PROTOCOL TITLE:

MEND 2: Making Treatment Decisions Using Genomic Testing

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Final Continuing Review completed 9/19/22

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1.0 Study Summary

Study Title	MEND 2: Making Treatment Decisions Using Genomic Testing
Study Design	Single Arm Feasibility and Efficacy Study
Primary Objective	• Examine intervention feasibility via patient and oncologist acceptability, recruitment and retention, and fidelity
Secondary Objective(s)	• Evaluate intervention effects on comprehension and treatment preferences. • Assess potential intervention mechanisms on comprehension, preferences, and satisfaction.
Research Intervention(s)/ Investigational Agent(s)	Two surveys and audio recordings of patient-physician encounter using the question prompt list.
IND/IDE #	N/A
Study Population	Patients
Sample Size	75
Study Duration for individual participants	About a month, depending on appointment schedule.
Study Specific Abbreviations/ Definitions	QPL: Question Prompt List HER2: Human Epidermal Growth Factor Receptor 2 ER: Estrogen Receptor PR: Progesterone Receptor LCCC: Lombardi Comprehensive Cancer Center WHC: Cancer Institute at Washington Hospital Center MCC: H. Lee Moffitt Comprehensive Cancer Center

2.0 Objectives*

2.1 Specific Aims.

- Specific Aim 1: Examine intervention feasibility in 3 areas: 1) patient and oncologist acceptability, 2) participant recruitment and retention, and 3) intervention dosage and fidelity.
- Specific Aim 2: Evaluate intervention effects on comprehension and treatment preferences.
- Specific Aim 3: Assess potential intervention mechanisms on comprehension, preferences, and satisfaction.

2.2 Hypotheses/Research questions.

- Aim 2 Hypothesis: Participants will demonstrate significant increases in comprehension about their disease and its treatments from pre- to post-QPL. Participants will be more likely to report Score-concordant preferences from pre to post-QPL.
- Aim 3 Hypothesis: Patient comprehension and satisfaction will be higher following encounters with greater shared decision making, greater perceived communication quality, and more frequent discussion of risks/benefits of treatments. Patient preferences will likely be more Score-concordant following encounters with greater shared decision making, greater perceived communication quality, and more frequent discussion of risks/benefits of treatments.

3.0 Background*

Breast cancer is the most common cancer among US women, with more than 230,000 new diagnoses and 40,000 deaths each year,[1] along with decrements in quality of life.[2] Half of all newly-diagnosed patients are affected with estrogen-receptor positive, early-stage disease. Clinical guidelines for these women integrate genomic tumor profiling tests such as the Onco*type* DX® Recurrence Score to refine recurrence estimates and systemic therapy selection when combined with existing markers. Thousands of women receive testing each year.[3–5] While these women should all receive hormonal therapy, guidelines suggest that the 25% with a high Score benefit from additional chemotherapy and the 50% with a low Score can safely avoid chemotherapy.[6] Appropriate treatment for the 25% of women with intermediate Recurrence Scores remains unclear until clinical trial (TAILORx) results are released in the next year.[7]

Despite continuing dissemination, many challenges remain to maximize the benefits offered by testing and refined treatment selection. Many women have a poor understanding of their

Recurrence Score and its impact of treatment selection.[8] Further, our data suggest that patients' pretesting preferences do not shift following the receipt of their Recurrence Score, even following discussion of test results that should guide treatment selection. These preferences are a powerful driver of treatment utilization, predicting treatment received over and above the effect of the Recurrence Score and other clinical variables. Indeed, many patients do not receive Score-concordant care.[4,9–11] Finally, tested patients who do not take an active role in their care and report poorer communication by their oncologist are at risk for higher distress and poorer quality of life.[12] Our data suggest a need to test interventions that support communication about the Recurrence Score, improving patient comprehension and better aligning patient preferences with evidence-based recommendations, ultimately impacting patient morbidity and mortality. TAILORx results will continue to strengthen the evidence for clinical utility and increase testing rates. An effective intervention should be ready to respond to this increasing need.

