

**TO:** ECOG-ACRIN Clinical Research Associates and Investigators with Patients for E4112

**FROM:** ECOG-ACRIN Operations Office

**ACTIVATION DATE:** February 17, 2016

**SUBJECT:** E4112, Addendum #3

Enclosed is Addendum #3, for E4112, *Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)*.

*Addendum #3 will activate on February 17, 2016.*

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

Expedited review is permitted, however, please consult your local IRB’s standard operating procedures, since their requirements may differ and require a full board review. It is the decision of the local IRB whether or not subjects are to be re-consented. This addendum must be submitted and reviewed by your IRB within 90 days of receipt of this notice, unless your local IRB has different written SOPs, which must be available at future ECOG-ACRIN audits.

Addendum #3 includes the following changes in the Protocol:

	<b>Section</b>	<b>Change</b>
1.	<a href="#">Cover Page</a>	Updated Version Date
2.	<a href="#">Contact Page</a>	Updated Study Chair’s contact information
3.	<a href="#">Schema</a>	Updated Schema
4.	<a href="#">1.6.5</a>	Updated Surgeon decision making information
5.	<a href="#">Section 3.1.3</a>	Added sentence, “if the core biopsy describes “suspicion of ‘microinvasion’, patients remain eligible”.
6.	<a href="#">Section 3.1.4</a>	Revised criteria to require both diagnostic mammogram and a two-view mammogram of both breasts.
7.	<a href="#">Section 3.1.10.2</a>	Changed eligibility to allow surgical clips or metal objects compatible with MR scanning.
8.	<a href="#">Section 3.2.2</a>	Added, “or patient has been diagnosed with invasive disease and added note.
9.	<a href="#">Section 3.3.1</a>	Added Notes for clarification.
10.	<a href="#">Section 4.1.3.4</a>	Added Note for clarification regarding patients registering to step 2.
11.	<a href="#">Section 4.2.3</a>	Added Note for clarification regarding patients registering to step 2.
12.	<a href="#">Section 5</a>	Step 1: Deleted first bullet to reduce redundancy. Deleted sentence, “if initial biopsies are performed, patients will proceed to step 2. Step 2: Revised section to provide clarification and reduce redundancy. Step 3: Added, “breast radiation should begin within 8 weeks of the final

		surgical procedure.”
13.	<a href="#">Section 5.1</a>	Updated imaging site qualification requirements.
14.	<a href="#">Section 5.2</a>	Replaced “A” with “The”. Added bullet point, “The in-plane pixel resolution, for the T1 weighted sequences, should be less than 1 mm in both the phase and frequency directions.
15.	<a href="#">Section 7.1</a>	Updated table to state that History and Physical should be done within 28 days of registration. Renumbered footnotes accordingly. Updated footnote 4 to state required studies include, “a diagnostic mammogram of the affected breast within 3 months prior to registration, and a two-view (full view CC and a full view MLO) mammogram of both breasts within 6 months of registration (if the patient has only one breast, a unilateral exam of the intact breast is required).” Updated footnote 6.
16.	<a href="#">Section 9</a>	Added, “margins <2mm”
17.	<a href="#">Section 9.1.2</a>	Added DCIS and sentence, “If DCIS is not present in surgical tissue, pre trial diagnostic material is to be submitted for the assessment.”
18.	<a href="#">Section 9.3.1, B &amp; C</a>	Added sentence, “If tumor is not present in surgical tissue, pre trial diagnostic material is to be submitted.”
19.	<a href="#">Section 10.2</a>	Changed 3mm to 2 mm.
20.	<a href="#">Appendix V</a>	Updated Oncotype DX Patient Report submission processes.

Addendum #3 includes the following changes in the Informed Consent:

	<b>Section</b>	<b>Change</b>
1.	<a href="#">Cover Page</a>	Updated Version Date
2.	<a href="#">“How long will I be in this Study?”</a>	Changed sentence from “...you will take endocrine therapy for up to 5 years” to “you may take endocrine therapy for up to 5 years”.
3.	<a href="#">“What possible risks can I expect from taking part in this study?”</a>	Added reproductive risks to be consistent with the informed consent template.

Enclosure

**Prospective Study of Magnetic Resonance Imaging (MRI)  
and Multiparameter Gene Expression Assay in Ductal  
Carcinoma In Situ (DCIS)**

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**Version Date:** January 7, 2016

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**ACTIVATION DATE**

January 7, 2015  
Addendum #1 - Incorporated Prior to Activation  
Addendum #2 - 5/15  
Addendum #3 - 2/16

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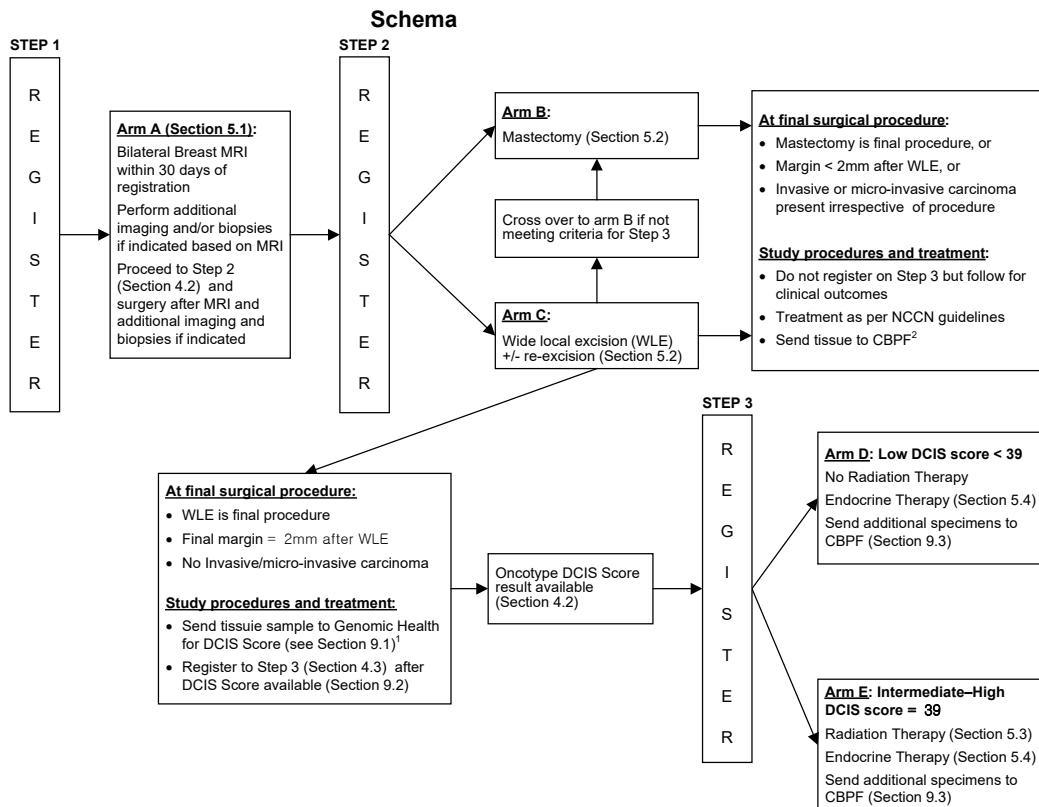
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Data collection will be performed exclusively in Medidata Rave:
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: <a href="mailto:CTSURegulatory@ctsu.coccg.org">CTSURegulatory@ctsu.coccg.org</a> (for submitting regulatory documents only)</p>	<p>Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network OPEN system which can be accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>.  Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</p>	<p>Please refer to the Forms Completion Guidelines for the Forms Submission Schedule.</p>
<p>The <b>study protocol and all related forms and documents</b> must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <a href="https://www.ctsu.org">https://www.ctsu.org</a>. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.  CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</p>		
<p><b>For patient eligibility or treatment-related questions</b> Contact the Study PI of the Lead Protocol Organization.</p>		
<p><b>For questions unrelated to patient eligibility, treatment, or data submission</b> contact the CTSU Help Desk by phone or e-mail:  CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><b>For detailed information on the regulatory and monitoring procedures for CTSU sites</b> please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website <a href="https://www.ctsu.org">https://www.ctsu.org</a> &gt; education and resources tab &gt; CTSU Operations Information &gt; CTSU Regulatory and Monitoring Policy</p>		
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Eligibility (Section 3.0)

- DCIS on core biopsy
- No invasive or micro-invasive carcinoma
- Diagnostic mammogram of the affected breast within 3 months prior to registration and a two-view (full view CC and a full view MLO) mammogram of both breasts within 6 months of registration (if the patient has only one breast, a unilateral exam of the intact breast is required).
- No prior breast MRI within 6 months of registration
- Candidate for wide local excision



1. **Oncotype DCIS Score at step 2 (Section 9.1):** This will be requested and sent to Genomic Health as part of routine care must meet the final criteria (a) wide local excision is final surgical procedure, (b) negative margin at final excision = 2 mm, (c) no invasive or microinvasive carcinoma. After the DCIS Score is available, patients may register to Step 3 and have radiation therapy assigned based on DCIS Score.
2. **Specimen shipment to CBPF in step 2 and 3 (Section 9.3):** All patients in Step 3 and those in Step 2 not proceeding to Step 3.



## 1. Introduction

### 1.1 Rationale for Proposed Study

Ductal carcinoma in situ (DCIS) of the breast is a clonal proliferation of cells within the lumen of the duct that does not invade beyond the epithelial basement membrane into the adjacent breast stroma, but which is a precursor to invasive ductal carcinoma.<sup>1</sup> DCIS lies along a spectrum of preinvasive lesions originating within normal breast tissue, with non-obligate histologic progression from atypical hyperplasia to invasive breast cancer<sup>2</sup>, and the term “ductal intraepithelial neoplasia” (DIN) has been proposed as an alternative classification of this spectrum.<sup>3</sup> The frequency of DCIS diagnosis has increased up to 7-fold since mammography became routine<sup>4</sup>, and now accounts for up to 28% of all breast carcinomas in the United States in 2012, or an estimated 63,300 new cases.<sup>5</sup> While this may be viewed as clear evidence for the benefit of screening mammography due to the low mortality rates associated with DCIS, another view is that detection of DCIS may be harmful because of “over diagnosis” of disease that would never become evident if not detected by mammography.<sup>6</sup>

About 75% of women diagnosed with DCIS in the U.S. are treated with wide local excision (WLE) and 25% with mastectomy; of those treated with WLE, about 75% also receive irradiation.<sup>7</sup> Randomized clinical trials have shown that radiation after WLE reduces local recurrence rates by about 50%. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of four randomized clinical trials, 10-year local recurrence was reduced from 28.1% after lumpectomy alone to 12.9% with radiotherapy (P < 0.00001).<sup>8</sup> The 10 year cumulative risk of breast cancer mortality (about 4%) and overall mortality (about 8%) were low, and not affected by radiotherapy. Two prospective randomized clinical trials have shown that adding adjuvant tamoxifen significantly reduced the risk of all breast cancer events (combined ipsilateral plus contralateral).<sup>9,10</sup>

For patients who are candidates of WLE, the primary objective of surgery is to achieve adequate surgical margins during the initial surgical resection while maintaining an acceptable cosmetic outcome. Although wider margins appear to result in lower recurrence rates, and there is no uniform consensus as the appropriate margin status, a margin status of at least 2 mm is considered acceptable<sup>11</sup>. Failure to achieve appropriate margins at the initial operation requires additional surgery, which may be associated with considerable psychological, physical, and economic consequences. Re-excision rates in many series cluster around 20-30%, and about 10% of patients are treated with mastectomy after initial WLE.<sup>1</sup>

***The ECOG-ACRIN research group proposes a prospective clinical trial that will address specific recommendations of an NIH State of the Science Conference<sup>12</sup>, and will build upon and leverage the expertise of each individual research group.*** The goal is to evaluate advanced imaging to more accurately identify the anatomic extent of the disease with molecular characteristics of DCIS (i.e., DCIS Score) to more accurately characterize the biology of the disease than clinicopathologic features. This integrated anatomical and biological characterization of DCIS lesions is expected to better stratify the need for therapeutic interventions, while maintaining excellent clinical outcomes, facilitating more informed shared decision making, and preserving quality of life.

**The goals of this trial are:**

- To determine the proportion of patients undergoing mastectomy after integrating MRI into the management of patients with DCIS who would otherwise be candidates for wide local excision based on standard mammographic imaging, physical examination, and a diagnostic core biopsy demonstrating DCIS (without invasion or microinvasion)
- To correlate the MRI findings with the DCIS Score
- To evaluate patient reported outcomes when managed with MRI in addition to standard care.
- To estimate 5 and 10 year ipsilateral breast event (IBE) rates in patients treated with wide local excision for DCIS after MRI with a low DCIS Score treated without radiation, and intermediate-high DCIS score treated with radiation

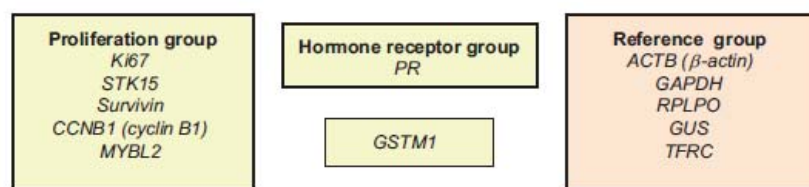
***The information obtained from this trial will provide the foundation for a randomized phase III trial evaluating the role of MRI in DCIS, similar to an ACRIN trial that is ongoing in patients with invasive breast cancer (Alliance A011104ACRIN 6694)(NCT01805076).***

## 1.2 Prospective Validation of the DCIS Score In E5194

In order to address the 2009 NIH recommendations to improve care of patients with DCIS by developing a diagnostic test to facilitate “*the accurate identification of patient subsets ... who may be managed with less therapeutic intervention without sacrificing the excellent outcomes...*”, ECOG-ACRIN in collaboration with Genomic Health, Inc., initiated a multi-step strategy to develop and to validate a multiparameter gene expression assay called the “DCIS Score”. The study was conducted using a rigorous prospective-retrospective design, a research method providing a high level of evidence to support the validity of a tumor biomarker.<sup>13</sup>

The first component of the process was the use of five developmental datasets to develop the DCIS Score, whereas E5194 was preserved for validation. These developmental datasets included studies of 1) either DCIS only or both DCIS and invasive breast carcinoma, but without clinical outcome data; or 2) invasive breast carcinoma with clinical outcome data. These datasets did not include ECOG E5194 tumor specimens. The development of the DCIS Score was based in part on evidence that quantitative expression of genes from the 21-gene *Oncotype DX* Recurrence Score (hereafter referred to as the Recurrence Score) may be useful for predicting local recurrence in DCIS. Two developmental studies without clinical outcomes showed a wide range of Recurrence Score values for DCIS. The first study compared expression levels of individual genes and Recurrence Scores for 30 patients with microdissected DCIS and invasive carcinoma when both were present within the same formalin-fixed paraffin-embedded tumor blocks. A strong correlation between gene expression levels of adjacent invasive and DCIS components was observed. The second study examined 96 DCIS specimens provided by Marin General Hospital, Greenbrae, California (Reference 35, [Supplementary Tables 1](#) and [2](#), available online), and showed a similar wide range of Recurrence Scores. Gene expression levels for the proliferation genes were generally lower for the DCIS components in both studies (Reference 35, [Supplementary Figure 1](#), available online). These results indicated that low Recurrence Score biology was not uniformly observed for DCIS and suggested that more aggressive biology for invasive breast carcinoma identified by Recurrence Score genes might also be present in DCIS. Although

selection of the Recurrence Score algorithm without modification was considered for DCIS, the algorithm was modified before the clinical validation study to have a score that would be predictive of local recurrence risk regardless of adjuvant tamoxifen use because tamoxifen use for DCIS is variable. Selection of the final genes and DCIS Score algorithm used published results for the 21 individual genes from invasive breast carcinoma studies. These studies showed that proliferation gene group score, *PR* (progesterone receptor), and *GSTM1* predicted distant recurrence and breast cancer mortality in both tamoxifen-treated and -untreated patients. Other genes, including *ER* (estrogen receptor), were primarily predictive of hormonal therapy benefit. The seven genes that were purely predictive of recurrence risk plus five reference genes were selected for the DCIS Score (Figure 1).

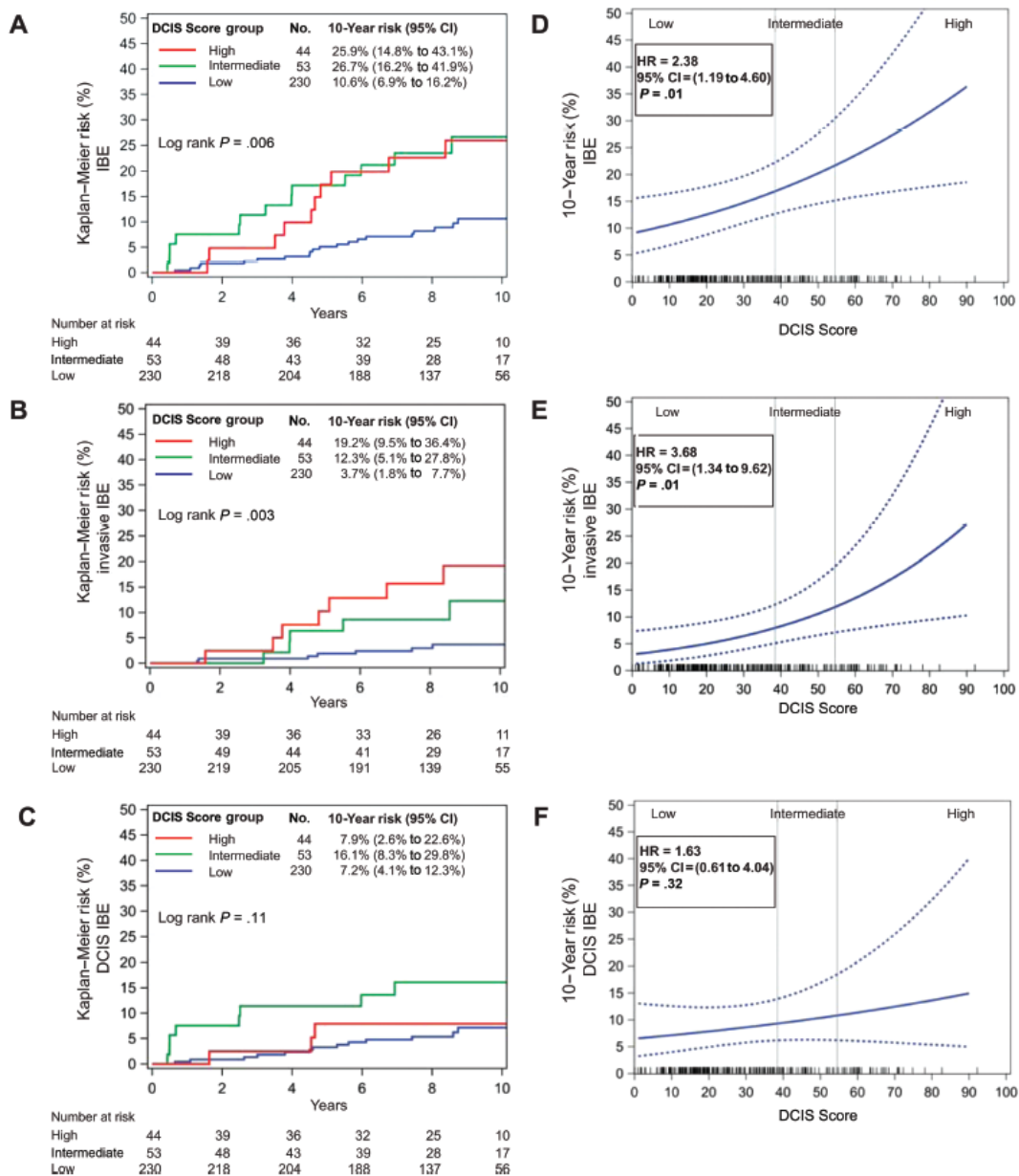


**Figure 1.** Panel of 12 genes included in the DCIS Score. Seven cancer-related genes: *Ki67* = MKI67; *STK15* = aurora kinase A; *survivin* = BIRC5; *CCNB1* = cyclin B1; *MYBL2* = v-myb myeloblastosis viral oncogene homolog (avian)-like 2; *PR* = progesterone receptor; and *GSTM1* = glutathione S-transferase M1. Five reference genes: *ACTB* = beta-actin; *GAPDH* = glyceraldehyde-3-phosphate dehydrogenase; *RPLPO* = large ribosomal protein; *GUS* = beta-glucuronidase; and *TFRC* = transferrin receptor.

