ (95% CI)
AM Acceptability						
AM Risk						

RR, relative risk; ARR, adjusted relative risk. Adjusted models include [covariate list] as covariates