Street et al.'s model of patient-centered communication[13] suggests pathways through which clinical communication has indirect effects on morbidity and mortality. Communication can influence more proximal outcomes, including patient comprehension of their disease and its treatments, treatment preferences and satisfaction, involvement in care decisions as well as longer-term outcomes of treatment adherence and quality of life.[14] We aim to test the feasibility and impact of a patient activation intervention to support effective integration of the Recurrence Score into clinical encounters and treatment decisions. Patient activation interventions utilizing a question prompt list (QPL) can impact proximal outcomes of preferences, comprehension, satisfaction and involvement.[15–18] A QPL could allow tested patients to better understand the rationale for their oncologist's treatment recommendation and its impact on the management of their disease, as well as encourage alignment of treatment preferences, the Recurrence Score and treatment selection. In this trial, we will recruit newly-diagnosed breast cancer patients to a single-arm trial to demonstrate feasibility and preliminarily assess the impact of the QPL on key outcomes.

4.0 Study Endpoints*

4.1 *Primary Endpoint:* Patient activation via a question prompt list intervention.

4.2 *Secondary Endpoints:* ____.

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

5.0 Study Intervention/Investigational Agent

N/A

6.0 Procedures Involved*

6.1 This is a feasibility and efficacy study. Two participant interviews will be conducted by the study staff. Audio recordings will be collected of patient-physician encounters using the QPL over a month time span.

6.2 Eligible patients will be contacted by study staff via phone call. The study staff will describe the study, answer questions, obtain verbal consent, and complete the first, T1 interview before the patient receives *Oncotype* DX results. After obtaining a signed informed consent and HIPAA authorization by mail, the QPL will be provided to the patient. They will receive the QPL by mail or email, depending on their preference, before their Score disclosure appointment. Study staff will be available to audio record the patient-physician encounter during their appointment. The second, T2 interview will be done after patients receive their test results but prior to initiation of adjuvant chemotherapy.

6.3 The risks of participation are minimal. The survey elements have been designed to minimize emotional distress. A distress protocol has been put in place to refer subjects to psychological consult when appropriate. It is possible that participants will derive benefit from the use of the QPL in how they communicate with their physician and make decisions regarding treatment options.

6.4 Measures will include:

Sociodemographics. We will assess age, race/ethnicity, education, marital, employment, income, insurance status, comorbidity, and family cancer history.

Disease variables and treatments. We will assess diagnosis date, pathology (staging, grade, ER/PR/HER2), treatments, and dates.

Oncotype DX Recurrence Score. We will assess the Recurrence Score and the related category.

Chemotherapy Selection. In our work, 95% of women make definitive treatment decisions by T2. If not, this will be noted and the interview will continue. *Data will be confirmed in the medical record*.

Self-Reported Measures:

Table 1. Variables and Data Sources

Variable	Measure/source	Timepoint		
Controlling and Clinical Variables		T1	Encounter	T2
Sociodemographics		X		
Disease Variables, Treatments	Self-report and chart review	X		X
Recurrence Score	Self-report and chart review			X
Outcomes and Mediators				
Chemo. Selection	Self-report and chart review			X

Chemo. Preferences	Preferences	X		X
Comprehension	Adjuvant treatment, Recurrence Score, treatment implications	X		X
Coding of clinical encounters	RS- and treatment related information, shared decision making, patient active participation and patient-centered communication		X	X
Decisional Satisfaction	SDS			X
Communication Quality	Makoul et al.			X

Chemotherapy Preferences. We will assess preferences for chemotherapy by assessing the perceived pros (8 items) and cons (8 items) of treatment as we do in our ongoing work. Women rate the importance of each item on a scale from 1 (*Not at all important*) to 4 (*Very important*). Ratings are averaged to create scales, with higher scores indicating greater importance of profs and cons. Internal relatability is high for pros-cons, with scores above zero indicating a preference for chemotherapy. Preference concordance will be determined through a match between post-Score preference and treatment received.

Comprehension. We will assess comprehension of adjuvant treatment, Recurrence Score and category, and treatment implications (*The Test helps women decide about chemotherapy (Y/N)).* We will apply existing comprehension items, in which patients average 70% correct.[14]

Satisfaction. We will assess Decisional Satisfaction with the valid and reliable 6-item Satisfaction with Decision Scale, rated on a 5-point Likert scale (*Strongly agree/ disagree*), with a higher score indicating greater satisfaction. The measure has been used to assess satisfaction with breast cancer adjuvant treatment decisions.[19]

Perceived communication quality. We will assess patients' perceptions of quality of patient-physician communication using a 7-item scale from 1 (*Very strongly disagree)* to 6 (*Very strongly agree*). This scale has good reliability and validity and we have used this measure in our current observational study. Items are relevant to chemotherapy decisions (*The doctor fully explained the risks of treatment recommended*). Patients will respond to these regarding their primary Medical Oncologist.[20]

Oncologist variables. We will record race, ethnicity, and gender of the patient's primary medical oncologist for our measurement of concordance.