In contrast with the Recurrence Score, the DCIS Score algorithm does not threshold the proliferation group score. Scaling of the DCIS Score and selection of the specific cutpoints for the three risk groups were based primarily on the distribution of scores in the DCIS cohort from Marin General Hospital. The calculation algorithm for the DCIS Score is as follows. The DCIS Score is scaled from zero to 100 and is derived from the reference normalized gene expression measurements in four prespecified steps. First, expression for each of the seven cancer-related genes is normalized relative to the expression of the five reference genes (*ACTB*, *GAPDH*, *RPLPO*, *GUS*, and *TFRC*). Reference-normalized expression measurements range from two to 15, with a one-unit increase reflecting approximately a doubling of RNA. Second, the proliferation group score is calculated as the average of the five proliferation genes as follows: proliferation group score = (*Ki67* + *STK15* + *Survivin* + *CCNB1* + *MYBL2*)/5. Third, the unscaled DCIS Score<sub>μ</sub> is calculated as: DCIS Score<sub>μ</sub> = +0.31 × proliferation group score − 0.08 × *PR* − 0.09 × *GSTM1*. A plus sign indicates that increased expression is associated with an increased risk of an ipsilateral breast event (IBE), and a minus sign indicates that increased expression is associated with a decreased risk of an IBE. Fourth, the DCIS Score is rescaled from the unscaled score as follows: DCIS Score = (66.7 × DCIS Score<sub>μ</sub>) + 10.0. If the DCIS Score is less than zero, then the DCIS Score equals zero. If the DCIS Score is greater than 100, then the DCIS Score equals 100. Three risk categories were prespecified: 1) low risk (DCIS Score < 39); 2) intermediate risk (DCIS Score = 39–54); and 3) high risk (DCIS Score ≥ 55).

After development of the DCIS Score without use of E5194 specimens, a rigorous prospective-retrospective validation study of the DCIS Score was performed using E5194 specimens with prespecified objectives and methods in

accordance with guidelines recommended by Simon et al.<sup>13</sup> E5194 was a single-arm prospective multicenter study that evaluated treatment using surgical excision without radiation for women with newly diagnosed DCIS of the breast.<sup>14</sup> Eligible patients had either: low or intermediate grade DCIS with tumor size  $\leq 2.5$  cm (Cohort 1); or high grade DCIS with tumor size  $\leq 1.0$  cm (Cohort 2). Paraffin blocks were collected during the study and used for validation of the DCIS Score. The DCIS Score, primary and secondary study objectives, analytic methodology, and statistical plan were documented and finalized before the study was conducted. There were 327 patients (49% of the parent study) with sufficient tissue for RNA extraction and multigene expression analysis. Tumors were graded by two grading systems, including the College of American Pathology.<sup>15 16</sup> In the prespecified primary analysis, the DCIS Score as a continuous variable was significantly associated with developing an ipsilateral breast event (IBE) when adjusted for tamoxifen use (hazard ratio 2.31;  $P = 0.02$ ). In multivariable analyses, factors significantly associated with developing an IBE were continuous DCIS Score, tumor size, and menopausal status (all  $P \leq 0.02$ ). The DCIS Score correlated moderately with grade ( $r_s=0.46$ ; 95% CI 0.37,0.55) and percentage comedo necrosis ( $r_s=0.49$ ; CI 0.41,0.57) and poorly with lesion size ( $r_s=0.18$ ; CI 0.07, 0.28); despite the modest correlation with grade and comedo necrosis, a wide range of expression in high and intermediate grade tumors, and in tumors with variable degrees of comedo necrosis was observed. **Using the DCIS Score for the three pre-specified risk groups, the 10-year rates of developing an IBE were 10.6%, 26.7%, and 25.9% for the low (70% of patients; DCIS Score < 39), intermediate (16% of patients; DCIS Score 39-54), and high risk (13% of patients, DCIS Score > 54) groups, respectively ( $P = 0.006$ ). (see Figure 2, next page)** The corresponding 10-year rates of developing an invasive IBE were 3.7%, 12.3%, and 19.2%, respectively ( $P = 0.003$ )<sup>35</sup>. It is noteworthy that 74% of patients with a high DCIS score with recurrence had a recurrence of invasive disease, compared with 46% of intermediate DCIS score lesions and 35% of low DCIS score lesions. **Thus we hypothesize that use of the DCIS score will optimize DCIS therapy by identifying biologically aggressive disease at greatest risk for recurrence, particularly invasive recurrence, and thereby providing greater absolute benefit from radiation. In this trial, we will tailor radiation therapy based on the DCIS Score in patients with DCIS (without invasive or microinvasive carcinoma) treated with wide local excision as their final surgical procedure who have adequate surgical margins (step 3 of study). Patients with a low DCIS score (< 39) will not receive irradiation, whereas patients with an intermediate-high DCIS score ( $\geq 39$ ) will receive breast irradiation. A tumor free margin of at least 2 mm will be required at Step 3.** Although a margin of 3 mm was required for inclusion in E5194, there is now data to support the safety of 2 mm margin<sup>11</sup>; in addition, we hypothesize that DCIS lesion size will be more accurately defined in the present study through the use of MRI, therefore a narrower than 3 mm margin is safe. Finally, it is likely that a narrower margin will spare some unnecessary re-excision procedures.



**Figure 2.** Kaplan–Meier plots and 10-year risk estimates with 95% confidence intervals (CIs) for developing an ipsilateral breast event (IBE), an invasive IBE, and a ductal carcinoma in situ (DCIS) IBE. The number of patients at risk are included below each plot for each prespecified risk group, based on the DCIS Score of low (< 39), intermediate (39–54), and high ( $\geq$  55). A) Probability of developing an IBE based on the DCIS Score according to the three prespecified risk groups. B) Probability of developing an invasive IBE based on the DCIS Score according to the three prespecified risk groups. C) Probability of developing a DCIS IBE (censored if an invasive IBE occurred) based on the DCIS Score according to the three prespecified risk groups. D) Estimated 10-year risk of developing an IBE as a continuous function using the DCIS Score based on a Cox proportional hazards model, including 95% confidence intervals demonstrating the level of precision in the estimates. More precise estimates are seen for lower values and lower risk levels because of the greater number of observations, as indicated in the rug plot along the x-axis. The hazard ratios are presented for a 50-point difference in the DCIS Score. E) Estimated 10-year risk of developing an invasive IBE as a continuous function using the DCIS Score based on a Cox proportional hazards model, including 95% confidence intervals. F) Estimated 10-year risk of developing a DCIS IBE as a continuous function using the DCIS Score based on a Cox proportional hazards model, including 95% confidence intervals



### 1.3 Role of MRI in DCIS

Over the past decade, MRI technology has improved, allowing a high level of performance for detection and characterization of DCIS. A recent NIH consensus conference recommended future research to compare MRI to conventional imaging for guiding DCIS management following biopsy and to evaluate breast MRI's ability to discriminate DCIS that requires radiotherapy from DCIS that may be managed with excision alone.<sup>12</sup> Advanced imaging with MRI presents an opportunity for better anatomic delineation of DCIS that would allow more complete excision, offering the possibility of lower recurrence after wide local excision with or without radiation. We hypothesize that MRI-directed surgical planning will decrease recurrence risk by allowing more complete resection of disease, including multicentric and invasive disease.

Although initially considered a poor imaging tool to assess DCIS, MRI has become the most accurate imaging modality for DCIS detection and characterization due to evolution of acquisition techniques to emphasize spatial resolution (thinner slice acquisitions) over temporal resolution (faster scan times). In 2004, Berg et al. demonstrated that MRI is superior to either mammography or ultrasound for the accurate assessment of DCIS extent of disease, with an 89% sensitivity of MRI compared with only 55% and 47% for mammography and ultrasound, respectively.<sup>17</sup> In 2007, Lehman et al reported results from the American College of Radiology Imaging Network (ACRIN) 6667 trial, which demonstrated that bilateral breast MRI of 969 women recently diagnosed with unilateral breast cancer on conventional evaluation identified 30 cancers in the contralateral breast, twelve of which (40%) were pure DCIS.<sup>18</sup> Additional data regarding the superiority of MRI for DCIS detection came from a series of 7319 women who underwent both MRI and mammography, with pure DCIS diagnosed in 167 patients. MRI sensitivity for detection of DCIS was 92% compared with only 56% by mammography, and was particularly strong in women with high-grade or comedo-type DCIS (98% versus 56%).<sup>19</sup> The majority (87%) of cases of DCIS not identified by MRI were low-grade DCIS. Age, menopausal status, personal or family history of breast cancer or of benign breast disease, and breast density did not differ in women with MRI-only diagnosed DCIS compared with those with mammography-diagnosed DCIS.

Through the use of high spatial resolution MRI techniques, it is now recognized that the classic morphologic patterns of enhancement commonly present in invasive carcinoma on MRI are not present in the majority of cases of DCIS, and patterns of contrast enhancement over time, central to the effectiveness of high temporal resolution imaging, do not distinguish DCIS lesions from normal tissue. Multiple studies have shown that delayed washout kinetics, a typical feature of breast malignancies, identify a small fraction of DCIS cases.<sup>19</sup> Instead, unique morphological features such as non-mass enhancement are more useful than kinetic features for diagnosis.<sup>20-22</sup> A recent study in a mouse model demonstrates that gadolinium diffuses from the vessels into the surrounding tissue, across the basement membrane, and into the ducts containing DCIS.<sup>23</sup> This suggests MRI may provide information regarding DCIS microenvironment such as basement membrane permeability.<sup>24</sup> An additional recent study further suggests that T2 signal and maximum lesion size on MRI may be useful to predict DCIS grade, indicating that MRI may provide biomarkers of DCIS aggressiveness.<sup>25</sup> MRI features of malignant lesions, including morphology and kinetics, may provide predictive information regarding likelihood of recurrence.

However despite the uniformly promising data on DCIS detection, there have been few attempts to translate this into data into improved short-term or long-term outcomes for DCIS patients. The only sizeable report on long-term outcomes included 756 women, 150 of whom were treated with breast conserving surgery and radiotherapy for pure DCIS, with no difference in 8 year actuarial rates of local recurrence or contralateral breast cancer.<sup>26</sup> Data on re-excision rates (postulated to be lower following MRI-based surgical planning) have shown no advantage for MRI-based DCIS excision.<sup>27,28</sup> Another retrospective study of 352 patients prospectively included in a database, of whom 217 were selected to have a preoperative MRI, found that patients in the MRI group were likely to undergo additional biopsies (38% vs. 7%); however, patients selected to have an MRI were significantly younger, (mean age 53 vs. 60 years,  $p < 0.0001$ ) and significantly more likely to be pre/perimenopausal (38.7% vs. 22.2%), have heterogeneously dense breasts on mammography (63.1% vs. 44.4%), present with a clinically detected mass (16.4% vs. 6.8%), and have microinvasion on core biopsy (123.8% vs. 3.7%).<sup>44</sup> All published studies to date have shown higher mastectomy rates for DCIS patients undergoing pre-operative MRI evaluation, but numbers are small and it is clear that women undergoing MRI in retrospective series differ in important ways from those not undergoing MRI.

The proposed study will fill many of these gaps; in addition it will allow comparison of DCIS Score to MRI features of DCIS to identify imaging-pathological correlations with the ultimate goal of clarifying whether MRI can provide complementary prognostic information.

In summary, the ability of MRI to detect the presence and extent of DCIS exceeds that of mammography or ultrasound and is associated with acceptable specificity. This improved sensitivity is particularly robust for high-grade DCIS lesions, which may exhibit unique imaging features. How this improved diagnostic accuracy will affect outcomes in patients with ductal carcinoma in situ warrants careful investigation.

#### 1.4 Impact of Surgeon Recommendations, Patient Preferences, and MRI on Surgical Management in Breast Carcinoma

Morrow et al<sup>33</sup> evaluated the association of patient-reported initial recommendations by surgeons, and those given when a second opinion was sought, with receipt of initial mastectomy, and assessed the use of mastectomy after attempted breast-conserving surgery (BCS). The study involved a survey of women aged 20 to 79 years with DCIS or stage I and II breast cancer diagnosed between June 2005 and February 2007 and reported to the SEER registries for the metropolitan areas of Los Angeles and Detroit. Patients were identified using rapid case ascertainment, and Latinas and blacks were oversampled. Of 3133 patients sent surveys, 2290 responded (73.1%). A mailed survey was completed by 96.5% of respondents and 3.5% completed a telephone survey. The final sample included 1984 female patients (502 Latinas, 529 blacks, and 953 non-Hispanic white or other). The rate of initial mastectomy and the perceived reason for its use (surgeon recommendation, patient driven, medical contraindication to breast conservation) and the rate of mastectomy after attempted BCS was ascertained. Of the 1984 patients, 1468 had BCS as an initial surgical therapy (75.4%) and 460 (24.6%) had initial mastectomy, including 13.4% following surgeon recommendation and 8.8% based on patient preference. Approximately

20% of patients (n = 378) sought a second opinion; this was more common for those patients advised by their initial surgeon to undergo mastectomy (33.4%) than for those advised to have BCS (15.6%) or for those not receiving a recommendation for one procedure over another (21.2%) (P < .001). Discordance in treatment recommendations between surgeons occurred in 12.1% (n = 43) of second opinions and did not differ on the basis of patient race/ethnicity, education, or geographic site. **Among the 1459 women for whom BCS was attempted, additional surgery was required in 37.9% of patients, including 358 with reexcision (26.0%) and 167 with mastectomy (11.9%).** Mastectomy was most common in patients with stage II cancer (P < .001). The authors concluded that breast-conserving surgery was recommended by surgeons and attempted in the majority of patients evaluated, with surgeon recommendation, patient decision, and failure of BCS all contributing to the mastectomy rate.

Houssami et al (34) reported a meta-analysis examining the effect of preoperative MRI compared with standard preoperative assessment on surgical outcomes, focusing on studies that used a controlled design. Using random-effects logistic meta-regression modeling, they estimated the proportion of women with each outcome in the MRI versus no-MRI groups, and calculated the odds ratio (OR) and adjusted OR (adjusted for study-level median age, and, where appropriate, for temporal effect) for each model. There were 9 eligible studies (2 randomized trials; 7 comparative/cohorts). In 5 of the 9 studies which specified whether DCIS was included, the proportion of patients with DCIS was 0%, 0%, 5.3%, 7.7%, 14.0%, and 49.4% in the MRI group, and did not differ significantly from the no MRI group. **Outcomes in 3112 patients with breast cancer (any histological tumor type) for MRI versus no-MRI (referent) were as follows: initial mastectomy 16.4% versus 8.1% [OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)]; re-excision after initial breast conservation 11.6% versus 11.4% [OR, 1.02 (P = 0.87); adjusted OR, 0.95 (P=0.71)]; overall mastectomy 25.5% versus 18.2% [OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)].** In 766 patients with invasive lobular cancer (ILC), outcomes were as follows: initial mastectomy 31.1% versus 24.9% [OR, 1.36 (P = 0.056); adjusted OR, 2.12 (P = 0.008)]; re-excision after initial breast conservation 10.9% versus 18.0% [OR, 0.56 (P = 0.031); adjusted OR, 0.56 (P = 0.09)]; overall mastectomy 43.0% versus 40.2% [OR, 1.12 (P = 0.45); adjusted OR, 1.64 (P = 0.034)]. The authors concluded that MRI significantly increased mastectomy rates, and that there was weak evidence that MRI reduced re-excision surgery in patients with invasive lobular cancer, a group postulated to benefit from MRI due to its poor delineation on mammography. **Given the widespread use of MRI in the community, and the limited information about the clinical utility of MRI specifically in DCIS, there is a need for a conducting prospective clinical trial such as E4112 that will determine how MRI impacts patient management. The information obtained from this trial will provide the foundation for a randomized phase III trial evaluating the role of MRI in DCIS, similar to an ACRIN trial that is ongoing in patients with invasive breast cancer (ACRIN 6694) (NCT01805076).**

#### 1.5 Significance of the Study

This proposed prospective study addresses gaps in current knowledge. The National Institute of Health hosted a “State of the Science” meeting in 2009



addressing the challenges and opportunities in the diagnosis and management of DCIS. The concluding report stated that “The primary question for future research must focus on the accurate identification of patient subsets diagnosed with DCIS, including those persons who may be managed with less therapeutic intervention without sacrificing the excellent outcomes presently achieved.”<sup>12</sup> The 2009 consensus statement agreed with the prior 1999 NIH Consensus Conference Statement that “Patients who may avoid radiation therapy have not been reproducibly and reliably identified by any clinical trials.” General recommendations of the panel regarding “Recommendations for Future Research Directions” included the following: (a) “Develop and validate risk stratification models to identify subsets of women with DCIS who are candidates for 1) active surveillance only, 2) local excision only, 3) local excision with radiotherapy, and 4) mastectomy. (b) Develop strategies to determine which patient is at high risk for recurrence of DCIS or the development of invasive carcinoma. (c) Perform comparative effectiveness analyses to further define the role of current therapies in DCIS patients. (d) Integrate patient-reported outcomes and data on patient perceptions of risk and preferences regarding treatment within current clinical research and, ultimately, decision-making algorithms.”

The Panel identified “the Most Critical Research Questions for the Diagnosis and Management of DCIS” including: (1) “Development and use of standardized reporting methods and terminology for DCIS detection and diagnosis across all disciplines. (2) Collection of consistent and detailed data on the clinical, pathological, radiological, and molecular characteristics of DCIS through the creation of multisite databases of DCIS that would include annotated specimen and imaging repositories. (3) Investigation and validation of combinations of new and existing clinical, radiological, pathological, and molecular factors to improve risk stratification of DCIS patients and thus to identify the optimal therapy for each individual. Ease of use, predictive ability, reproducibility, and generalizability are important components of prognostic model development. (4) Research on patient–provider communication, informed consent (at the time of screening), patient preferences, and decision making concerning the diagnosis and treatment of DCIS. Decision aids should be further developed, evaluated for their impact on quality of care, and integrated into clinical practice. (5) Investigations of the impact a diagnosis and treatment of DCIS has on the quality of life. (6) Investigations into the comparative effectiveness of the methods of treatment for DCIS.”

***This trial is designed to determine the proportion of patients undergoing mastectomy after integrating an MRI into the management of patients with DCIS who would be otherwise candidates for wide local excision, correlate the findings of MRI with the DCIS Score, and determine the impact of MRI on patient reported outcomes, which address research priorities 2, 3, and 5 noted above.***

## 1.6 Patient-Reported Outcomes (PRO), Quality of Life Component (QOL) and Decision Making (DM)

### 1.6.1 Background and Rationale

Data on the effect of pre-operative MRI on QOL of patients with newly diagnosed breast cancer is scant. The impact of MRI on QOL has been determined in a few studies conducted on women with newly

diagnosed breast cancer, the vast majority of whom had invasive carcinoma, a group with higher incidence of recurrence and generally poorer prognosis compared to patients with DCIS. Most notably, the COMICE trial in the United Kingdom randomized 1623 women with biopsy proven breast cancer (90% of which were invasive carcinomas) to receive either MRI or no further imaging. The primary endpoint was the proportion of patients undergoing repeat operation or avoidable mastectomy.<sup>36</sup> Using the FACT-B QOL and EQ-5D instruments, the COMICE trial found no difference in breast cancer specific- and overall QOL between the two arms of the study. The QOL data from recently launched United States trial (ACRIN 6694), mirroring the COMICE trial, are not yet available. Neither the COMICE nor ACRIN 6694 trials compared the impact of pretreatment MRI on decision making quality and satisfaction, post-treatment concern and overall quality of life.

The data on the effect of pre-operative MRI on QOL among patients with newly diagnosed DCIS is even more limited. The studies available describing QOL in DCIS are cross-sectional, conducted among women already diagnosed and treated for DCIS, or small.<sup>37</sup> The largest cross-sectional study identified 2268 women treated for breast cancer from the Los Angeles and Detroit SEER registries including 12% with DCIS or Stage 0 breast cancer.<sup>38</sup> Women with earlier stage cancer reported significantly higher physical and functional well-being (as measured by the FACT-B) and fewer breast concerns; however, no differences in emotional well-being were demonstrated controlling for cancer stage. None of these studies evaluated the impact of pretreatment MRI on decision making quality and satisfaction, post-treatment concern and overall quality of life.

A key innovation in the current study is the provision of a woman's DCIS score after breast conservation or mastectomy and a personal estimate of her risk of IBE including invasive cancer. This score provides an objective measure that should impact a woman's perception of future cancer risk. However, literature on provision of tailored risk information in other disease contexts (including colon cancer and diabetes risk communication) suggest that people fail to understand risk information and fail to accept that information as valid.<sup>39, 40, 41</sup> Among 690 women who participated in an online decision aid for breast cancer chemoprevention, 52% misreported their personalized risk of breast cancer and 20% disagreed with the personalized risk assessment provided.<sup>42</sup> To date, no studies of DCIS score and patient-reported recurrence risk perception have been conducted.

The impact of pretreatment MRI on the surgeon's recommendation represents a key component of patient treatment decision making and QOL. To date, no studies have evaluated the role of MRI in surgeon recommendation in patients with newly diagnosed DCIS.

In order to fully understand the comparative effectiveness of pre-treatment MRI, a more complete understanding of the incremental burden of diagnostic testing associated with MRI (particularly the experience of additional MRI-prompted breast biopsies), compared to

the standard of care, is needed. Swan et al have developed the Testing Morbidity Index to evaluate the temporary burden or QOL decrement associated with imaging tests.<sup>52</sup> This tool has the potential to inform cost-effectiveness analyses.

1.6.2 Study hypotheses:

Primary PRO hypothesis:

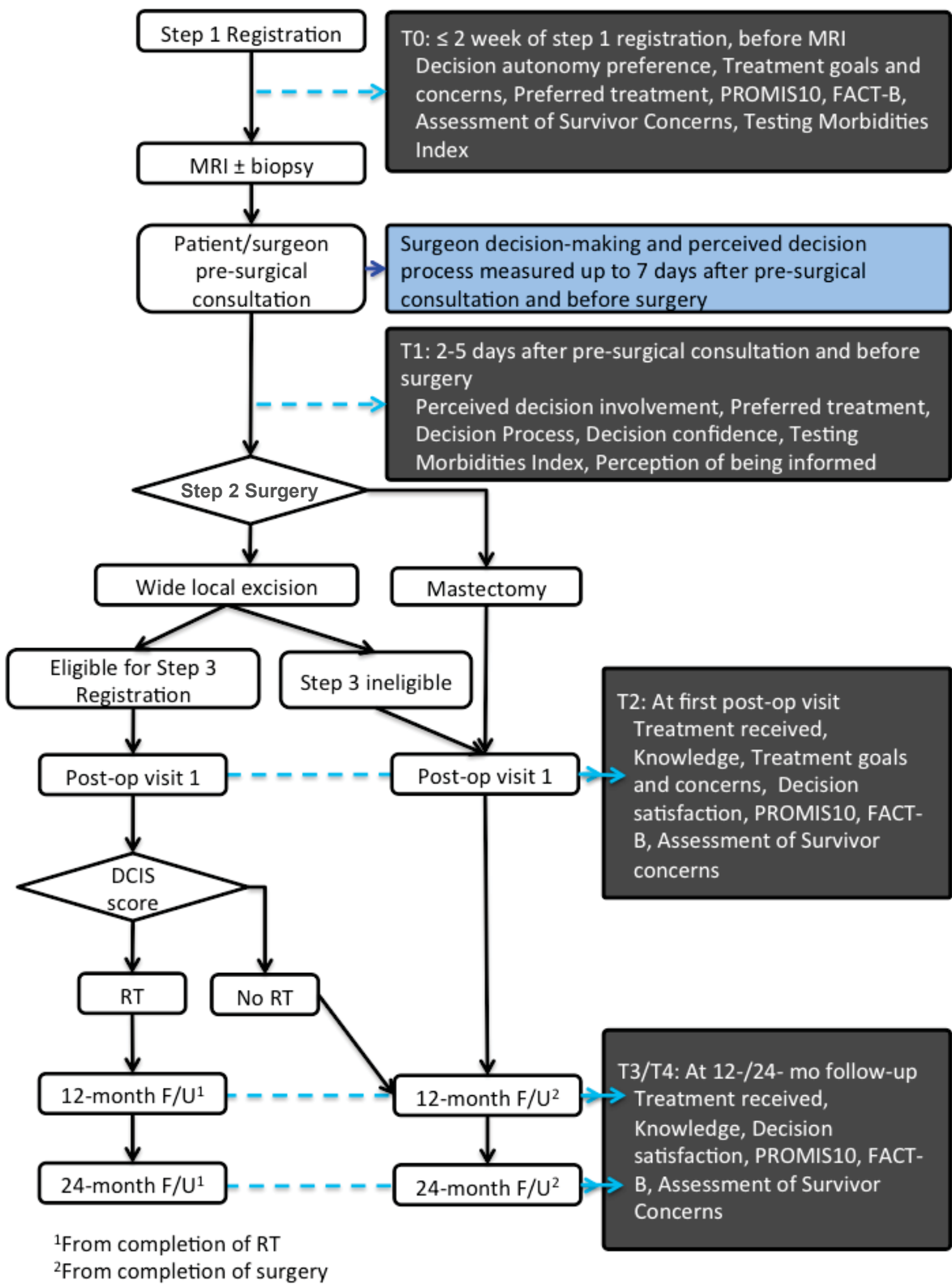
1. Women with DCIS receive treatment that is concordant with their treatment goals and concerns.

Secondary PRO hypotheses:

1. Concordance between decision autonomy preference and perceived level of decision involvement is associated with more decision satisfaction and better quality of life after treatment
2. Decision quality is associated with more decision confidence and better quality of life after treatment
3. Quality of life correlates with decision quality, patient reported outcomes such as fear of recurrence and post-treatment concerns, as well as disease stage, MRI result including disease upstaging and treatment received.
4. Patient-level factors and surgeon recommendation predict treatment received.

1.6.3 QOL Study Design

The schema describes the measures to be administered and the time points of survey administration.



1.6.4 Rationale for PRO and QOL Measure Selection

The PRO instruments selected will evaluate the following domains hypothesized to contribute to overall QOL.

**Patient Decision Making Quality and Satisfaction**

**Decision Autonomy Preference and Perceived Decision Involvement** will be measured using the same instrument. The Control Preferences Scale, a theory-based measure, assesses patient decision involvement in treatment selection, and is reliable across different cancer types and different populations as demonstrated in a recent meta-analysis.<sup>46,47</sup> The scale consists of a single item on a five point scale, typically reduced to a three-category scale (patient-based, shared, surgeon-based) for analysis. In a population-based racially and ethnically diverse group of 1651 women with nonmetastatic breast cancer eligible for breast conservation surgery with radiation identified in the Los Angeles and Detroit SEER registries, women who reported a patient-based decision were more likely to receive mastectomy rather than breast conservation surgery with radiation.<sup>45</sup>

**Treatment Goals and Concerns** will be measured using items adapted from the Breast Cancer Surgery Decision Quality Instrument Worksheet developed by Sepucha et al.<sup>57,58</sup> The five items had a good short term retest reliability (ICC ranged from 0.61-0.72 depending on the item.) Items include “keeping your breast”, and “relieve worries about getting breast cancer in the future.” To ensure full coverage of relevant treatment goals and concerns, the Sepucha instrument will be augmented with 7-item measure of concerns about fear of recurrence, radiation, body image correlates with surgery received from Katz et al.<sup>45</sup> Among the 1651 women with nonmetastatic breast cancer eligible for breast conservation surgery with radiation identified in the Los Angeles and Detroit SEER registries who reported concerns about recurrence or radiation effects were more likely to receive mastectomy rather than breast conservation surgery with radiation. Women who reported greater body image concerns were more likely to receive breast conservation surgery with radiation.

**Preferred treatment** will be queried with a single item adapted from the Sepucha Treatment Goals and Concerns scale, “Which treatment do you want to do to treat your DCIS?”

**Decision Process** will be measured using items adapted from the Breast Cancer Surgery Decision Quality Instrument Worksheet developed by Sepucha et al.<sup>57</sup> The 7-item scale queries whether patients were offered a choice, how much the pros and cons were discussed and whether they were asked for their preferences.

**Decision Confidence** and **Perception of being informed** will each be queried using a single item adapted from Sepucha.

**Knowledge** regarding DCIS and treatment pros and cons will be queried using a 5-item instrument adapted from Breast Cancer Surgery Decision Quality Instrument Worksheet developed by Sepucha et al.<sup>57</sup>

**Decision Satisfaction Scale:** Developed by Holmes-Rovner, Katz et al used four item revised version to measure satisfaction with type of surgery received in the same population-based sample of 1651 women described above; confirmatory factor analysis demonstrated high internal validity of these four items (Cronbach alpha=0.90).<sup>48,49</sup>

#### **Patient Risk Perception**

**Assessment of Survivor Concerns (ASC):** The ASC is a six item instrument specific to fear of general cancer recurrence and fear of health issues in general. It is designed to serve as an adjunct to other QOL instruments including the PROMIS 10. This instrument is valid in both short term and long term survivor populations.<sup>34</sup>

#### **Quality of Life**

**Testing Morbidities Index (TMI):** The TMI is a seven-item preference-based instrument addressing short-term effects on quality of life from diagnostic testing before, during, and after testing procedures.<sup>52</sup> The instrument was initially validated in a specific test (breast biopsy) and transformative functions allow for calculation of a preference-based measure using a modified time trade-off function. This preference-based measure will permit incorporation into cost-effectiveness models to assess QALY decrement from diagnostic testing.

**PROMIS 10:** The Patient Reported Outcomes Measurement Information System (PROMIS 10) is a 10 item questionnaire that addresses physical and mental health. It is a relatively new QOL measure developed by the National Institutes of Health PROMIS Network. In addition, the PROMIS 10 has been shown to predict EQ-5D preference scores and thus can estimate quality adjusted life years (QALY).<sup>54-56</sup>

**FACT-B Additional Concerns:** is a 10-item questionnaire assessing breast cancer treatment related concerns.

#### **Surgeon Treatment Decision Making**

This 12-item instrument adapted from Katz et al queries surgeon treatment recommendation, the impact of breast MRI results on recommendation and surgeon knowledge of patient-related concerns leading to mastectomy.<sup>45</sup>

### 1.6.5 PRO/QOL Data Collection Process

#### **Patient completed outcomes:**

Patients will be recruited at the time of registration in the patient reported outcomes portion of the study. There is a potential for the patient to experience distress during the evaluation and treatment process for DCIS, including related to decision-making. Distress related to decision-making that comes up in this trial will be managed similarly to how distress related to decision-making is managed in routine clinical practice. Therefore, at Step 1 registration, the research personnel will discuss with all patients the potential for the process of getting evaluated and treated for DCIS and for some parts of the



study to be upsetting and that the care team is available to provide primary support. The patients will be provided a toll-free telephone number (800-813-HOPE (4673)) to CancerCare (cancer.org) as an additional resource for any cancer-related distress or anxiety. In addition, during survey administration for patient-reported outcomes, quality of life and decision making, patients will be instructed to seek support from care team if they experience any distress with the provision of the same toll-free number to CancerCare as an additional resource at the end of each survey.

At the time of registration at the sites, patients will complete contact information sheets. These will include name, address, phone number, and e-mail (if available). Patients contact information forms will be faxed to the central ACRIN Outcomes and Economic Assessment Unit. This information will be maintained in a dedicated SQL server independent of the main study database. At this time, patients will be asked to express a preference for on-line or paper completion of patient reported outcome (PRO) forms. Patients may choose to complete questionnaires using a web-based application or by mail. Administration of questionnaires, both web-based and paper will be coordinated by the ECOG-ACRIN Outcomes and Economics Assessment Unit (OEAU). Administration of the questionnaires will be triggered based on completion of study milestones marked by submission of forms in RAVE.

#### **Web-based questionnaire completion**

Patients will be prompted to complete web-based forms via an email prompt. These emails will include a link to the web site for questionnaire completion. Questionnaires will be completed on line using a unique patient account. The web site will reference a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance. All data will be stored on a secure server. For T0, T2, T3 and T4 questionnaires, if patients do not complete the web questionnaire within 10 working days of the date of the e-mail, a second email will be sent, it will ask to confirm that the patient has been able to access the questionnaire on the web. If patients have still not responded within 20 working days of the original e-mail, the OEAU Research Associate will attempt to telephone the patient and administer the questionnaire by telephone. If questionnaires are telephone-administered, they will be marked as such. For T1 questionnaires, if patients do not complete the web questionnaire within 3 working days of the date of the e-mail, a second email will be sent, it will ask to confirm that the patient has been able to access the questionnaire on the web. If patients have still not responded within 5 working days of the original e-mail, the OEAU Research Associate will attempt to telephone the patient and administer the questionnaire by telephone.

#### **Mailed questionnaire completion**

Mailed questionnaire packets will include a letter introducing the study and include a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need

assistance, together with pre-addressed, stamped envelopes for return mailing to the OEAU. If patients do not complete the web or paper questionnaire within 10 working days of the date of the mailing, the OEAU RA will attempt to telephone the patient. If they have not received the paper questionnaires, additional questionnaires will be sent after confirming the correct mailing address. If the questionnaire is available to the patient, the BC RA will urge the study patient to complete and return the questionnaire. If patients have still not responded within 20 working days of the original mailing, the OEAU will attempt to telephone the patient and telephone administer the questionnaire. If questionnaires are telephone-administered, they will be marked as such.

**Surgeon decision making information:**

All surgeons will be expected to complete decision-making questionnaires as provided to them by the research personnel.

Surgeons will be prompted to complete paper-based forms by the site CRA. Research personnel will then collect and enter the surveys online via the EASEE-PRO. See Section [4.1.3.6](#) for details.

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## 2. Objectives

### 2.1 Primary Objective

To estimate the proportion of patients with DCIS diagnosed on core needle biopsy judged to be breast conservation candidates based upon standard imaging (mammography +/- sonography) and physical examination (a) who convert to mastectomy in step 1 based on MRI findings, and (b) who have a mastectomy as the final surgical procedure in step 2.

### 2.2 Secondary Objectives

- 2.2.1 To assess the relation between baseline clinical covariates (e.g., tumor grade, necrosis, histologic type, mammographic lesion size), MRI morphologic and kinetic features, and the DCIS score.
- 2.2.2 To assess the diagnostic accuracy of MRI in extent of disease evaluation in patients with DCIS.
- 2.2.3 To estimate the proportion of patients who require re-operation because of inadequate excision after MRI.
- 2.2.4 To estimate the proportion of patients who proceed to mastectomy after an initial attempt at wide local excision because of either inadequate tumor-free margins (< 2mm), or other reasons.
- 2.2.5 To estimate the 5-year and 10-year ipsilateral breast event (in situ and invasive) rate (IBE) among women with DCIS assessed with MRI preoperatively and treated with wide local excision without radiation therapy (if there is a low DCIS score) or with radiation therapy (if there is an intermediate-high DCIS score).
- 2.2.6 To estimate the proportion of women with DCIS who receive treatment that is concordant with their treatment goals and concerns.
- 2.2.7 To estimate the proportion of women with DCIS whose decision autonomy preference was concordant with perceived level of decision involvement
- 2.2.8 To assess decision quality using knowledge score and decision process.
- 2.2.9 To assess concordance between decision autonomy preference and perceived level of decision involvement, knowledge and decision process scores as independent predictors of decision satisfaction at the first post-operative visit.
- 2.2.10 To assess the relationship of patient-reported outcomes and disease-specific covariates, and quality of life after treatment.
- 2.2.11 To assess the role of disease status, diagnostic test results and surgeon recommendation as predictors of treatment received
- 2.2.12 To compare the patient-reported diagnostic testing burden of bilateral mammography and MRI as measured by TMI

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### 3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

**In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.**

ECOG-ACRIN Patient No. \_\_\_\_\_

Patient's Initials (L, F, M) \_\_\_\_\_

Physician Signature and Date \_\_\_\_\_

**NOTE:** All questions regarding eligibility should be directed to the study chair or study chair liaison.

**NOTE:** Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

#### 3.1 Registration to Step 1

3.1.1 Age  $\geq$  18 years.

3.1.2 Patients must be females. Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.

3.1.3 Patients must have pathologically confirmed diagnosis of unilateral ductal carcinoma in situ with no evidence of microinvasive or invasive disease obtained by core needle biopsy within 4 months of registration. If the core biopsy describes "suspicion of microinvasion", patients remain eligible. Patients diagnosed by surgical excision are not eligible. Patients with synchronous bilateral disease (i.e., synchronous DCIS or invasive cancer) are not eligible.

Patients will be staged prior to registration according to the clinical staging criteria adapted from the American Joint Committee on Cancer (AJCC) Cancer Staging Data Forms of the AJCC Cancer Staging Manual, 7th Edition, 2009 (See Appendices). Note: For consistency purposes, AJCC 7th Edition will continue to be used throughout the entire study enrollment period.

3.1.4 Required studies include a diagnostic mammogram of the affected breast within 3 months prior to registration, and a two-view (full view CC and a full view MLO) mammogram of both breasts within 6 months of registration (if the patient has only one breast, a unilateral exam of the intact breast is required).

3.1.5 Patients must not have previous ipsilateral invasive breast cancer or DCIS.

3.1.6 Patients must not have known deleterious mutations in BRCA genes.

- 3.1.7 Patients must not have received hormonal therapy (i.e., tamoxifen, raloxifene, and/or aromatase inhibitors) for prevention of breast cancer within 3 months of the biopsy documenting DCIS.
- 3.1.8 Patients must not have history of chemotherapy for cancer within 6 months prior to registration.
- 3.1.9 No prior history of breast radiotherapy that will prevent the use of radiotherapy for the present DCIS.
- 3.1.10 Patients must be judged to be suitable to undergo MRI and receive the contrast agent gadolinium (exclusions follow):
  - 3.1.10.1 No history of untreatable claustrophobia;
  - 3.1.10.2 No presence of metallic implants that, in the opinion of the radiologist, would make MRI a contraindication.
  - 3.1.10.3 No history of sickle cell disease;
  - 3.1.10.4 No contraindication to intravenous contrast administration;
  - 3.1.10.5 No known allergy-like reaction to gadolinium or moderate or severe allergic reactions to one or more allergens as defined by the American College of Radiology (ACR); patient may be eligible if willing to undergo pre-treatment as defined by the institution's policy and/or ACR guidance (see [www.acr.org/SecondaryMainMenuCategories/quality\\_safety/contrast\\_manual.aspx](http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx) for reaction definition and premedication guidance);
  - 3.1.10.6 No findings consistent with renal failure, as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m<sup>2</sup> based on a serum creatinine level obtained within 28 days prior to registration;
  - 3.1.10.7 Weight lower than that allowable by the MRI table;
- 3.1.11 No prior MRI of the breasts within the 6 months prior to registration
- 3.1.12 Patients must be eligible for BCT based on clinical examination and mammography. If ultrasound is performed, findings must also be consistent with eligibility for BCT.
- 3.1.13 Patients must not have multicentric disease scheduled to undergo multiple lumpectomies. Multifocal disease that can be encompassed in a single operative bed are eligible
- 3.1.14 Women must not be pregnant or breast-feeding.

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All females of childbearing potential must have a blood test or urine study within 28 days prior to registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? \_\_\_\_\_ (Yes or No)

Date of blood test or urine study: \_\_\_\_\_

- 3.1.15 Women of childbearing potential must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

---

Physician Signature

---

Date

3.2 Registration to Step 2

3.2.1 MRI has been performed in Step 1, and additional imaging studies and biopsies performed if indicated.

3.2.2 The clinician/patient has made the decision as to whether the patient will proceed to wide local excision or mastectomy or patient has been diagnosed with invasive disease.

**NOTE:** If surgical decision is delayed greater than 10 weeks after the MRI or patient is diagnosed with invasive disease, the patient should register to Step 2, Arm B, and proceed to follow-up to capture all relevant data.

---

Physician Signature

---

Date

3.3 Registration to Step 3

3.3.1 Patient's most recent surgery was wide local excision with or without re-excision and for which there was obtained clear ( $\geq 2$  mm) margins at breast conserving surgery, and the pathology reveals pure DCIS. Patients with invasive cancer or DCIS with microinvasion will not be registered on step 3, but will be followed for clinical outcomes.

**NOTE:** If resection is documented to have reached pectoral fascia and deep margin is free but less than 2mm, the patient is eligible.

**NOTE:** If no residual DCIS is found on wide local excision as it was fully removed in core biopsy, the patient is eligible.

**NOTE:** Patients with LCIS as well as DCIS are eligible.

3.3.2 The OncotypeDX Patient Report of the DCIS Score from the OncotypeDX Breast Cancer Assay performed by Genomic Health on the excision tissue have been uploaded by the site into the Rave eCRF.

The OncotypeDX for DCIS assay result:

GHI Requisition Number: \_\_\_\_\_

DCIS RS score: \_\_\_\_\_

**NOTE:** Prior to registration to Step 3, the institution must upload a redacted copy of the first page of the "OncotypeDX Patient Report" to the 'DCIS Score' eCRF in Rave. After submission of the OncotypeDX Patient Report, the institution may proceed to register the patient to Step 3.

---

Physician Signature

---

Date

**OPTIONAL:** This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

#### 4. Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at <https://www.ctsu.org>; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at <https://www.ctsu.org>.

Requirements for E4112 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form
- MRI Qualification

#### Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office  
Coalition of National Cancer Cooperative Groups  
1818 Market Street, Suite 1100  
Philadelphia, PA 19103  
FAX: (215) 569-0206

#### Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

**NOTE:** Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.  
**Or**  
B. Signed HHS OMB No. 0990-0263 (replaces Form 310).  
**Or**  
C. IRB Approval Letter

- NOTE:** The above submissions must include the following details:
- Indicate all sites approved for the protocol under an assurance number.
  - OHRP assurance number of reviewing IRB
  - Full protocol title and number
  - Version Date
  - Type of review (full board vs. expedited)
  - Date of review.
  - Signature of IRB official

**The CTSU encourages you to go to the following CTSU RSS webpage so that more information on RSS2.0 as well as the submission forms can be accessed.** Log in to <http://www.ctsu.org> and click on the Regulatory tab to access the RSS webpage. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail [CTSUContact@westat.com](mailto:CTSUContact@westat.com). **Please refer to CTSU website for the hours of operation.**

**Patients must not start protocol prior to registration.**

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- The site has an MRI qualified scanner
- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.