Coding of Oncology Encounters. We will audio record, transcribe, and code clinical encounters to inform potential intervention mechanisms. Broadly speaking, coding systems capture an encounter's content and process. No single coding system has emerged as definitive or captures our specific encounter content and communication processes. We will code encounters for RS- and treatment related information, shared decision making, patient active participation and patient-centered communication.[21,22] Dr. O'Neill will merge these data with patient self-report using study ID.

7.0 Data and Specimen Banking*

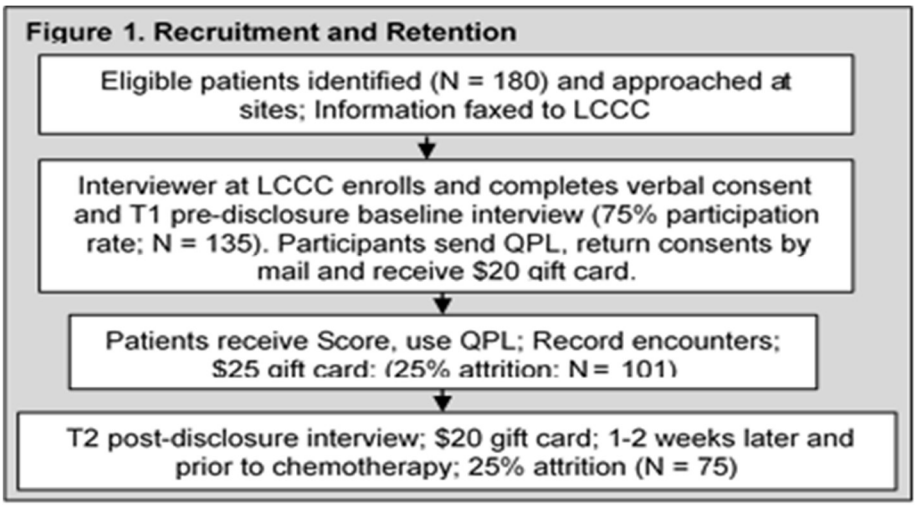
7.1 N/A

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 The participants will be enrolled for about a month. They will complete the first interview after consenting and will also complete a follow up interview right after receiving Oncotype DX results. All study activities should be completed within 2 months. Recruitment and retention are described in Figure 1.



10.0 Inclusion and Exclusion Criteria*

10.1 Study staff at each site will monitor electronic patient records systems that track test orders, attend weekly Breast Cancer Meetings, and coordinate with clinic staff to recruit patients they determine to be eligible.

10.2 Participants will be females aged 40-75 who will receive Oncotype DX testing prior to initiation of systemic treatment.

10.3 We will not include patients with cognitive impairment that precludes informed consent as determined by self-report, our trained study personnel, or patient records. We will also exclude those who are unable to provide consent in English.

11.0 Vulnerable Populations*

11.1 **Pregnant women, students, those economically disadvantaged and employees** will not be excluded from this study if they are otherwise eligible to participate. We will ensure that all informed consent such

that they will be asked to repeat back the purposed of the study after a member of the study team has gone over written informed consent. In addition, although we will be providing incentives for participation in the form of a gift card the incentives are not so large as to be coercive.

12.0 Local Number of Subjects

60

13.0 Recruitment Methods

13.1 Participants will be recruited via phone call, identified as below, by research staff.

13.2 Participants will be drawn from breast clinics at LCCC, Moffitt Cancer Center, and WHC.

13.3 PI/Collaborators will recruit participants from his/her/their own patient population.

13.4 Study materials include participant information/consent and interview done over a phone call. It will also include mailed introductory contact letter, informed consent form, study information sheet, and HIPPA waiver to be physically signed by participants.

13.5 Participants will receive a $20 gift card to thank them for their time completing interviews and $25 for recording of their clinical encounter.

14.0 Withdrawal of Subjects*

14.1 Reason for withdrawing include lack of time and not being interested in participating in research related to breast cancer.

14.2 N/A

14.3 Participants will be informed that they can withdraw from the study at any time. We will track the number of eligible participants that withdraw. Data from participants that withdraw from the study will not be used.