**NOTE:** The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

#### 4.1 Step 1 Registration

4.1.1 The following information will be requested

4.1.1.1 Protocol Number

4.1.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3.1](#). Upon registration, patient will be assigned to arm A.

4.1.3 Additional Requirements

4.1.3.1 Patients must provide a signed and dated, written informed consent form.

**NOTE:** Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.1.3.2 Images are to be submitted as indicated in Section [5.1.2.2](#).

4.1.3.3 Pathology materials are to be submitted for central diagnostic review as outlined in Section [9.3](#).

4.1.3.4 If patients do not proceed to Step 2 registration: data, imaging, and sample collection and submissions schedules and requirements are to follow the requirements for Arm B.

**NOTE:** If surgical decision is delayed greater than 10 weeks after the MRI or patient is diagnosed with invasive disease, the patient should

register to Step 2, Arm B, and proceed to follow-up to capture all relevant data.

- 4.1.3.5 Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS after IRB approval is obtained. To access iMedidata/Rave the site user must have an active CTEP IAM account (<https://eapps-ctep.nci.nih.gov/iam>). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at <http://www.ctsu.org/RAVE/> or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

- 4.1.3.6 Site CRAs will be asked to administer and enter both the participant baseline and surgeon surveys. To enter these surveys, the CRA must first set up a valet account in the ECOG-ACRIN System for Easy Entry of Patient Reported Outcomes (EASEE PRO). CRAs should complete the CRA account request form, and fax it to the ECOG-ACRIN Outcomes and Economics Assessment Unit (EA-OEAU: 1 401 863 9635), which will set up the account. Once it's established, the system will send the CRA a verification email with a link to verify the account. After the CRA has

verified their account, they will be able to enter these surveys into the system (<https://provides.stat.brown.edu>).

**NOTE:** For optimal data quality, the CRA should ask the surgeon to complete the surgeon survey within 24 hours after the pre-surgical consult. The CRA should collect and enter the completed survey into the EASEE PRO system within 5 working days.

Patients will have the choice of reporting outcomes via mailed surveys or through a web-based application. After registering patients, the site CRA should have the participant complete the participant contact form, ensuring that the participant has selected their preferred contact method (Mail or Web-based), and fax the completed form to the EA-OEAU (1 401 863-9635) within 24 hours of completion.

Participants requesting web-based surveys will automatically be provided with a system account and will be sent an email requesting that they login and verify their account. Once their account has been verified they will be able to login to the EASEE PRO - Patient Reported Outcome Web Entry Systems (<https://prowess.stat.brown.edu>).

**NOTE:** More information about how to use the EASEE PRO is available at <https://provides.stat.brown.edu/Help>. The OEAU also may be contacted at 1-855-404-3278 during normal business hours, and via email at [help-4112@stat.brown.edu](mailto:help-4112@stat.brown.edu).

## 4.2 Step 2 Registration

4.2.1 The following information will be requested

4.2.1.1 Protocol Number

4.2.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.2.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code

- Method of payment
- Country of residence

#### 4.2.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3.2](#).

#### 4.2.3 Breast Surgery

Upon registration, the treating physician will choose either arm B (mastectomy) or wide local excision (arm C) based upon the results of MRI and other imaging/biopsies performed during step 1 if indicated.

**NOTE:** If patient has surgery delay, they should be enrolled in Arm B and proceed to follow up to capture all relevant data”

#### 4.2.4 Additional Requirements

4.2.4.1 Samples must be submitted as indicated in Section [9](#).

- From patients who have undergone wide local excision surgery as their final surgical procedure during step 2 with surgical margin status  $\geq 2$ mm and have DCIS only, pathology materials are to be submitted to Genomic Health, Inc. for determination of Oncotype DX DCIS Score as outlined in Section [9.1](#). Kits are to be requested directly from GHI.
- Upon receipt of the DCIS Score, prior to registration to Step 3, the institution must upload a redacted copy of the first page of the “OncotypeDX Patient Report” to the ‘DCIS Score’ eCRF in Rave. After submission of the OncotypeDX Patient Report, the institution may proceed to register the patient to Step 3
- Surgical tumor tissue is to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) from patients who have: (a) undergone mastectomy or (b) are diagnosed with invasive disease at time of surgery or (c) have surgical margin status  $< 2$ mm. Additional tissue is to be submitted for research from consenting patients. See Section [9.3](#).

### 4.3 Step 3 Registration

4.3.1 The following information will be requested

4.3.1.1 Protocol Number

4.3.1.2 Investigator Identification

- Institution and affiliate name
- Investigator’s name

4.3.1.3 Patient Identification

- Patient’s initials (first and last)
- Patient’s Hospital ID and/or Social Security number
- Patient demographics

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- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

#### 4.3.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3.3](#). Upon registration to step 3, patients will be assigned to arm D (Low DCIS Score – no breast radiation) or arm E (Intermediate-high DCIS Score – breast radiation).

#### 4.3.3 Classification Factors

- OncotypeDX DCIS score: Low (< 39) vs. Intermediate/High (≥ 39)

#### 4.4 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E4112 Forms Completion Guidelines.

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## 5. Treatment Plan

### Step 1:

- The specifications for performance of MRI and management of findings identified on MRI will follow methods outlined below.
- Additional imaging and/or biopsies may be performed if indicated based on suspicious MRI findings (see Section [5.1](#) for management guidelines) .
- Proceed to step 2 after MRI performed, all additional biopsies completed, and clinical decision has been made regarding the planned surgical procedure (i.e., wide local excision or mastectomy or a delayed decision).

### Step 2:

- This will take place after the MRI has been performed in Step 1, additional imaging studies and biopsies performed if indicated, and the clinician/patient has made the decision as to whether the patient will proceed to wide local excision or mastectomy (see Section [5.2](#) for surgery guidelines).
- All patients treated with wide local excision as their final surgical procedure and have an adequate tumor free margin of at least 2 mm in step 2 who are found to have pure DCIS will have tissue obtained at time of surgery submitted for assessment of DCIS Score and for research studies. Tissue will be submitted directly to Genomic Health, Inc (GHI) and the DCIS Score will be returned to the site.
- For patients who have undergone mastectomy or do not meet Step 3 criteria for any other reason, surgical tissue will NOT be submitted to GHI, but rather to the CBPF. These patients will be managed as clinically indicated in accordance with NCCN guidelines, and will be followed for clinical outcomes
- Registration to step 3 may take place after the DCIS Score report has been received by the site/treating physician.

### Step 3:

- Only patients with pure DCIS treated with wide local excision and adequate negative margins ( $\geq 2$  mm) will be enrolled to step 3 after the results of the DCIS Score have been received by the site/treating physician.
- Patients will be assigned to radiation therapy based upon the DCIS Score: breast radiation should begin within 8 weeks of the final surgical procedure.
- Low DCIS Score ( $< 39$ ): No radiation therapy
- Intermediate-High DCIS Score ( $\geq 39$ ): Standard whole breast radiation (see Section [5.3](#))
- All patients with hormone receptor positive DCIS should be offered endocrine therapy for 5 years irrespective of the DCIS Score (see Section [5.4](#)). If patient declines despite physician recommendation, this must be documented.

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## 5.1 Imaging

### 5.1.1 Magnetic Resonance Site Qualification

Prior to patient enrollment, all participating scanners must be ACR Accredited for Breast MRI.

Sites meeting the ACR [Breast MRI Accreditation Program Requirements](#) are automatically eligible to participate, once

documentation of scanner accreditation has been submitted via CTSU.

All interpreting physicians must meet ACR Breast MRI Radiologist Training Requirements (see link to PDF embedded above).

#### 5.1.2 Magnetic Resonance Imaging (MRI) Procedures

MRI will be performed within 30 days after step 1 registration of study.

The bilateral breast MRI should be acquired on a 1.5T or 3.0T MRI scanner with a dedicated breast radiofrequency coil. The patient should be scanned in prone position with in-dwelling IV catheter for a single dose contrast agent injection (FDA-approved gadolinium-based contrast agent).

Exam MRI examination should contain, at a minimum, the following sequences:

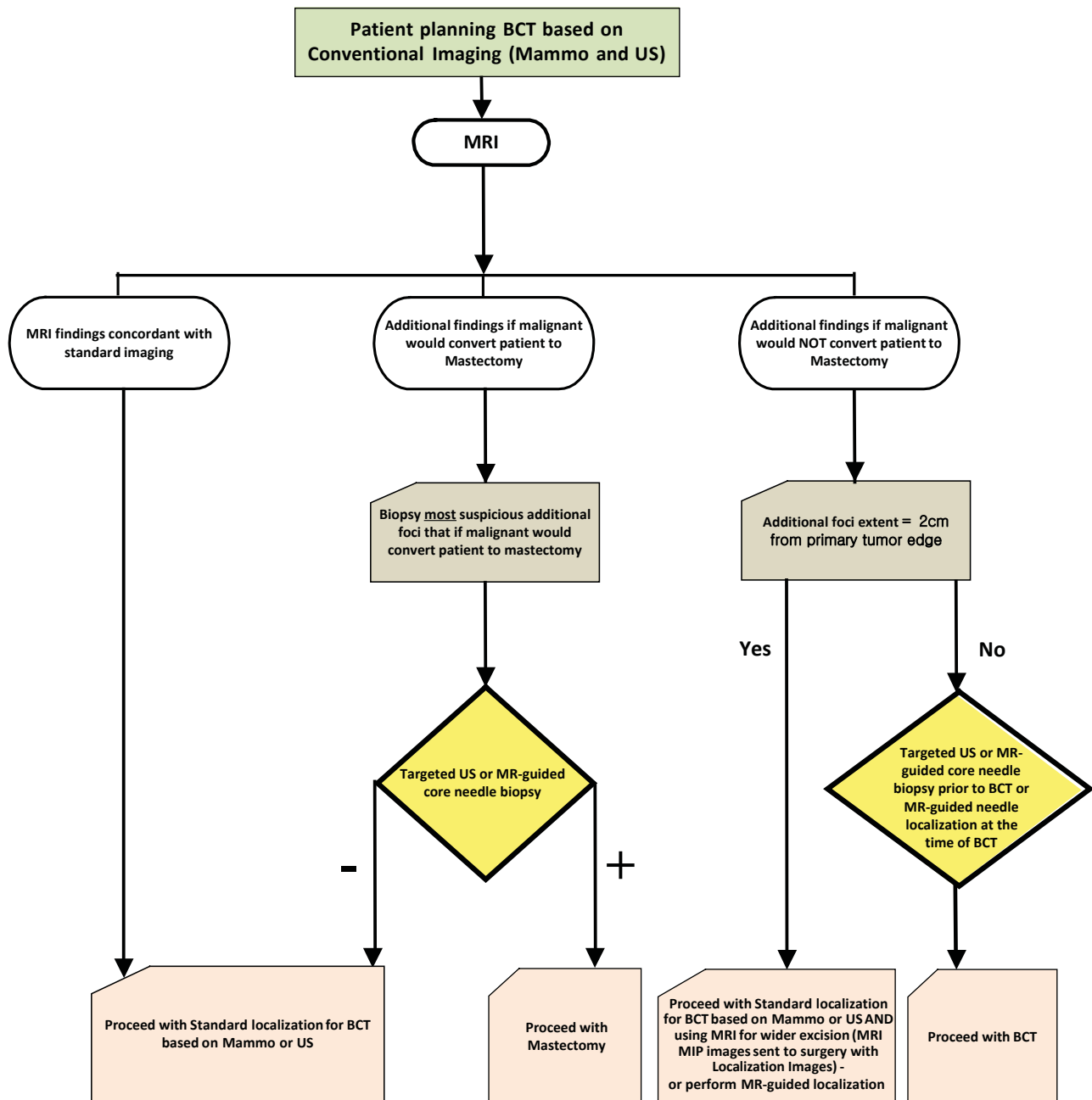
- a localization scan and a T2-weighted sequence followed by a contrast-enhanced T1-weighted series:
  - The T2-weighted sequence should be performed before contrast with fat saturation (4-5 mm slice thickness)
  - The T1-weighted sequence should be performed once pre-contrast and multiple times post-injection using identical sequence parameters; transmit and receive gain settings should remain constant for pre-contrast and post-contrast T1-weighted imaging
  - The in-plane pixel resolution, for the T1 weighted sequences, should be less than 1mm in both the phase and frequency directions.
  - Pre-contrast T1 images should be checked prior to contrast injection to confirm acceptable fat-suppression
  - Post-contrast imaging should continue for at least 8 minutes following contrast agent injection
  - Care should be taken to select the smallest FOV and slice coverage that completely encompasses both breasts and axilla

Contrast Medium: An intravenous catheter will be inserted in the arm or hand prior to the start of imaging. For the contrast-enhanced study following the T2-weighted, gadolinium contrast agent will be administered intravenously at a dose of 0.1 mmol/kg body weight and rate of 2 ml/second, followed by a 20 ml saline flush. Contrast injection will begin simultaneously with the start of data acquisition.

MRI Findings: The following algorithms will be utilized for reporting MRI findings and determining subsequent management. Site radiologist will use the study specific forms to document MRI results. These MRI results will be communicated to surgical team and documented. Each breast MRI finding will be reported using the following standard BIRADS guidelines.

BI-RADS® Category	Breast MRI Overall Final Assessment
1	Negative
2	Benign Finding(s)
3	Probably Benign Finding – Short-Interval Follow-Up Suggested
4	Suspicious Abnormality – Biopsy Should Be Considered
5	Highly Suggestive of Malignancy – Appropriate Action Should Be Taken
6	Known Biopsy-Proven Malignancy – Appropriate Action Should Be Taken

MRI Findings Management Flow Chart:





Disease Management: The size estimation of the primary DCIS on MRI should include all suspicious enhancement in the location of the known carcinoma that is similar in morphology, kinetics and in a continuing distribution.

1. If MRI findings match mammographic or US findings: Localization for surgical excision may be guided by either mammography or ultrasound.
2. If MRI shows cancer extent larger than on mammography or US but would not convert patient to mastectomy:
  - a. If primary tumor size on MRI is larger than expected, proceed with standard localization.
  - b. Furthest extent  $\leq$  2 cm from primary tumor: May proceed with localization based on mammography or US but should try to incorporate MRI findings during surgery
  - c. Furthest extent  $>$  2 cm from primary tumor: Second-look US or MR-guided core biopsy prior to surgery or MR-guided needle localization at the time of surgery. If second look ultrasound is negative, an MRI-guided core biopsy is required.
3. If MRI shows cancer extent that would convert patient to mastectomy:
  - a. MRI shows primary tumor size too large for BCS—biopsy to confirm extent of disease required prior to proceeding with mastectomy.
  - b. MRI shows additional foci of disease: Second-look US or MR-guided core biopsy prior to surgery of the most suspicious lesion that would confirm the need for mastectomy. If second look ultrasound is negative, an MRI-guided core biopsy is required.
4. BI-RADS 3 lesion management should be based on the institution's standard management.
5. Contralateral BI-RADS 4 and 5 lesions require biopsy.
  - a. If the lesion cannot be biopsied under ultrasound or Stereotactic mammographic guidance, an MR-guided biopsy will be required.
  - b. If no enhancement is seen on the day of MRI guided biopsy, then no further attempt at biopsy is required.
6. Management of pathologic findings from biopsy of BI-RADS 4 and 5 lesions:
  - a. If the results of biopsy are consistent with benign findings (adenosis, hyperplasia without atypia, etc) and :
    - i. the findings are concordant with imaging- no further intervention required

- ii. the findings are discordant with imaging- further sampling required, to include as appropriate surgical excision
- b. If the results of biopsy demonstrate increased risk lesions (ADH, ALH, LCIS), patients should be managed according to the standard practice at the institution with excision as appropriate

If MRI work-up and biopsy demonstrates contralateral breast cancer, and patient remains interested in BCT, then management should be based on same algorithms as for the index breast.

#### 5.1.2.1 Localization Guidelines (any modality)

Single wire: Total involvement  $\leq$  2 cm or solitary round lesions of any size. Bracketed localization: Non spherical tumor involvement  $>$  2cm in total size.

For all localizations: Mammogram and/or US localization images should be sent with the patient to the OR. For all MRI patients, MR maximum intensity projection (MIP) images should be provided in the axial and sagittal projections.

#### 5.1.2.2 Central Review of Imaging

All breast imaging (including mammography, ultrasound, and MRI) will be transferred and stored at the ACR Imaging Core Laboratory for central review.

##### **Image Submission to ACR Core Lab:**

TRIAD® is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. TRIAD can be installed on one or several computers of choice within the institutional "firewall" and on the institutional network; internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACR Imaging Core Laboratory image archive in Philadelphia.

Please use the link below to download TRIAD 4 software:

<https://triadinstall.acr.org/triadclient/>

For more information regarding your TRIAD installation, please contact:

[TRIAD-support@phila.acr.org](mailto:TRIAD-support@phila.acr.org) or call 703-390-9858

For this protocol, the following images will be collected and submitted to ACRIN:

- All clinical imaging exams performed as part of standard of care;
- MRIs performed as part of disease assessment and surgery evaluation;
- Any other imaging scans performed as part of the study.

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## 5.2 Surgery

5.2.1 For quality control purposes, surgery must be performed at the registering institution or at an affiliated site with IRB approval for the study.

Oncoplastic techniques can be utilized at the surgeon's discretion.

Orientation of the specimen in two dimensions is required. Specimen radiography is required.

Cavity shave margins, if taken, should be documented.

A margin negative excision, defined as at least 2 mm, is required.

For patients with margins < 2 mm after initial attempt at BCS, decision regarding re-excision vs. completion mastectomy will be made at surgeon's discretion.

Sentinel node biopsy may be performed as per the surgeon's discretion.

For mastectomy patients, nipple-sparing and skin-sparing techniques are acceptable. Reconstruction technique is by plastic surgery and patient choice.

## 5.3 Radiation Therapy

After breast conservation surgery, all patients with intermediate or high DCIS Scores will receive definitive breast irradiation. Definitive breast irradiation will initially include the whole breast, followed by a boost to the primary tumor bed. Nodal radiation is not allowed (except for incidental irradiation of the lower axilla as included in breast tangential fields).

CT based simulation and treatment planning is required. IMRT is allowed provided NCI guidelines are followed and all required Benchmarks have been completed (see below). For left sided radiation treatment, the volume of heart included within the radiation fields should be carefully assessed.

### 5.3.1 Credentialing Requirements

Centers using IMRT to treat patients on this protocol and not previously credentialed for use of IMRT in clinical trials must complete or update their Facility Questionnaire on the IROC Houston website and irradiate IROC Houston's IMRT head and neck phantom. Contact IROC Houston (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms. **Cases will be considered unevaluable if credentialing requirements have not been met at the time of final review.**

5.3.2 Equipment

Modality: All patients must be treated with a linear accelerator with nominal photon energy between 4 to 18MV (typically 6 MV). Electron therapy is permitted for supplemental boost to the primary tumor bed. Co-60 is not allowed.

Calibration: The calibration of therapy machines used in this protocol shall be verified by the IROC Houston QA Center(RPC).

5.3.3 Target Dose

5.3.3.1 Dose Definition

The absorbed dose is specified as Gy to muscle.

5.3.3.2 Total Dose

Allowable radiation dose fraction schedules are as follows:

a) Whole breast radiation initially to dose of 45 – 50.4 Gy using conventional fractions of 1.8 – 2.0 Gy per day. A boost dose to the tumor bed of 10 – 16 Gy using conventional fractions of 1.8 – 2.0 Gy is then added to bring the total dose to the tumor bed of 60 – 66 Gy.

(b) Accelerated whole breast radiation to a dose of 42.56 Gy using 2.66 Gy daily fractions, followed by a boost dose to the tumor bed of 10 Gy using 2 - 2.5 Gy daily fractions.

5.3.4 Time and Dose Considerations

5.3.4.1 Fractionation

Patients will receive one treatment per day, five days per week (Monday through Friday). All fields will be treated each day. At least two fractions must be given during the first week of treatment.

5.3.4.2 Interruptions

No special considerations need to be made for treatment delays of 1 week or less. If treatment is delayed more than 1 week but less than 2 weeks, notify the study chair. If treatment delays of more than two weeks occur, the patient will be considered off-study. The reason(s) for any break must be clearly recorded in the treatment record.

If there are any changes in the patient's status (i.e., early discontinuation of protocol treatment, delay in starting radiotherapy, or break in radiotherapy) these should be communicated in writing to IROC Rhode Island (QARC) by fax (401) 753-7601 or email to [DataSubmission@qarc.org](mailto:DataSubmission@qarc.org) with a copy to the Radiation Oncology Co-Chair.

5.3.5 Treatment Technique

CT- based WBI Treatment Plan

CT Planning

This includes dose distribution evaluated on a single central axis CT slice or multiple CT levels after tangents are established clinically (by fluoroscopy or CT) or target breast volume defined on CT and tangents and dose distribution based on dose-volume specification to breast and constraints for critical nontarget organs.

#### Target Breast Volumes

At the time of the simulation/CT, the clinical breast volume to be targeted in the tangent fields, with appropriate margin, is determined by the radiation oncologist.

#### Tangential Fields

The borders for the tangent fields are set so that they include the targeted clinical breast volume determined above plus a 1–2 cm margin. Examples of typical clinical boundaries for tangent fields are:

Medial: usually midsternum

Lateral: usually midaxillary line

Caudad: 1-2 cm below the inframammary line

Cephalad: commonly at the base of the clavicle heads or the sternal manubrium joint. These boundaries may need to be modified depending on the location of the lumpectomy cavity when it is visualized on CT. For CT-based planning, radiopaque markers are placed on these borders. It is recommended that techniques be applied that assure posterior or deep borders are co-planar in order to minimize exit into the lungs.

#### Constraints for critical non-target organs

The perpendicular distance from the chest wall to the posterior field edge can include **at maximum** 3 cm of lung tissue at any point along the length of the tangent on a film, or a digitally reconstructed radiograph (DRR) of the field. For left-sided cancers, field arrangements that minimize inclusion of the heart in the field should be used, and include no more than 1.5 cm of heart within the field.

#### Dose prescription and evaluation of isodose distribution

The dose will be prescribed at two thirds the perpendicular distance from the skin overlying the breast to the posterior border of the tangent field at mid-separation on the central axis slice. Wedges and compensators, may be used to keep the maximum dose within 15% of the prescription. The use of bolus is strongly discouraged.

#### Tissue Heterogeneity

Calculations shall take into account the effect of tissue heterogeneities.

#### Verification of the lumpectomy cavity coverage within the prescription isodose for the whole breast

- Verification process when the lumpectomy cavity can be identified on CT: Review of the dose distribution on CT slices that include the lumpectomy cavity is requested to verify that

the cavity, as demarcated by surgical clips or post operative seroma, is being covered by the prescription isodose. Acceptable WBI must demonstrate that the cavity is included in  $\geq 90\%$  isodose line. If not, changes in the field width, gantry, collimator, or selection of wedges or other adjustment must be done to achieve this. The radiation oncology facility is to submit one axial CT slice demonstrating that the identified lumpectomy cavity is covered by  $> 90\%$  isodose line and a DRR of the tangent field.

- Verification process when the lumpectomy cavity cannot be identified on CT: For some patients receiving WBI after chemotherapy, the lumpectomy cavity may have resolved and is no longer visible on the CT for radiation planning. In these instances, the postoperative CT submitted for registration to this study can be used. The radiation oncologist can identify on the postoperative registration CT a representative axial slice with the lumpectomy cavity present. A comparable anatomic axial slice from the radiation planning CT with the isodoses present should be found and verify that the  $\geq 90\%$  isodose line is covering the region where the lumpectomy cavity was previously visible. Both the CT slice from the registration scan demonstrating the cavity location and the radiation planning scan documenting the isodose coverage are to be submitted. A DRR of the WBI tangent fields should also be submitted.

### IMRT

#### Treatment Volumes

The definition of target volumes will be in accordance with ICRU Reports #50 and #62.

The target volume will include the entire breast and surgical cavity. The breast will be drawn as a CTV with a 5 mm PTV. Modifications of the PTV into pulmonary and cardiac tissue are permitted based on dose histogram guidelines listed below. PTV will be modified to maintain 3-5mm distance below the skin surface. The surgical cavity will be drawn as a CTV with a 5 mm PTV. The breast should be contoured from the inframammary fold to the inferior clavicular head. The surgical cavity should be contoured to include the entire excision cavity including a 1-2 cm extension beyond the image guided abnormality in all planes.

#### Dose Prescription

Dose shall be prescribed to an isodose surface that encompasses the PTV and that satisfies the dose uniformity requirements below.

#### Tissue Heterogeneity

Calculations shall take into account the effect of tissue heterogeneities.

#### Dose Uniformity

For IMRT the entire PTV shall be encompassed within the 95% isodose surface and no more than 10% of the PTV should receive more than 110% of the prescription dose, as evaluated by dose volume histogram.

#### Organs at Risk (OAR)

Dose constraints and guidelines should be as follows:

No more than 40% of the lung in the involved side should receive greater than 2000 cGy.

No more than 25% of the total lung volume should receive more than 2000 cGy.

The heart should be contoured as a single object from the apex to the aortic root (heart base). No more than 30% of the volume should receive more than 3000 cGy.

No more than 10% of the chest wall should receive more than 7000 cGy.

### 5.3.6 Dose Calculation and Reporting

#### Dose Volume Histograms

Dose volume histograms must include the CTV, PTV, and OARs as noted above. If IMRT is used, a DVH in absolute dose must also be submitted for “unspecified tissue,” i.e., tissue contained within the skin, but excluding the CTV, PTV and OARs.

#### IMRT Plan Verification

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient’s first treatment. Measurements in a QA phantom can suffice for a check as long as the plan’s fluence distributions can be recomputed for a phantom geometry.

#### Digital Submission

Submission of treatment plans in digital format (DICOM RT) is required. Digital data must include CT scans, structures, plan and dose files. Submission may be either by SFTP or CD. Instructions for data submission are on the IROC Rhode Island Web site at [www.irocri.garc.org](http://www.irocri.garc.org) under Digital Data. Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

### 5.3.7 QA Documentation

#### Post-Treatment Review

Within one week of the completion of radiation therapy, submit the following items:

#### Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.



- Dose volume histograms (DVH) of the GTV, spinal cord, chest wall, heart, esophagus, and liver. When using IMRT, a DVH shall be submitted for a category of tissue called “unspecified tissue.” This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH’s are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field, showing outlines of the target volumes only. Submission of DRR’s is not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

#### Supportive Data

- Postoperative CT in cases where the lumpectomy cavity is not visible on the treatment planning CT.
- A copy of the patient’s radiotherapy record including prescription, and the daily and cumulative doses to all required areas and specified dose points.
- RT-1 Dosimetry Summary Form (located at [www.irocri.qarc.org](http://www.irocri.qarc.org)).
- Copy of the ECOG-ACRIN E4112 Checklist for Submission of Radiation Oncology Quality Assurance Materials (located at [www.irocri.qarc.org](http://www.irocri.qarc.org)).

#### 5.3.8 Data Submission

Data that can not be submitted digitally may be forwarded to:

IROC Rhode Island QA Center  
640 George Washington Highway  
Building B, Suite 201  
Lincoln, RI 02865-4207  
Phone: (401) 753-7600  
Fax: (401) 753-7601

Instructions for digital data submission are available on the IROC Rhode Island website at <http://www.irocri.qarc.org/> (see Digital Data section).

E-mailed data can be sent to: [DataSubmission@QARC.org](mailto:DataSubmission@QARC.org)

#### Questions

Questions regarding the dose calculations or documentation should be directed to:

Physics/Dosimetry  
IROC Rhode Island QA Center  
640 George Washington Highway  
Building B, Suite 201  
Lincoln, RI 02865-4207  
Phone: (401) 753-7600  
Fax: (401) 753-7601



Questions regarding the radiotherapy section of this protocol should be directed to the Radiation Oncology Co-Chair.

#### 5.3.9 Definitions of Deviations in Protocol Performance

##### Prescription Dose

Variation Acceptable: The dose to the prescription isodose surface differs from that in the protocol by between 6% and 10%.

Deviation Unacceptable: The dose to the prescription isodose surface differs from that in the protocol by more than 10%.

##### Dose Uniformity

Variation Acceptable: Any part of the CTV receives less than 95% of the protocol dose, or more than 10% of the PTV receives more than 110% of the protocol dose.

##### Volume

Variation Acceptable: Margins less than specified or fields excessively large as deemed by the study.

Deviation Unacceptable: Transection of tumor or potentially tumor bearing area (CTV).

#### 5.4 Endocrine Therapy

All patient with estrogen receptor (ER) and/or progesterone receptor (PR) positive disease determined by standard immunohistochemistry must be offered a five year course of endocrine therapy because it has been shown to reduce the risk of ipsilateral breast recurrence and contralateral breast cancer. Patients should be treated in accordance with NCCN guidelines. Current options include tamoxifen (20 mg daily), or an aromatase inhibitor for patients who do not tolerate tamoxifen.

#### 5.5 Adverse Event Reporting Requirements

##### 5.5.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- Routine reporting: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- Expedited reporting: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

##### 5.5.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug (or imaging, surgery or radiation that are used as therapeutic interventions) in humans, whether or not considered drug related. Therefore, an AE can

be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is <i>clearly NOT related</i> to treatment.
Unlikely	The AE is <i>doubtfully related</i> to treatment.
Possible	The AE <i>may be related</i> to treatment.
Probable	The AE is <i>likely related</i> to treatment.
Definite	The AE is <i>clearly related</i> to treatment.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent (or imaging, surgery or radiation that are used as therapeutic interventions). An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol (Section [5.6](#)).

### 5.5.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at <http://ctep.cancer.gov>.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (1-800-FDA-1088)

An electronic report **MUST** be submitted immediately upon re-establishment of internet connection.

**Supporting and follow up data:** Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

**NCI Technical Help Desk:** For any technical questions or system problems regarding the use of the CTEP-AERS application, please

contact the NCI Technical Help Desk at [ncictephelp@ctep.nci.nih.gov](mailto:ncictephelp@ctep.nci.nih.gov) or by phone at 1-888-283-7457.

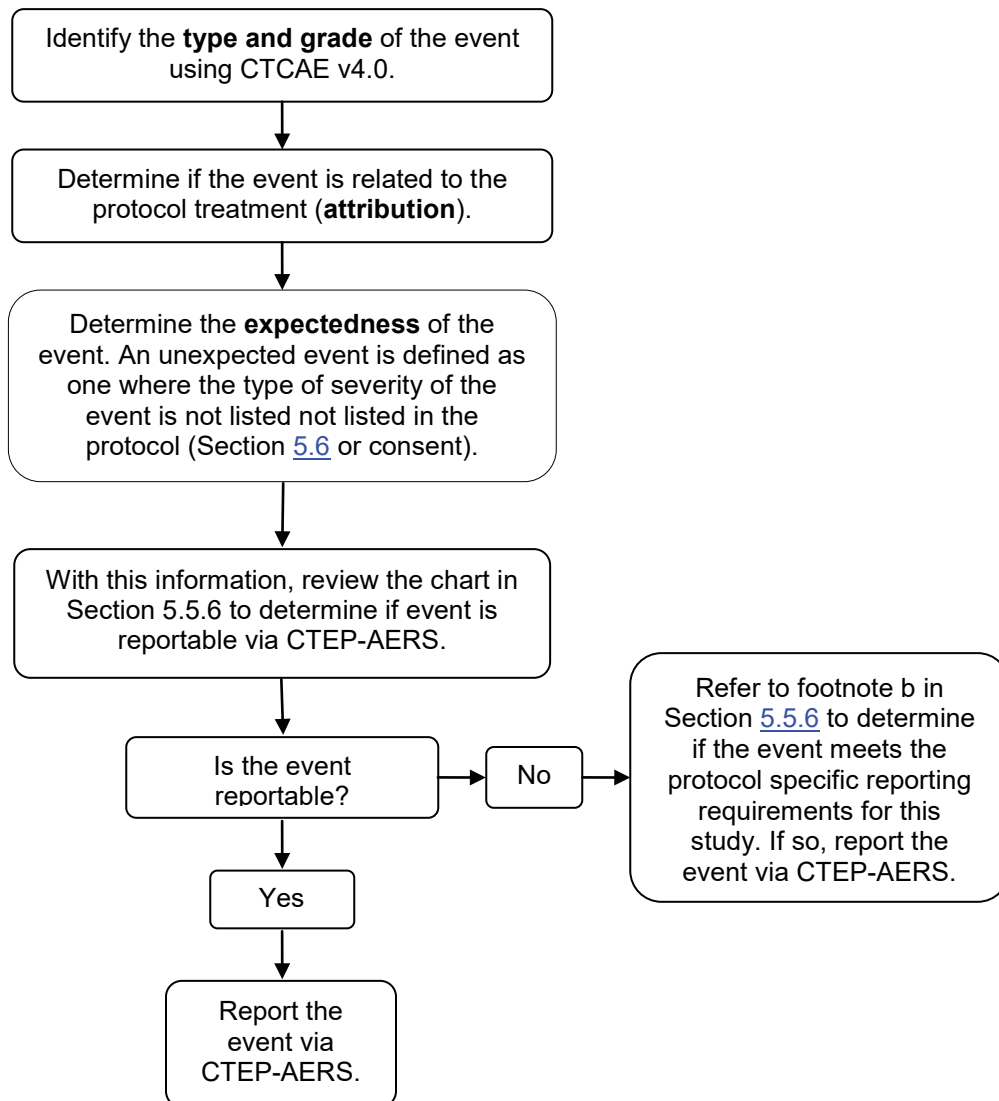
#### 5.5.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol E4112 and outline the specific expedited adverse event reporting requirements for study E4112.

5.5.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A, B, C, D, E and F



5.5.6 Expedited Reporting Requirements for Arms A, B, C, D, E and F on protocol E4112

Expedited reporting requirements for adverse events experienced by patients with commercial agents, imaging, surgery or radiation that are used as therapeutic interventions.					
Attribution	Grade 4		Grade 5 <sup>a</sup>		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	
<b>7 Calendar Days:</b> Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.					
<p><b>a</b> This includes all deaths within 30 days of the last day of treatment regardless of attribution.  <b>NOTE: Any death that occurs &gt; 30 days after the last day of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.</b></p> <p><b>b</b> Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:  <b>Serious Events:</b> Any event following treatment that results in <u>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</u> must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at <a href="mailto:aemd@tech-res.com">aemd@tech-res.com</a> or 301-897-7497. This will need to be discussed on a case-by-case basis.</p>					

5.5.7 Other recipients of adverse event reports and supplemental data

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.5.8 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at <http://ctep.cancer.gov>  
Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

**NOTE:** The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

**NOTE:** If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

## 5.6 Expected Adverse Events

**All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**

**All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (<http://ctep.cancer.gov>).**

### 5.6.1 MRI

- Anxiety/stress;
- Claustrophobia;
- Discomfort;
- Rare, but Serious: Injury associated with foreign bodies and the MR magnet; this is most likely to occur should the institution fail to ask or should a participant fail to inform the site of contraindications to MR use (e.g., presence of metallic or surgical implants or metal pieces in the body).

5.6.2 Contrast injection/IV Needle Placement

- Hematoma at the injection site
- Phlebitis;
- Bleeding;
- Infection;
- Bruising;
- Minor discomfort;
- Headache;
- Nausea;
- Vomiting;
- Hives;
- Temporary low blood pressure;
- Allergic-type reaction;
- Rare, but Serious: Kidney impairment, details follow.

Precautions should be exercised for patients with severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic-like or cardiovascular reactions, should be considered, especially for patients with a known sensitivity to gadolinium or history of asthma.

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease (glomerular filtration rate < 30 mL/min/1.73m<sup>2</sup>) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with gadolinium-based MR contrast agents.

NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels.

Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007 Available at:

[http://www.fda.gov/cder/drug/infopage/gcca/qa\\_200705.htm](http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm).

5.6.3 Surgery

Pain rating > 5 at more than 2 weeks post-op, edema in breast or arm, numbness at incision site and in arm more than 6 weeks post-op, cosmesis rating of poor or fair, bleeding/hematoma requiring surgical procedure to resolve, wound infection, flap necrosis, loss of tissue expander/ implant, failure of flap reconstruction, symptoms from injury to the brachial plexus.



5.6.4 Radiation Therapy

- Reddening, tanning, or peeling of the skin
- Mild pain
- Hair loss
- Tiredness
- Infection
- Thickening and numbness of the skin

5.7 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

5.8 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E4112 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.

5.9 Duration of Follow-up

All registered patients will be monitored for relapse and survival for 10 years from the date of surgery, as required by the Study Calendar. Patients will be followed a minimum of every 6 months for the first 5 years from diagnosis and a minimum of every 12 months during years 5-10. Patients will be monitored for local, regional and distant relapse, and vital status.

## 6. Measurement of Effect

The diagnosis of a first breast cancer recurrence or second primary can be made only when both the clinical and laboratory findings confirm the presence of disease. Suspicious findings do not constitute criteria for breast cancer recurrence. Any suspicion for recurrence of malignant disease in either breast must be proven by biopsy; suspicion of recurrence at non-breast sites must be biopsy-proven whenever possible. Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the enrolling physician.

### Follow-up of Patients with Disease Relapse after Surgery

Patients who develop local, regional, or distant relapse after surgery will be followed for local-regional control. Patients may be treated at the physician's discretion.

Patients who develop a second primary cancer (including cancer in the contralateral breast) after surgery will be followed for all study endpoints. Patients may be treated at the physician's discretion.

Local Recurrence: Local recurrence is defined as evidence of invasive or in situ breast cancer (except LCIS) in the ipsilateral breast or chest wall. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast or chest wall must have a biopsy of the suspicious lesion to confirm the diagnosis.

Given the challenges of defining a reliable definition of local recurrence vs. new primary, all recurrences in the ipsilateral breast will be considered in the analysis of the primary endpoint. This definition of local recurrence is also in keeping with a hypothesis of this trial, namely that MRI will reduce local recurrence events by detecting clinically relevant occult disease in other quadrants of the breast.

Regional Recurrence: Regional recurrence is defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular, and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after surgery. This can be confirmed with positive cytology or histologic biopsy.

Distant Recurrence: Distant recurrence is evidence of tumor in any areas of the body, with the exception of those defined as local or regional recurrence above.

Second Primary Breast Cancer: A second primary breast cancer is evidence of invasive or in situ breast cancer (except LCIS) in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed histologically.

Second Primary Cancer (non-breast): Any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma of the cervix, or colon carcinoma in situ will be considered an event in the analysis of disease-free survival. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

### Patient-Reported Outcomes and Quality of Life:

Quality of life (QOL) will be measured using the PROMIS10 instrument, a continuous variable measuring global physical and mental function by summing responses across the 10 items.

Decision satisfaction will be measured using the four item scale initially developed by Holmes-Rovner and adapted from Katz et al. Items include "I am satisfied that I was

adequately informed about the issues important to the decision about what kind of surgery to have."

Decision autonomy preference and perceived decision involvement will be assessed using the five-point Control Preferences Scale recoded to a three-category scale by Katz et al (surgeon-based decision, shared decision, patient-based).

Radiation concerns will be measured with two items ("How important was it that the type of surgery you had would allow you to avoid going back and forth to radiation treatment?" and "How important was it that the type of surgery you had would allow you to avoid exposing yourself to radiation?")

Fear of recurrence will be measured with three items ("How important was it that the type of surgery you had would allow you to avoid the possibility of a second surgery to remove more cancer? How important was it that the type of surgery you had would reduce the chances of the cancer coming back? How important was it that the type of surgery you had would keep you from worrying about the cancer coming back?")

Body image and sexual function concerns will be measured with three items ("How important was it that the type of surgery you had would not interfere with your sex life in the long term? How important was it that the type of surgery you had would not make you feel bad about your body, like it was disfigured? How important was it that the type of surgery you had would allow you to feel feminine?")

Cancer worry will be measured using the three-item subscale from the Assessment of Survivor Concerns

The importance of the patient's spouse (or partner), family and friends on treatment decision will be assessed using three items (e.g. "How important was your husband's or partner's opinion in the decision about which surgical treatment to have for your DCIS?") on a 5-point scale

Diagnostic testing burden, a continuous variable measuring physical and mental burden before, during and after testing, will be measured using the TMI summing the responses across the 7 items.

## 7. Study Parameters

### 7.1 Therapeutic Parameters

	Prior to Step 1	Prior to Surgery	Surgery	Post-Op Visits <sup>1</sup>	Follow-up <sup>2</sup>
History and Physical	X <sup>3</sup>				
Height, Weight, and ECOG Performance Status	X <sup>3</sup>				
Visit to monitor for ipsilateral breast event (IBE)					X <sup>2</sup>
Serum creatinine	X <sup>3</sup>				
Pregnancy test (for women of childbearing potential)	X <sup>3</sup>				
Mammogram (+/- ultrasound) <sup>5</sup>	X <sup>4,5</sup>				X <sup>2</sup>
Core needle biopsy documenting DCIS	X				
MRI		X <sup>5</sup>			
FFPE Tissue Submission <sup>6</sup>	X		X		
Patient and Surgeon Surveys	See Section <a href="#">7.2</a>				

1. As clinically indicated; all data should be submitted for all post-operative visits.
2. Annually for 10 years from study entry. Monitoring for an IBE studies are to be performed per standard of care, which includes an annual breast examination and annual bilateral diagnostic mammography for those treated with WLE.
3. Within 28 days prior to registration to Step 1
4. A diagnostic mammogram of the affected breast is required within 3 months prior to registration, and a two-view (full view CC and a full view MLO) mammogram of both breasts within 6 months of registration (if the patient has only one breast, a unilateral exam of the intact breast is required).
5. MRI should be performed within 30 days after registration. All imaging studies, including ultrasound and any additional imaging which may have resulted from performance of the MRI, are to be submitted to ACRIN as outlined in Section [5.1.2.2](#).
6. MANDATORY - See Section [9](#). Baseline diagnostic materials and surgical tissue samples must be submitted for central evaluation from all patients. Surgical tissue will be submitted either: (a) for determination of DCIS Score from patients who have DCIS only who have undergone WLE, or (b) To CBPF from all other patients. If surgical specimen is found to have no disease, pre-trial diagnostic material may be submitted instead.