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, interviews may contain questions that make participants feel uncomfortable or bring up unwanted thoughts or feelings. There is also minimal risk that using the QPL will increase any psychological distress. 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*

16.2 There is no direct benefit to individual subjects.

17.0 Data Management* and Confidentiality

17.1 We will calculate descriptive and frequency distributions for all variables. We will assess the quality of the data and evaluate the extent and impact of missing data. For categorical variables, we will use Chi-Square tests or Fisher's exact tests if needed. We will test continuous variables with Student t-tests or Mann-Whitney U tests for non-normal data. Any variable that exhibits a $p<.10$ association with the key predictors or outcomes will be controlled in multivariable analyses. Potential covariates include sociodemographic and clinical variables as well as differenced.

Our primary endpoint is the percentage of patients activated via a question prompt list intervention. Women will demonstrate significant increase in comprehension from pre- to post-QPL.

Using a 2-tailed $\alpha=0.05$ and assumed a minimum of 75 participants at T2 and accounting for clustering by oncologist, we calculated effective sample sizes assuming an average cluster size of 10 patients per oncologist and an ICC of 0.02. This reduces the sample size by a factor of 1.18, leaving an effective N=64 at T2. We will have 80% power to detect changes in mean comprehension of 0.4 SD assuming a correlation of 0.5 between pre- and post- scores. We will use multilevel models to address the clustering of observations within patients and of patients within oncologists. These mixed effects regression models will include random effects for patient and oncologist and fixed effects for time, the main predictor, and covariates. The multilevel model for 2a will be a linear model and we will estimate the adjusted mean change in comprehension and the corresponding 95% confidence interval. We will estimate an adjusted odds ratio with the corresponding 95% confidence interval.

17.2 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 downloaded from REDCap or gathered from other sources will reside in a HIPAA-compliant study folder. Access 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.

REDCap (Research Electronic Data Capture) is a research tool developed at Vanderbilt University as a secure web application to allow users to build and manage online surveys and databases, and to support data capture for research studies. It is a secure, IRB-approved, web-based application designed for managing online surveys and for communication between study sites. A locally hosted instance of REDCap will be used to store study data (Surveys, selected clinical data and tracking information such as participant names, phone numbers, address, etc). Questionnaires or other paper forms collected from each participant will be identified solely by participants' confidential study identification number and stored in a locked filing cabinet in study offices.

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.

17.3 N/A

17.4 N/A

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.

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. Only a code number will be used to identify study-related data. Matching lists of names and code numbers will be kept in locked storage facilities in the PI's office and/or laboratory space. All data will be similarly stored in locked facilities. All computer files containing participant data will be accessed only through password protected security systems and are stored on a secure and private server.

20.0 Compensation for Research-Related Injury

20.1 We do not anticipate more than minimal risk to participants.

21.0 Economic Burden to Subjects

21.1 n/a

22.0 Consent Process

22.1 We will obtain consent from participants prior to their first interview, QPL distribution, recorded patient-physician interaction, and follow up interview.

- Consent will be obtained verbally via phone call and physically through mailed consent form.

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.
- Consent will be obtained as an online consent.

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 Participants will complete verbal consent to all study activities either in clinic or over the phone. They will receive a printed copy of the consent over the mail along with a self-addressed, pre-stamped return envelope.

24.0 Setting

24.1 We anticipate recruiting from across the LCCC/MedStar clinical research (surgery and medical oncology) network. This network includes the main academic hospital and several local community referral hospitals in the metro-DC area.

Eligible breast cancer patients will also be recruited from Moffitt Cancer Center. The Clinical Research Department at MCC utilized several means to screen patients to ascertain their potential eligibility for clinical trials. This site has a central Research Department to assist and facilitate with participant recruitment as follows. This includes screening of the electronic scheduling system, review of schedules posted within clinical care areas, attendance at tumor boards, and regular interaction with physicians and nurses.

1) Access is sough solely to review PHI as necessary to prepare a research protocol for similar purposes preparatory research (i.e. screening),
2) No PHI will be removed, and
3) The PHI access and review is necessary for the research purposes.

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. We will collaborate with existing shared resources within the cancer center for recruitment.

26.0 Multi-Site Research*

*26.1 Study-Wide Number of Subjects**
We very conservatively project 60 eligible participants per year from LCCC/WHC and 120 eligible participants per year at MCC.

26.2 Subjects will be recruited according to methods under the control of the local site. Sites will have bi-monthly meetings to discuss strategies and any issues as they arise.

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