7.2 Patient and Surgeon Survey Schedule

	Baseline <sup>1</sup>	Prior to Surgery <sup>2</sup>	First Post-Op Visit	12 month post-op	24 month post-op
Patient Surveys: # items, time	42 items, 9 mins	15 items, 3 mins	47 items, 10 mins	28 items, 6 mins	28 items, 6 mins
Surgeon Decision Making					
Surgeon decision making survey		X			
Patient Decision Making					
Decision Autonomy Preference	X				
Treatment Goals and Concerns (BCS-DQI)	X		X		
Preferred Treatment	X	X			
Perceived Decision Involvement		X			
Decision Process (BCS-DQI)		X			
Decision Confidence		X			
Decision Satisfaction			X	X	X
Treatment Received			X		
DCIS Knowledge (adapted from BCS-DQI)			X		
Perception of being informed		X			
Quality of Life and Patient Reported Outcomes					
PROMIS10 (Global Health QOL)	X		X	X	X
Testing Morbidities Index	X	X			
Assessment of Survivor Concerns (Risk Perception)	X		X	X	X
FACT-B (Disease-specific QOL)	X		X	X	X

1. Survey to be performed up to 2 weeks after Step 1 registration and prior to the MRI
2. Up to 2-5 days after pre-surgical consultation and before surgery. Surgeon survey may be done up to 7 days after the pre-surgical consultation.

## 8. Statistical Considerations

### 8.1 Endpoints

The primary endpoint is conversion to mastectomy among patients in the study cohort undergoing a pre-operative MRI examination.

Secondary endpoints include

- Ipsilateral breast event, in situ and invasive (IBE).
- Re-operation rate following attempted wide local excision (WLE). This rate will be computed as the number of women for whom WLE was indicated by MRI who had a re-operation (including mastectomy) divided by the number of women for whom WLE was indicated by MRI. Note that women who proceed directly to mastectomy as the result of MRI findings will not be included in the denominator (or numerator).
- False positive rate for MRI detection of multiple disease foci. All biopsies prompted by MRI will be included, regardless of whether they are performed with MRI or ultrasound guidance.
- Patient-reported quality of life
- Patient-reported decision satisfaction
- Patient-reported diagnostic testing burden of bilateral mammogram, MRI, and biopsies

### 8.2 Study Design

Prior evidence suggests that about 8-12% of patients initially considered candidates for breast conservation surgery based on mammographic imaging will require mastectomy<sup>33, 43</sup>, and the use of MRI in addition to mammography increases the likelihood of requiring a mastectomy by about 1.5-fold.<sup>24</sup> Therefore, we assume that about 10% of patients enrolled on Step 1 would have required a mastectomy if they had never had an MRI, all of whom would have had the mastectomy after an initial attempt at wide excision. In addition, we assume that the integration of MRI may increase the likelihood of requiring mastectomy by about 1.5-fold, or to about 15%. Moreover, we anticipate that more mastectomies done after MRI and before wide local excision may result in fewer mastectomies done after wide local excision, and assume a 50:50 distribution (7.5% before wide excision, 7.5% after wide local excision). The following table shows required sample sizes to achieve a Wilson 95% confidence interval of expected length no larger than 8%. A sample size of 350 participants, will be sufficient to ensure an interval of expected length 0.08 if the actual proportion is, conservatively, as high as 16% for the end point of interest, and we assume that complete data will be available on at least 95% of participants. Computations for this table were performed using the PASS11 (32) software.

Sample Size	Width of 95% CI	True Proportion	Lower limit of 95% CI	Upper limit of 95% CI	Width if true P=0.5
286	0.070	0.100	0.070	0.140	0.115
310	0.070	0.110	0.080	0.150	0.111
333	0.070	0.120	0.089	0.159	0.107
356	0.070	0.130	0.099	0.169	0.103
378	0.070	0.140	0.109	0.179	0.100
400	0.070	0.150	0.118	0.188	0.098
421	0.070	0.160	0.128	0.198	0.095
219	0.080	0.100	0.067	0.147	0.131
238	0.080	0.110	0.076	0.156	0.126
255	0.080	0.120	0.086	0.166	0.122
273	0.080	0.130	0.095	0.175	0.118
290	0.080	0.140	0.105	0.185	0.114
306	0.080	0.150	0.114	0.194	0.111
323	0.080	0.160	0.124	0.204	0.108

8.3 Analysis plan for primary and secondary objectives

8.3.1 Primary Objective

*To estimate the proportion of patients with DCIS diagnosed on core needle biopsy judged to be breast conservation candidates based upon standard imaging (mammography +/- sonography) and physical examination (a) who convert to mastectomy in step 1 based on MRI findings, and (b) who have a mastectomy as the final surgical procedure in step 2.*

We will estimate the overall proportion of patients who have mastectomy in Steps 1 and 2, as well as the individual proportions at each step.

8.4 Secondary Objectives

8.4.1 *To assess the relation between baseline clinical covariates (e.g., tumor grade, necrosis, histologic type, mammographic lesion size), MRI morphologic and kinetic features, and the DCIS score.*

We will assess correlation and concordance between DCIS score and MRI results (morphologic and kinetic features and BI-RADS interpretation) over the entire study cohort and in subsets of interest as defined by baseline clinical covariates. In these analyses, variables will be used in their original form (continuous or discrete) as previously established in the literature. Measures appropriate for continuous or discrete scales will be reported.

8.4.2 *To assess the diagnostic accuracy of MRI in extent of disease evaluation in patients with DCIS.*

The primary analysis for this aim will address the ability of MRI to detect the presence of significant disease beyond the known biopsy proven cancer. The reader's suspicion about the presence of such



disease will be assessed using the BI-RADS scale for MRI, as showing in Section 5.1.2. For analysis purposes, BI-RADS scores of 4 or 5 will be considered as “positive” test results while all other scores will be considered as “negative” test results. The reference standard determination of whether significant disease beyond the known cancer is present or absent will be made on the basis of information from the pathologic examination of surgical specimens combined with clinical follow-up for 1 year. The test results and reference information will be used to estimate the sensitivity and specificity of MRI for the detection of the presence of significant disease beyond the known cancer. Wilson confidence intervals will be used to quantify uncertainty of the estimates. In a secondary analysis we will examine the impact of patient characteristics and other covariates on the sensitivity and specificity and on the positive and negative predictive value MRI, using logistic regression modeling.

- 8.4.3 *To estimate the proportion of patients who require re-operation because of inadequate excision after MRI.*

We will identify all patients who underwent reoperation following inadequate excision and estimate the proportion of such patients in the study cohort. A two-sided 95% Wilson confidence interval will also be derived.

- 8.4.4 *To estimate the proportion of patients who proceed to mastectomy after an initial attempt at wide local excision because of either inadequate tumor-free margins (< 2mm), or other reasons.*

We will identify all patients converting to mastectomy following BCS and estimate the proportion of such patients in the study cohort. A two-sided 95% Wilson confidence interval will also be derived. In addition to the overall probability of conversion in this cohort we will also report estimates stratified by the reason for the conversion.

- 8.4.5 *To estimate the 5-year and 10-year ipsilateral breast event (in situ and invasive) rate (IBE) among women with DCIS assessed with MRI preoperatively and treated with wide local excision without radiation therapy (if there is a low DCIS score) or with radiation therapy (if there is an intermediate-high DCIS score).*

We project that about 250 patients will reach the RT/noRT decision node in this trial. Based on prior information about the distribution of DCIS scores in similar populations we expect that about 50% of the patients will be assigned to be treated with RT and the rest will not be treated with RT. For each of the two groups we will derive Kaplan-Meier curves for the time to ipsilateral breast event and will develop point estimates and 95% two-sided confidence intervals for the 5-year and 10-year IBE rates.

- 8.4.6 *To estimate the proportion of women with DCIS who receive treatment that is concordant with their treatment goals and concerns.*

For each participant, concordance will be determined using the method described by Sepucha et al.<sup>58</sup> The proportion of patients with concordant care will be calculated and a 95% Wilson confidence interval will also be derived.

- 8.4.7 To estimate the proportion of women with DCIS whose decision autonomy preference was concordant with perceived level of decision involvement
- For this analysis, we will define concordance as an exact match between decision autonomy preference (patient-based, shared, surgeon-based) and perceived level of decision involvement (patient-based, shared, surgeon-based) as assessed by the Control Preferences Scale, reduced to three categories. The proportion of patients with concordance will be calculated for the sample. In addition, the degree of concordance over the group will be determined using kappa analysis.
- 8.4.8 *To assess decision quality using the knowledge score and the decision process score.*
- To calculate knowledge score, a point for each correct answer on the knowledge questionnaire will be assigned, with missing responses receiving 0 points. A total score will be calculated for all patients who complete at least half of the items and scaled from 0-100%. To calculate a decision process score, a point will be assigned for each “yes” or “a lot/some” response. The sum will be scaled from 0-100%.
- 8.4.9 To assess the role of concordance between decision autonomy preference and perceived level of decision involvement, knowledge and decision process scores as predictors of decision satisfaction at the first post-operative visit.
- We will use linear regression modeling in which the response variable will be decision satisfaction. The independent variables will be the indicator of concordance between decision autonomy preference and perceived level of decision involvement, the knowledge score and the decision process score. Two-way interactions between predictors will also be examined.
- 8.4.10 *To assess the relationship of patient-reported outcomes and disease-specific covariates, and quality of life after treatment.*
- We will use linear regression modeling in which the response variable will be quality of life at 12 months after treatment, as measured by PROMIS10 global health measure. The independent variables will include covariates describing patient decision involvement (such as the decision autonomy preference scale) and treatment concerns (as measured via the 7-item questionnaire) as well as disease-specific covariates (such as stage, MRI results, treatment received). The above analysis will be repeated using quality of life at 24 months after treatment as the response variable.
- 8.4.11 *To assess the role of disease status, diagnostic test results and surgeon recommendation as predictors of treatment received.*
- We will use logistic regression modeling in which the response variable will be the indicator of conversion to mastectomy (vs lumpectomy). The independent variables will include covariates describing disease status at baseline, MRI results, surgeon recommendation, patient decision involvement (such as the decision

autonomy preference scale) and treatment concerns (as measured via the 7-item questionnaire). Separate analyses will be performed for conversion to mastectomy directly post MRI and conversion to mastectomy following BCS as the response variable.

8.4.12 *To compare the patient-reported diagnostic testing burden of bilateral mammography and MRI as measured by TMI*

We will use a Wilcoxon signed rank test to compare TMI scores for mammography and MRI. In a secondary analysis we will use regression modeling to examine the effect of patient characteristics on the patient's perception of diagnostic test burden for the two modalities.

8.5 Gender and Ethnicity Numbers

Based on previous data from ACRIN 6694 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender			Total
	Females	Males	Unknown	
Hispanic or Latino	4	0	0	4
Not Hispanic or Latino	346	0	0	346

Unknown	0	0	0	0
<b>Ethnic Category: Total of all subjects*</b>	<b>350</b>	<b>0</b>	<b>0</b>	<b>350</b>
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	4	0	0	4
Black or African American	15	0	0	15
Native Hawaiian or other Pacific Islander	0	0	0	0
White	331			331
More than one race	0			0
Unknown	0			0
<b>Racial Category: Total of all subjects*</b>	<b>350</b>			<b>350</b>

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

## 9. Sample Submissions

The submission of pre-trial diagnostic materials and surgical tumor from all patients is MANDATORY and will be used for the studies outlined in Section [10](#). This section provides guidelines for the submission of biological materials as follows:

- Section [9.1](#): SUBMISSIONS TO GENOMIC HEALTH, INC.(GHI) - From patients who have DCIS only, have undergone wide local excision with surgical margins  $\geq$  2mm submission of surgical tissue for the OncotypeDX DCIS Score Assay.
- Section [9.2](#): Reporting of DCIS Score results to the ECOG-ACRIN Operations Office – Boston. This is required from all patients for whom tissue is submitted to GHI as outlined in Section [9.1](#) and must be submitted prior to registration to step 3. For patients who, for whatever reason, will not proceed to step 3 registration, reports are to be submitted to ECOG-ACRIN within 2 weeks of receipt of DCIS Score report from Genomic Health Inc.
- Section [9.3](#): SUBMISSIONS TO THE CBPF –
  - Pre-trial diagnostic tissue: Mandatory from all patients
  - Surgical tissue: Mandatory from patients diagnosed with invasive (including microinvasive) disease , margins < 2mm,
  - or who have undergone mastectomy, submission of surgical tumor tissue to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

**NOTE:** For patients with invasive disease who undergo BCT, any request for the Oncotype DX score for invasive disease would be performed at the physician's discretion as part of the patients standard care and outside of the realm of this trial and thus, if not covered by insurance, the patient would be held responsible for additional costs.

**NOTE to CRAs and Pathologists:** Additional guidelines for the requested pathology submissions (tissue and related reports) are found in [Appendix I](#).

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**Submission Summary:**

Identify all submitted materials with ECOG-ACRIN protocol #, ECOG-ACRIN E4112 patient ID#, and, if applicable, the GHI requisition number/bar code from the kit. All samples must be logged and tracked via the ECOG-ACRIN Sample tracking system (STS) [see Section 9.4].

Patients	Material	Report/Forms	Ship to:
<ul style="list-style-type: none"> <li>• DCIS only</li> <li>• wide local excision</li> <li>• surgical margins <math>\geq</math> 2mm</li> </ul>	Surgical Tissue <sup>1</sup>	<ul style="list-style-type: none"> <li>• Oncotype DX Requisition Form (example in <a href="#">Appendix II</a>), select Breast Cancer Assay for Ductal Carcinoma in Situ</li> </ul> <p><b>NOTE:</b> Pathology reports to be faxed to ECOG CBPF. Label with E4112, protocol specific patient ID#, and the GHI requisition number</p> <p>OncotypeDX Patient Report to be uploaded</p>	<p>Customer Service <b>Genomic Health, Inc.</b> 301 Penobscot Drive Redwood City, CA 94063 Telephone: 866-662-6897</p>
All patients registered to Step 1	Pre-trial diagnostic tissue samples	<ul style="list-style-type: none"> <li>• Pathology Report with immunologic studies, if available</li> </ul>	<p><b>ECOG-ACRIN Central Biorepository and Pathology Facility</b> MD Anderson Cancer Center Department of Pathology, Unit 085 Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586 1515 Holcombe Blvd Houston, TX 77030 Phone: Toll Free 1-844-744-2420 <b>Fax forms to:</b> 713-563-6506</p>
<ul style="list-style-type: none"> <li>• Mastectomy is final procedure,</li> <li>or</li> <li>• Margin &lt; 2mm after WLE,</li> <li>or</li> <li>• Invasive or micro-invasive carcinoma present irrespective of procedure</li> </ul>	Surgical Tissue	<ul style="list-style-type: none"> <li>• Pathology Report with immunologic studies, if available</li> <li>• Surgical Report</li> <li>• STS-generated Shipping Manifest</li> </ul>	
<p>All patients</p> <ul style="list-style-type: none"> <li>• Following Step 1 registration</li> <li>• Following Surgery</li> </ul>		Pathology and/or Surgical Reports	upload via Medidata Rave™

1. If slides only are submitted, additional tissue is to be submitted to the CBPF as outlined in Section 9.3. Copies of the pathology report, surgical reports are to be submitted to the CBPF, labeled with E4112, patient ID#, and the GHI requisition number.

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## 9.1 Surgical Tissue Submissions to GHI

### **MANDATORY from all patients who have**

- **DCIS ONLY**
- **Have undergone wide local excision as their final surgical procedure**
- **≥ 2mm surgical margins**

This section outlines the submission of surgical tissue for the *OncotypeDX* DCIS Score Assay. Surgical tissue from patients who do not meet the criteria above must be submitted to the CBPF as indicated in Section [9.3](#) as the DCIS Score is not a validated assessment for that patient population.

#### 9.1.1 Ordering the *OncotypeDX* Specimen Kit

Prior to pre-registration, contact Genomic Health Customer Service (866-662-6897) and request the “*Oncotype* Specimen Kit”.

The kit will be shipped overnight and will contain instructions, a shipping kit (includes cryotubes and slide cassette), a mailer, and a requisition form containing barcode labels to place on the submitted materials. One *Oncotype* Specimen Kit and Requisition form should be completed per patient.

**DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.**

Summary submission guidelines, including a draft requisition form, are provided in Appendices I and II.

#### 9.1.2 Sample and Form Submissions

Sample submissions to GHI must be logged into the ECOG-ACRIN Sample Tracking System (STS) to allow tracking of sample submissions on the E4112 trial. Participating sites will correspond directly with GHI, not via STS. The CBPF will log receipt of materials from GHI into the STS. Receipt logging will not occur in real time. For more information on the STS, see Section [9.4](#).

- Submit the following utilizing the kit and forms provided by GHI:
- Completed requisition form and STS manifest
- Surgical DCIS Tumor Tissue Block (place barcode label on back of cassette). If DCIS is not present in surgical tissue, pre trial diagnostic material is to be submitted for the assessment.

OR

- Fifteen (15) 5 um serial unstained slides, oriented similarly and air dried. Label each slide with barcode and number in the order they were cut.

**NOTE:** Proper sterile sectioning technique **MUST** be followed. Failure to follow sterile technique can affect testing and delay results. If sterile technique cannot be followed, submission of a tumor block is strongly recommended. If only slides are submitted, additional materials are to be submitted to the CBPF per Section [9.3](#)

9.1.3 Notification of Results

Genomic Health will notify the institution of the DCIS Score (DS) via the mechanism selected on the *OncotypeDX* Requisition Form within 14 days of receipt of the tissue by Genomic Health. If you do not receive a report within 14 days, contact GHI Customer Service at 866-662-6897. Genomic Health will not distribute reports directly to the ECOG-ACRIN Operations Office – Boston.

9.2 Submission of the DCIS Score Report via RAVE

**MANDATORY from all patients who have surgical tissue submitted for the *OncotypeDX* Breast Cancer Assay for Ductal Carcinoma in Situ**

Prior to registration to Step 3, the institution must upload a redacted copy of the first page of the “*OncotypeDX* Patient Report” to the ‘DCIS Score’ eCRF in Rave. After submission of the *OncotypeDX* Patient Report, the institution may proceed to register the patient to Step 3.

For patients who will not proceed to step 3 registration, for whatever reason, the redacted “*OncotypeDX* Patient Report” is to be uploaded to the ‘DCIS Score’ eCRF in Rave.

9.3 Submissions of Samples to the CBPF

If the required materials cannot be submitted, the institution is to contact Adekunle Raji at the CBPF ([ARaji@mdanderson.org](mailto:ARaji@mdanderson.org)) to discuss alternative submission requirements.

9.3.1 Tissue Submission Requirements

A copy of the patient’s pathology and surgical reports, as appropriate, must be submitted with the tissue samples.

A. Pre-Trial Diagnostic Tissue – MANDATORY from all patients

At least one DCIS representative diagnostic H&E slide

Submit within 4 weeks following registration to step 1.

**NOTE:** Additional tissue from consenting patients is requested for research.

B. Surgical Tumor Tissue – MANDATORY from all patients who undergo mastectomy, or are diagnosed with invasive disease, or have margin status < 2mm

Formalin paraffin-embedded DCIS/tumor tissue block. If tumor is not present in surgical tissue, pre trial diagnostic material is to be submitted.

Submit within 4 weeks following surgery.

C. Surgical Tumor Tissue – From all patients from whom only slides were submitted to Genomic Health, Inc for the *OncotypeDX* assessment.

Formalin paraffin-embedded DCIS/tumor tissue block

Submit within 4 weeks following surgery.



**NOTE:** If an institution will not allow block release, the following is requested:

- H&E slides, cut before and after those below are processed.
- Fifteen (15) 5 um serial unstained slides, oriented similarly and air dried. Label each slide with barcode and number in the order they were cut.
- Two (2) 4mm core punches.

### 9.3.2 Shipping Guidelines

Fixed paraffin-embedded tissue is to be submitted at ambient or with cool pack during warm weather.

It is required that the tissue be shipped using a service which has tracking capabilities.

Shipping manifest generated from the ECOG-ACRIN STS system must accompany the samples.

Ship to:

MD Anderson Cancer Center  
Department of Pathology  
Tissue Qualification Laboratory for ECOG-ACRIN Room G1.3586  
ECOG-ACRIN Central Biorepository and Pathology Facility  
1515 Holcombe Blvd  
Houston, TX 77030

Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)

Fax: 713-563-6506

Email: [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org)

## 9.4 ECOG-ACRIN Sample Tracking System

It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking <https://webapps.ecog.org/Tst>

Important: Any case reimbursements associated with specimen submissions will not be credited if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link:

<http://www.ecog.org/general/stsinfo.html>. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to [ecog.tst@jimmy.harvard.edu](mailto:ecog.tst@jimmy.harvard.edu)

### Study Specific Notes

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Laboratory on the submission form:

- ECOG-ACRIN Central Biorepository and Pathology Facility
- Genomic Health Inc

Retroactively enter all specimen collection and shipping information when STS is available.

Note that GHI will not indicate sample receipt within STS. Tracking of receipt of tissue will be via the submission of the OncotypeDX Patient Report to the ECOG-ACRIN Operations Office – Boston.

### 9.5 Use of Specimens in Research

Tissue routed to the CBPF from patients who have undergone mastectomy or are diagnosed with invasive disease, samples will be routed to GHI who will perform the Oncotype DX Breast Cancer Assay. These evaluations are for research purposes only, results will be reported directly to ECOG-ACRIN only. No reports or results will be reported to the treating sites from these assessments.

Samples submitted and derivatives of the submitted materials will be retained at the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies per patient consent. Residual materials from any laboratory studies, including the DCIS Score Assay by Genomic Health, will also be returned to the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

Blocks from patients who have consented to banking will be available for purposes of individual patient management on specific written request. Submit requests to the CBPF.

### 9.6 Lab Data Transfer Guidelines

Data from any other laboratory study utilizing these materials will be submitted electronically to the ECOG-ACRIN Operations Office – Boston by the central laboratory(ies) on a pre-arranged schedule. Electronic submissions should be via secure FTP transmission.

### 9.7 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used will be submitted to the ECOG-ACRIN Operations Office – Boston upon request. Inventories will be submitted electronically by any laboratory holding and/or using any specimens associated with this study. All other correspondence should be addressed to the attention of the Translational Science Team.

## 10. Biomarker and Central Review Assessment

This section outlines the central reviews and biomarker studies to be conducted on samples submitted from patients participating in E4112.

### 10.1 Central Confirmation of DCIS

Central review will be performed to confirm the diagnosis of DCIS. For the central review, one slide from the original diagnostic biopsy will be analyzed. If a diagnostic biopsy sample is not available, an slide from the surgery will be utilized for the review. The slides will be collated at the CBPF and will be shipped in a batched manner to Dr Badve (Indiana University) for central review.

The review will consist of verification of the diagnosis of DCIS and grading of the DCIS using histological criteria. More specifically, the review will exclude the presence of invasive carcinoma and collate histological data for correlating with outcomes and the DCIS Score. Data with regards to excision margin status will be obtained from the reports and this will not be confirmed centrally.

### 10.2 Oncotype DX for DCIS Score Assay

The Oncotype DX Breast Cancer Assay will be performed on tissue submitted from all patients participating on E4112 as follows:

- From all patients who have DCIS ONLY and have undergone wide local excision as their final surgical procedure, surgical tumor tissue will be submitted directly to GHI for the determination of the DCIS Score as a component of routine care. This will include only patients with pure DCIS who have had wide local excision as their final surgical procedure and adequate margins ( $\geq 2$  mm). The DCIS Score must be reported to the ECOG-ACRIN Operations Office – Boston as outlined in Section 9.2 and will be used to assign whether radiation therapy is indicated at time of registration to step 3.
- For all other patients, tissues will be sent to the CBPF as outlined in Section 9.3, and the DCIS Score will be performed as a research test that will inform some of the secondary objectives (Section 2.2.1). The Oncotype DX DCIS assay is not validated and not billable to insurance for this patient population and no DCIS Score report will be returned to the site for these patients.

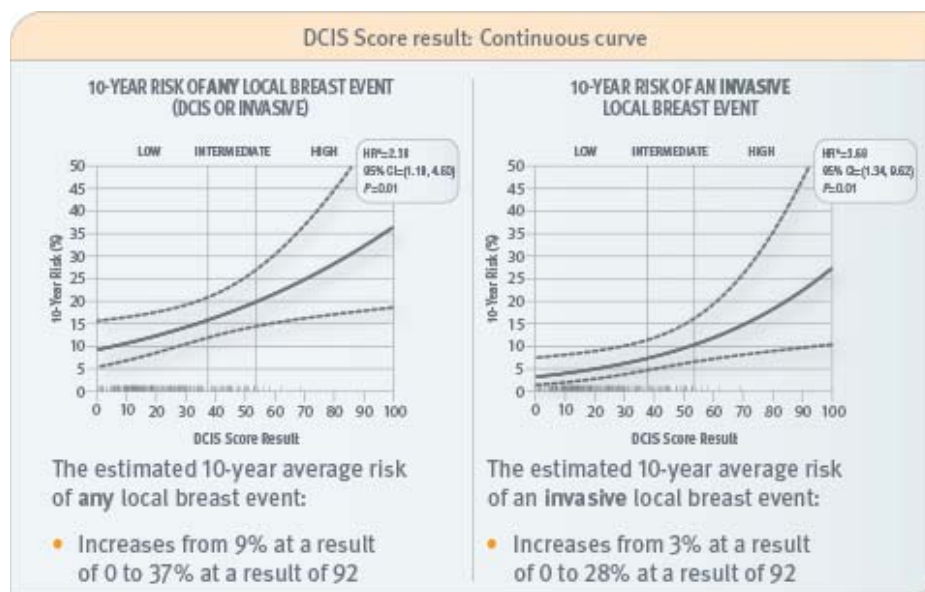
The Oncotype DX<sup>®</sup> Breast Cancer Assay analyses RNA derived from fixed paraffin-embedded tissue using RT-PCR. The quantitative RT-PCR assay is capable of quantifying up to 400 genes from small RNA fragments (50–250 bp) extracted from three 10-micron FPET sections. The assay machine measures mRNA abundance by recording real-time fluorescence and time to a certain amplification threshold. The assay (Oncotype DX<sup>™</sup> Breast Cancer Assay, Genomic Health, Redwood, CA; <http://www.genomichealth.com/oncotype>) is performed within 10-14 days.

Using manually microdissected DCIS tissue the Oncotype DX<sup>®</sup> Breast Cancer Assay is run which includes all 21 genes from the Recurrence Score. The DCIS Score result is generated from 12 of the 21 Recurrence Score, these genes specific to the calculation of the DCIS Score result, and they include 7 cancer-related and 5 reference genes (Table 1). This subset of genes were selected for inclusion in the DCIS Score algorithm because they are strongly prognostic and predict local recurrence risk regardless of tamoxifen use.

**Table 1: Genomic Health DCIS Score Algorithm (Oncotype DX)**

<u>Group</u>	<u>Genes</u>
Proliferation	Ki67, STK15, survivin, cyclin B1, MYB2
Hormone Receptor	PR
Reference	Beta-actin, GDPDH, RPLPO, GUS, TFRC
GSTM-1	GSTM-1

The DCIS Score result is evaluated both as a continuous variable (from 0 to 100) and as a categorical variable (based on 3 prespecified risk groups: low, intermediate and high). The DCIS Score™ result quantifies the risk of any local recurrence, as well as the risk of an invasive local recurrence.<sup>35</sup>



\*HR=hazard ratio.

**Table 2. Genomic DCIS Score, Results from Validation Study<sup>35</sup>**

<b>Recurrence Score (1–100)</b>	<b>Risk group</b>	<b>No. (%)</b>	<b>10-year risk of any local breast event (95% C.I.)</b>	<b>10-year risk of an invasive local breast event (95% C.I.)</b>
< 39	Low	230 (70%)	10.6% (6.9, 16.2)	3.7% (1.8, 7.7)
39 –54	Intermediate	53 (16%)	26.7% (16.2, 41.9)	12.3% (5.1, 27.8)
> 54	High	44 (13%)	25.9% (14.8, 43.1)	19.2% (9.5, 36.4)

## 11. Electronic Data Capture

Please refer to the E4112 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

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### 11.1 Records Retention

This study is not intended to support any FDA-related filings. However, ECOG-ACRIN requires clinical investigators to retain all trial-related documentation, including source documents, for at least one year from the posting of the final technical report of the outcome of this trial to support any publication of the data. Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

### 11.2 ECOG-ACRIN Radiation Oncology Quality Assurance Materials

All radiotherapy quality assurance materials should be submitted to the IROC Island QA Center (QARC).

See Section [5.3.7](#) for data to be submitted. The E4112 RT data checklist may be found on the IROC Rhode Island website ([www.irocri.qarc.org](http://www.irocri.qarc.org)).

A copy of the checklist should be submitted with the required radiation oncology materials.

## 12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

## 13. References

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**Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene  
Expression Assay in Ductal Carcinoma In Situ (DCIS)**

**Appendix I**

**Pathology Submission Guidelines**

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials  
(instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists

### Guidelines for Submission of Pathology Materials

ECOG-ACRIN requires that all samples submitted from patients participating in this study be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS).

If STS is down, a completed ECOG-ACRIN Generic Specimen Submission Form (#2981) may be submitted in place of the STS shipping manifest, and the submission retroactively logged into STS. Form #2981 may also be used as a worksheet for requesting the specimens from your pathology department.

1. **MANDATORY SUBMISSIONS OF SURGICAL TUMOR TISSUE TO GENOMIC HEALTH from patients with DCIS only who have undergone wide local excision and have  $\geq 2$ mm margins**

Contact Genomic Health Customer Service (866-662-6897) and request the "Onco*type* Specimen Kit". If the kit is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration.

One Onco*type* Specimen Kit and Requisition form should be completed per patient.

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

\_\_\_\_\_ Surgical Tumor Tissue Block (place barcode label on back of cassette)

OR

Fifteen (15) 5 um serial unstained slides, oriented similarly and air dried. Label each slide with barcode and number in the order they were cut.

**NOTE:** Proper sterile sectioning technique **MUST** be followed. Failure to follow sterile technique can affect testing and delay results. If sterile technique cannot be followed, submission of a tumor block is strongly recommended.

\_\_\_\_\_ Shipping Manifest from Sample Tracking System (STS)

\_\_\_\_\_ Completed Onco*type* DX Requisition Form

The form is to be completed ONLINE or written as instructed in the kit except for the following fields (see sample requisition form in this appendix):

- "STUDY NAME/CODE" **enter the protocol number E4112 and the ECOG-ACRIN E4112 patient case number** assigned at registration (e.g. E4112/41001).
- BILLING INFORMATION (section V): Complete with patient's insurance information.
- ADDITIONAL PHYSICIAN (section III): Enter the contact information of the Institutional CRA coordinating the PACCT-1 study.
- "**BLOCK RETURN**" information (section VI). After testing, all residual block material will be forwarded by Genomic Health to the ECOG-ACRIN Central Tissue Repository at CBPF.
  - BLOCK RETURN CONTACT = ECOG-ACRIN Central Biorepository and Pathology Facility
  - BLOCK RETURN PHONE NUMBER = 1-844-744-2420

## 2. SUBMISSIONS OF SURGICAL TUMOR TISSUE TO THE CBPF

- \_\_\_\_\_ Pathology and surgical reports, including immunological studies reports if performed.
- \_\_\_\_\_ Shipping Manifest from Sample Tracking System (STS) for material being submitted to the CBPF
- \_\_\_\_\_ Mandatory from patients if tissue was not submitted on study to GHI for the Oncotype DX assessment for DCIS. Surgical Fixed Tumor Tissue block. If block is unavailable, contact the CBPF to discuss alternative submission requirements. Form patient from whom only slides are submitted to GHI, surgical tissue specimens are to be submitted.
- \_\_\_\_\_ Frozen surgical tumor tissue, if available

Mail pathology materials to:

MD Anderson Cancer Center  
Department of Pathology  
Tissue Qualification Laboratory for ECOG-ACRIN Room G1.3586  
ECOG-ACRIN Central Biorepository and Pathology Facility  
1515 Holcombe Blvd  
Houston, TX 77030

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact ECOG-ACRIN Central Biorepository and Pathology Facility by telephone 1-844-744-2420 or by fax 713-563-6506.



Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD  
Group Co-Chairs

**MEMORANDUM**

**TO:** \_\_\_\_\_  
(Submitting Pathologist)

**FROM:** Stanley Hamilton, M.D., Chair  
ECOG-ACRIN Laboratory Science and Pathology Committee

**DATE:** \_\_\_\_\_

**SUBJECT:** Submission of Pathology Materials for E4112: *Prospective II Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)*

The patient named on the attached Material Submission Form (#2981) has been entered onto an ECOG-ACRIN protocol by \_\_\_\_\_ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials to Genomic Health Inc for the OncotypeDX Breast Cancer Assay and, to the ECOG-ACRIN Central Biorepository and Pathology Facility for use in central diagnostic review and laboratory research studies.

For submission of tissue to Genomic Health for the OncotypeDX Assay, complete the Oncotype DX Requisition Form (online or written) as outlined in [Appendix II](#):

- The STUDY NAME/CODE must be completed with the protocol number E4112, and the patient's ECOG-ACRIN E4112 case number (e.g. E4112/41001).
- Complete the BLOCK RETURN section with the CBPF information as indicated on page 2 of [Appendix I](#). All residual material will be forwarded to the ECOG-ACRIN Central Biorepository and Pathology Facility –Research Laboratory (CBPF) after testing. Copies of the completed forms and pathology report are to be forwarded to the CBPF.

For materials submitted to the CBPF, a shipping manifest from the ECOG-ACRIN Sample Tracking System (STS) must be submitted with the material.

Keep copies for your own records, and return the completed Forms, the surgical pathology report(s), the slides and/or blocks, and any other required material (see attached List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the appropriate laboratories.

Blocks, slides and frozen tissue submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned by the ECOG CBPF upon written request for purposes of patient management.

Questions may be directed to Genomic Health Customer Service (650-556-9300) or the CBPF (Tel: 1-844-744-2420 or FAX: 713-563-6506).

The ECOG-ACRIN CRA at your institution is:

Name: \_\_\_\_\_ Address: \_\_\_\_\_

Phone: \_\_\_\_\_

Thank you.

**ECOG-ACRIN Generic Specimen Submission Form**

Form No. 2981v3

Page 1 of 1

**Institution Instructions:** This form is to be completed and submitted with **all specimens ONLY** if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number \_\_\_\_\_ Patient ID \_\_\_\_\_ Patient Initials Last \_\_\_\_\_ First \_\_\_\_\_

Date Shipped \_\_\_\_\_ Courier \_\_\_\_\_ Courier Tracking Number \_\_\_\_\_

Shipped To (Laboratory Name) \_\_\_\_\_ Date CRA will log into STS \_\_\_\_\_

**FORMS AND REPORTS:** Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				Additional fields for tissue submissions				Completed by Receiving Lab
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	Quantity	Collection Date and Time 24 HR		Surgical or Sample ID	Anatomic Site	Disease Status (e.g., primary, mets, normal)	Stain or Fixative	Lab ID

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	Diagnosis	Intended Treatment Trial	Peripheral WBC Count (x1000)	Peripheral Blasts %	Lymphocytes %
Study Drug Information:	Therapy Drug Name	Date Drug Administered	Start Time 24 HR	Stop Time 24HR	
Caloric Intake:	Date of Last Caloric Intake		Time of Last Caloric Intake 24HR		

CRA Name \_\_\_\_\_ CRA Phone \_\_\_\_\_ CRA Email \_\_\_\_\_

Comments \_\_\_\_\_



**Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)**

**Appendix II**

**Sample Genomic Health Oncotype DX<sup>®</sup> Requisition Form**

From patients who have DCIS only, have undergone wide local excision with surgical margins  $\geq$  2mm submission of surgical tissue for the OncotypeDX DCIS Score Assay.

Study specific completion guidelines:

- The STUDY NAME/CODE must be completed with the protocol number E4112, and the patient's ECOG-ACRIN E4112 case number (e.g. E4112/41001).
- Complete the BLOCK RETURN section with the CBPF information as indicated on page 2 of [Appendix I](#).



THIS IS AN EXAMPLE REQUISITION FORM  
PLEASE DO NOT USE



## BREAST & COLON PATHOLOGY GUIDELINES

### SELECTING THE MOST REPRESENTATIVE BREAST OR COLON TUMOR BLOCK

- Choose the one block with the greatest amount/area of the highest grade carcinoma, morphologically consistent with the submitting diagnosis.
- Neutral buffered formalin is the preferred fixative. Alternative fixatives are not recommended.
- Hemorrhage, necrosis, and adipose tissue do not need to be minimized. They contain little RNA and thus do not significantly impact this assay.
- For breast carcinoma submissions, microinvasive carcinomas (one or more foci < 0.1 cm) are not acceptable samples.
- For DCIS submissions, total mastectomy specimens are not appropriate samples.

### SPECIMEN PREPARATION INSTRUCTIONS

#### BLOCKS



- Follow your laboratory's standard practice guidelines for the processing of fixed paraffin embedded (FPE) tissue.
- Apply one S barcode label, obtained from the inner top lid of the Oncotype DX<sup>®</sup> Specimen Kit, to each block. (See photo, left).
- Place the tumor block in the small plastic bag and seal the bag.
- Do not* submit an H&E slide when you are submitting tumor blocks. Genomic Health<sup>®</sup> will prepare an H&E slide on site.
- Secure the specimen in the foam insert inside the Oncotype DX Specimen Kit.
- Include a frozen ice pack (provided with the Oncotype DX Specimen Kit) on top of the foam insert and seal the secondary containment bag.

**NOTE:** The ice pack included with the kit should be frozen overnight for best use.

#### UNSTAINED SLIDES

**NOTE:** Follow your laboratory's standard practice guidelines for the processing of FPE tissue.

To reduce cross-contamination:

- Use a new section of the microtome blade (or a new blade) between cases.
- Clean the water bath between cases (e.g., using a clean Kimwipe).
- Wear clean gloves during the cutting and mounting process.

- Prepare **fifteen** 5 µm serial unstained slides with one 5 µm serial section on each slide.
  - Use charged glass slides (standard 1" x 3" or 25mm x 75mm size).
  - Ensure the sections on each slide are oriented similarly.
  - Allow the slides to air dry. Do not place the slides on a hot plate.
  - Do not place the cover slips on the unstained slides.
- Label the slides as follows:
  - Apply one S barcode label, obtained from the inner top lid of the Oncotype DX Specimen Kit, to each slide (See photo, right).



- Hand number the serially sectioned unstained slides (1-15) to indicate the order in which they were cut.
- Once the slides are dry, insert them into slide carriers and place one S barcode label from the Oncotype DX Specimen Kit on the outside of each slide carrier. Place the slide carriers in the Oncotype DX Specimen Kit for shipping.
  - Seal the large secondary containment bag and close the box using the tab.

### SHIPPING INSTRUCTIONS

#### MATERIALS AND EQUIPMENT:

- Oncotype DX Requisition Form
- Copy of Pathology Report
- Oncotype DX Specimen Kit containing the patient specimen
- FedEx<sup>®</sup> US Airbill pre-printed with Genomic Health shipping information
- FedEx<sup>®</sup> Clinical Pak, Large — a plastic "over wrap" used to ship the specimen to Genomic Health
- FedEx<sup>®</sup> adhesive airbill pouch for the FedEx<sup>®</sup> Airbill

**NOTE:** To order additional kits, e-mail Genomic Health Customer Service at [customerservice@genomichealth.com](mailto:customerservice@genomichealth.com) or call the number listed below.

#### REQUISITION FORM AND SUPPORTING MATERIALS:

- Complete one Oncotype DX Specimen Kit and Requisition Form for each patient and each primary tumor (if applicable). Extra S barcode labels should be left in the Oncotype DX Specimen Kit and should NOT be used for another patient or primary tumor.
- Before shipping, make a copy of the Oncotype DX Requisition Form and retain it for your records.
- Place the Oncotype DX Requisition Form, a copy of the pathology report, and relevant patient insurance materials in the Oncotype DX Specimen Kit, between the box and the large secondary containment bag.

QUESTIONS? PLEASE CALL 866-ONCOTYPE (866-662-6897)

301 Peninsula Drive | Redwood City, CA 94063, USA | [www.oncotypedx.com](http://www.oncotypedx.com)  
©2011 Genomic Health, Inc. Oncotype DX is a registered trademark of Genomic Health, Inc. 010201-0 Rev 9.9 May-2013

**Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)**

**Appendix III**

**Patient Thank You Letter**

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG-ACRIN web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

---

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of **[INSTITUTION]** and the ECOG-ACRIN Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

**Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)**

**Appendix IV**

**ECOG-ACRIN Performance Status**

<b>PS 0</b>	Fully active, able to carry on all pre-disease performance without restriction
<b>PS 1</b>	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
<b>PS 2</b>	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
<b>PS 3</b>	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
<b>PS 4</b>	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

**Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)**

Rev.2/16

**Appendix V**

**Oncotype DX Patient Report**

This appendix contains **examples** of the “Oncotype DX Patient Report” and information sheets (provided in the Oncotype DX Specimen Kit) distributed by Genomic Health.

To order the “Oncotype Specimen Kit” contact Genomic Health Customer Service (866-662-6897). The kit will be shipped overnight and will contain instructions, shipping supplies (including cyrotubes and slide cassette), and a requisition form containing barcode labels to place on the submitted materials.

Tumor tissue collected at time of surgery and forms are submitted to Genomic Health Inc as outlined in [Appendix I](#), which contains an example of the “Oncotype DX Requisition Form” and instructions on how the requisition form MUST be completed

Only one Oncotype Specimen Kit and Requisition form should be completed per patient.

After receipt of the patient report, **upload** a redacted copy of the “Oncotype DX Patient Report” (labeled with protocol number (E4112), patient initials and case number) to Medidata RAVE, DCIS Folder, DCIS Score Form.

**Registration to step 2, for patients diagnosed with DCIS only and have undergone excisional surgery only with margin status  $\geq$  2mm, may proceed 24 to 72 hours after submission of the report the ECOG-ACRIN Operations Office – Boston.**



For women with ductal carcinoma *in situ* (DCIS) treated by local excision, with or without tamoxifen

# Oncotype DX® reveals the underlying biology that can help guide DCIS treatment decisions

## Sample report for DCIS

1. REDACT

2. Add Pt. initials

DO NOT REDACT

The DCIS Score™ is obtained by performing the Oncotype DX Breast Cancer Assay, using a distinct DCIS algorithm and coefficients that were pre-specified because of their ability to predict recurrence in patients with DCIS, regardless of whether adjuvant tamoxifen therapy was given.

The first page of the report contains the patient's DCIS Score, which can be between 0 and 100. However, a score above 70 is not plotted in the report.\*

The DCIS Score provides an estimate of the likelihood of 10-year recurrence for any local event (DCIS or invasive carcinoma) as well as a separate estimate specifically for an invasive carcinoma local event. The likelihood of local recurrence at 10 years increases continuously with an increase in the DCIS Score.

**PATIENT REPORT**  
 PatientID: Doe, Jane **E4112/##### - D,J**  
 Sex: Female  
 Date of Birth: 01-Jan-1950  
 Medical Record/Patient #: 558877771  
 Date of Surgery: 25-Sep-2008  
 Specimen TypeID: Breast/SURQ-0001

**BREAST CANCER ASSAY DESCRIPTION**  
 Oncotype DX Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The DCIS Score™ is calculated from a subset of the genes using a distinct algorithm optimized for ductal carcinoma *in situ* (DCIS) and is different from the Recurrence Score® for invasive breast cancer. The DCIS Score range is from 0-100.

**RESULTS**  
**DCIS Score = 10** The findings summarized in the Clinic patient population. It is unknown whether

**CLINICAL EXPERIENCE: PROGNOSIS FOR D**

**Any Local Event (DCIS or Invasive)**  
**11% (95% CI: 7%-17%)**

**Invasive Local Event**  
**4% (95% CI: 2%-8%)**

**DCIS**

Laboratory Director: Patrick Joseph, MD  
 CLIA Number: 05D1018272  
 This test was validated and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. The test results are intended for the referring physician's workflow.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com  
 © 2014-2015, Genomic Health, Inc. All rights reserved. Oncotype DX, Recurrence Score, and DCIS Score are trademarks of Genomic Health, Inc.

4. FAX REDACTED COPY OF REPORT (labeled as above)  
TO 617-582-8578, ATTN: E4112/Step 3 Registration

For women with ductal carcinoma *in situ* (DCIS) treated by local excision, with or without tamoxifen

# Oncotype DX<sup>®</sup> provides quantitative ER and PR Scores for DCIS

## Sample report for DCIS

The second page of the DCIS report provides quantitative ER and PR scores.

Page 2 of 2

Genomic Health, Inc.  
301 Peninsula Drive  
Redwood City, CA 94063 USA  
Toll Free Tel: 866-ONCOTYPE (866-662-6897)  
Brookline Tel: +1 855-559-2910  
www.oncotypedx.com


**PATIENT REPORT**

PatientID: Doe, Jane      Requisition: R00003G  
Sex: Female      Specimen Received: 05-May-2009  
Date of Birth: 01-Jan-1950      Date Reported: 15-May-2009

**QUANTITATIVE SINGLE GENE REPORT**

The Oncotype DX assay uses RT-PCR to determine the RNA expression of the genes below. These results may differ from ER or PR results reported using other methods or reported by other laboratories.<sup>1</sup> The PR Score is also included in the calculation of the DCIS Score.

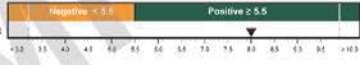
**ER Score = 10.0**      Positive      Range: Negative < 5.5      Positive ≥ 5.5



The ER Score positive/negative cut-off of 5.5 units was validated in a study of 761 invasive breast cancer samples using the 1D5 antibody (immunohistochemistry) and 607 invasive breast cancer samples using the SPI antibody (immunohistochemistry). The standard deviation for the ER Score in invasive breast cancer is less than 0.5 units.<sup>2</sup>  
**There is no data on the relationship between the ER Score and ER by immunohistochemistry in DCIS.**

**Clinical Experience:**  
For patients diagnosed with ER positive invasive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 0.5 to a 12.5.<sup>3</sup>  
There is no data on the relationship between the ER Score and tamoxifen benefit in DCIS.

**PR Score = 8.0**      Positive      Range: Negative < 5.5      Positive ≥ 5.5



The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 invasive breast cancer samples using the PR206 antibody (immunohistochemistry) and another study of 607 invasive breast cancer samples using the PR206 antibody (immunohistochemistry). The standard deviation for the PR Score in invasive breast cancer is less than 0.5 units.<sup>2</sup>  
**There is no data on the relationship between the PR Score and PR by immunohistochemistry in DCIS.**

References:  
1. ER Score based on quantitative ERB1 expression (erbB1 receptor); PR Score based on quantitative PGR expression (progesterone receptor)  
2. Dabbs DG, Baumner FL, Gray RP, et al. Estrogen and progesterone receptor status in ECOG 2107: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription-polymerase chain reaction by central laboratory. *J Clin Oncol*. 2005; 23(15):2473-81.  
3. ABCO Annual Meeting 2002 Abstract #510 by S. Paik et al.

Laboratory Director: Patrick Joseph, MD      CLIA Number 05D10 10279  
This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are applicable to the ordering physician's work.

Online Ordering and Results Available — Please Contact Customer Service at [customerservice@genomichealth.com](mailto:customerservice@genomichealth.com)

**DO NOT FAX THIS PAGE OF THE REPORT**

Note: There are no data on the relationship between the ER or PR Scores and ER or PR by immunohistochemistry in DCIS.  
Genomic Health, Oncotype DX, Recurrence Score, and DCIS Score are trademarks of Genomic Health, Inc. © 2011 Genomic Health, Inc. All rights reserved.      GH10054\_1111



## Value of breast MRI to treat patients diagnosed with ductal carcinoma in situ

Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>:  
Prospective Study of Magnetic Resonance Imaging (MRI) and  
Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ  
(DCIS)

Version Date: January 7, 2016

### Informed Consent Template for Cancer Treatment Trials (English Language)

#### **WHAT IS THE USUAL APPROACH TO MY BREAST CANCER (DUCTAL CARCINOMA IN SITU)?**

You are being asked to take part in this research study because you have had a needle biopsy of the breast showing ductal carcinoma in situ, (also known as DCIS)

You are eligible for this study because you have DCIS and your treating physician has determined that you could be treated with lumpectomy.

The usual treatment for DCIS is one of two types of surgery: lumpectomy, or mastectomy.

- Lumpectomy is the removal of the portion of the breast that contains the DCIS tumor, but leaves the rest of the breast intact. Lumpectomy can be done if the DCIS tumor involves only a limited portion of the breast. If lumpectomy is done, radiation therapy to the same breast is usually recommended to reduce the chances that the DCIS will come back in that breast.
- Mastectomy is a surgery that involves the removal of all the breast tissue. Mastectomy is done if the DCIS tumor is thought to be too large for lumpectomy. Mastectomy is also done if there is concern that the DCIS may involve other parts of the breast. When mastectomy is performed radiation therapy is usually not needed.

Most often the decision to treat DCIS with either lumpectomy or mastectomy is based on the results from mammograms, ultrasounds or tumor biopsies.

## **WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?**

If you decide not to take part in this study, you have other choices for your care. For example:

- you may choose to have the usual treatment for DCIS described above
- you may choose to take part in a different research study, if one is available
- or you may choose not to be treated for DCIS (please discuss with your doctor)

## **WHY IS THIS STUDY BEING DONE?**

The purpose of this research study is to determine how often the results of breast MRI change the recommended surgery for the treatment of DCIS from lumpectomy to mastectomy.

In addition, another purpose of the study is to see if radiation therapy can be avoided in some women who have lumpectomy and have a low risk of recurrence with lumpectomy alone. Participants in this study will also have a test called the DCIS Score, which is a test that is performed on the tumor tissue. From other research studies we have learned that the DCIS score may identify women at a low risk for recurrence of DCIS in their breast when treated with lumpectomy alone without radiation.

At the present time, using the DCIS score to decide whether or not to give radiation therapy following lumpectomy is investigational.

About 350 women will take part in this study.

## **WHAT EXTRA TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?**

### **Before you begin the research study**

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical exam and medical history
- Mammogram (with ultrasound if recommended by your doctor)
- Core needle breast biopsy to confirm your diagnosis.
- Pregnancy test if you are of childbearing potential

### **During the research study**

You will have the following procedures during the research study:

- Breast MRI-all study participants
- Surgery- all study participants

- DCIS score-will be performed on the tumor specimens from participants who have had lumpectomy as their final surgical procedure. Your specimens will be sent to the laboratory of Genomic Health for testing. Any remaining tissue will be returned to the ECOG-ACRIN Biobank.
- Radiation therapy - will be performed in some study participants, including only those who have had a lumpectomy as their final surgical procedure and have an intermediate or high DCIS Score.
- Questionnaires/surveys - this will be performed at 5 time points as described below:

You will have a breast MRI (including both breasts) before your surgery. Based on the results of the MRI, you and your doctor will decide which type of surgery – lumpectomy or mastectomy – is best for you, and then you will have surgery that you and your doctor decide upon. There is a possibility of a need to do additional imaging and/or biopsy if the MRI results are suspicious for cancer other than the DCIS that we already know about, including the same breast and/or the opposite breast.

MRI is a medical imaging method that uses magnets to make images of the body. MRI helps doctors to tell the difference between cancer and normal tissue in the body. MRI uses a dye (“contrast agent”) that is injected into a vein to help see images of the body’s tissues.

#### Surgery and DCIS Score:

If you have a lumpectomy as the final surgical procedure and the tumor includes only DCIS, some of the breast tumor tissue removed during the lumpectomy surgery will be sent for DCIS score test. The DCIS score (also known as Oncotype DX Breast Cancer Assay for DCIS, and owned by Genomic Health, Inc, Redwood, CA) is performed on the tumor tissue that has already been removed during your surgery. The test requires that several small shavings of the tumor tissue are sent to a specialized laboratory that measures a specific panel of genes in the tumor. The results of the test are reported a score (called the DCIS Score), which may be low (< 39), intermediate (39-54), or high (> 54).

The DCIS Score will be sent to your doctor and will be placed in your medical record. This score will affect your care on this study and may affect your medical treatment in the future.

If you have a mastectomy, and not a lumpectomy, or if an invasive breast cancer is found in tissue obtained before or during your final lumpectomy surgery, tissue will not be sent for DCIS score test as part of this study. You will remain in this study, but you and your doctor will together decide upon your treatment based on established treatment guidelines. At the end of this consent, you will be asked if any tissue samples remaining from the research study or from the DCIS Score test may be stored at the ECOG-ACRIN Biobank to be used for research studies in the future.

#### Radiation therapy:

Radiation therapy will be used in some patients treated with lumpectomy. It is

usually not indicated for patients with DCIS treated with mastectomy. For those treated with lumpectomy for DCIS, the DCIS Score will be used to personalize your treatment as follows:

- Low DCIS Score (less than 39): You will not receive radiation therapy to the breast.
- Intermediate or High DCIS Score (equal to or greater than 39): You will receive radiation therapy to the breast.

#### Questionnaires/Surveys:

You will receive a survey five times over the course of the study asking you about how you make decisions about your health, quality of life, and concerns about DCIS and its treatment. The surveys will be given at the following times: 1) when you enroll; 2) just before your surgery; 3) at your first visit after surgery; 4) at 12 months after surgery; and 5) at 24 months after your surgery. Each time, the survey should take no more than 10 minutes to complete.

#### Other research related procedures:

Images and reports from the MRI exam will be sent to the ECOG-ACRIN Cancer Research Group for review by the study radiologist. This is for quality assurance purposes. The images and reports will contain very limited identifying information (e.g. your birth date and medical record number will not be given). The accompanying paperwork will contain your initials and a study identification number.

In addition to the possible use of your tumor tissue for the DCIS score, tumor tissue samples from your original biopsy or your surgery will be sent to a central reviewer. This review is to confirm the diagnosis of DCIS. The results of this central review will not be sent to your doctor and will not be placed in your medical record. However, if the central reviewer identifies a different diagnosis, your cancer doctor will be notified of that finding.

## **HOW LONG WILL I BE IN THIS STUDY?**

You will receive the study interventions consisting of the MRI, breast surgery, and possibly radiation therapy. After you finish the study interventions, if your tumor is ER (estrogen receptor) and/or PR (progesterone receptor) positive, you may take endocrine therapy for up to 5 years. You will see your doctor at your regular follow-up visits. The visits will occur at least every 6 months for the first 5 years and then at least every 12 months during years 5-10.

## **WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

**You should talk to your study doctor about any side effects that you have while taking part in the study.**

**Possible side effects related to the MRI exam:**

**Likely:**

- Anxiety/stress
- Claustrophobia
- Discomfort

**Rare, but serious:**

- Injury related to the presence of metallic or surgical implants or metal pieces in the body and the MR magnet; it is important that you let the MRI team know about whether you have these before the MRI procedure.

**Risks of MRI**

Because the MRI machine acts like a large magnet, it could move objects containing iron in the MRI room during your examination, which could possibly harm you. We will take precautions to prevent this from happening. Loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia (a "closed-in" feeling) and by the loud banging noise during the test. Temporary hearing loss has been reported from this loud noise. This is why we will ask you to wear earplugs. At times during the test, you may be asked not to swallow for a while, which can be uncomfortable.

**Risks and side effects related to the drug used for MRI (called Gadolinium):**

**Less likely:**

- Headache
- Nausea
- Vomiting
- Hives
- Temporary low blood pressure
- Allergic-like reaction

**Rare but serious:**

- Kidney impairment

**Possible side effects related to the IV Needle Placement:**

**Likely:**

- Minor discomfort

**Less likely:**

- Swelling
- Bleeding
- Infection
- Bruising

**Risks and side effects related to surgery:**

There are no additional risks from surgery beyond the risks related to standard breast cancer surgery. Your doctor will provide more information about these risks.

For more information about risks and side effects related to surgery, ask your study doctor.

**Possible Side Effects of Research Radiation Therapy:**

<b>COMMON, SOME MAY BE SERIOUS</b> <b>In 100 people receiving radiation therapy, more than 20 and up to 100 may have:</b>
<ul style="list-style-type: none"><li>• Reddening, tanning, or peeling of the skin</li><li>• Mild pain</li><li>• Hair loss</li><li>• Tiredness</li><li>• Infection, especially when white blood cell count is low</li></ul>

<b>OCCASIONAL, SOME MAY BE SERIOUS</b> <b>In 100 people receiving radiation therapy, from 4 to 20 may have:</b>
<ul style="list-style-type: none"><li>• Thickening and numbness of the skin</li><li>• Sores or ulcers on the skin or near the cancer location</li><li>• Permanent hair loss</li></ul>

<b>RARE, AND SERIOUS</b> <b>In 100 people receiving radiation therapy, 3 or fewer may have:</b>
<ul style="list-style-type: none"><li>• Heart damage</li><li>• Coronary artery disease</li><li>• Rib fracture</li><li>• Swelling of the arm tissue</li><li>• Inflammation of the lung tissue</li></ul>

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The MRI used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

## **WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?**

This research study has only a small chance of helping you because we do not know if the study approach is effective. This research study may help researchers learn things that may help other people in the future.

## **CAN I STOP TAKING PART IN THIS STUDY?**

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

## **WHAT ARE MY RIGHTS IN THIS STUDY?**

Taking part in this research study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the \_\_\_\_\_ (insert name of center) Institutional Review Board at \_\_\_\_\_ (insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)

## **WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

You and/or your health plan/insurance company will need to pay for all of the other costs of treatment while in this research study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are being done at no charge. Before you decide to be in the research study, you should check with your health plan or insurance company to find out exactly what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will be undergoing an MRI as part of the research study. In many patients with DCIS, breast MRI would be performed as part of their usual care. If this is the case for you, the MRI costs will be billed according to routine clinical practice and you would be responsible for any co-pays. If your doctor would not normally order a breast MRI for your care, the MRI costs will be borne by the study and you will not be responsible for associated costs. Therefore, participating in this study should not impact any of your costs associated with the Breast MRI.

The Oncotype DX® test that is used to determine the DCIS Score in this trial is commercially available for patients who have DCIS only and have not had a mastectomy and the Genomic Health laboratory is certified by federal and state agencies (CLIA) in the United States to perform this test. Your insurance company will be billed for the cost of the test. Representatives from Genomic Health are available to answer any questions that you or your insurance company may have about the cost of the test or reimbursement for the test (1-866-662-6897).

If your insurance company denies payment of the test, Genomic Health will appeal this denial. It is likely that you will be receiving statements, or Explanation of Benefits forms (EOB), from your insurer. These are not bills.

We would like to assure you that, as a participant in this trial, should GHI be unsuccessful in receiving reimbursement for all or some of the cost of this assay after appeal, you will have no financial responsibility for the Oncotype DX test for DCIS. Patients on this study will not be responsible for a co-pay or a deductible for cost of this test.

You or your insurance company will not be charged for the laboratory research studies performed by designated central laboratories for this study.

You will not be paid for taking part in this research study.

## **WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?**

If you are injured or hurt as a result of taking part in this research study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for research study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to



receive payment for this even though you are in a research study.

## WHO WILL SEE MY MEDICAL INFORMATION?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

The ECOG-ACRIN Cancer Research Group is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Genomic Health, the laboratory company responsible for the Oncotype DX tests and its performance. Genomic health will provide your DCIS score to your doctor and may ask your doctor to provide medical information in order to assist them in processing insurance claims, in a way very similar to the process used to cover other costs of their care.
- Other regulatory agencies and/or their designated representatives
- Central Laboratories who receive your samples for testing or research
- Cancer Trials Support Unit (CTSU). The CTSU is a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- The ECOG-ACRIN Research Group, which is coordinating the study

## **OPTIONAL STUDIES SECTION: RESEARCH ON TISSUE AND BLOOD**

### **THIS SECTION IS ABOUT OPTIONAL STUDIES YOU CAN CHOOSE TO TAKE PART IN.**

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

### **Optional Sample Collections for Laboratory Studies and Biobanking for Possible Future Studies**

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples of tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

If you participate in the main part of this study, samples of the tissue from your surgery will be sent for tests and research. At this time, we are requesting that you allow any samples leftover from the tests and from the research study to be kept for future research studies to learn more about DCIS, breast cancer and other health problems. We also request permission to allow additional tissue from your surgery, if available, to be stored and used for future research.

These specimens will be stored in a "biobank". The Biobanks are run by ECOG-ACRIN staff and researchers and they are financially supported by the National Cancer Institute.

### **What is involved if you provide your samples for research?**

If you agree to take part, here is what will happen next:

1. Tissue samples remaining after the central review and the tests performed by Genomic Health, Inc. will be sent to and stored in the ECOG-ACRIN Biobank.
2. Some additional tumor tissue from your surgery, if available, may be sent to and stored in the ECOG-ACRIN Biobank.
3. With your samples, some related health information will be stored in the Biobank. The samples information will be kept with samples and information from other people who took part in this or other research studies. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
4. Only qualified researchers can submit a request to use the materials stored in the Biobanks. A committee of experts at ECOG-ACRIN, and/or the National Cancer

Institute, will review each request to use the samples for research. All research projects using these samples will also be reviewed by an ethics or institutional review board to ensure that the request is necessary and proper. Researchers who use your samples stored in the ECOG-ACRIN Biobank will not be given your name or any other information that could directly identify you.

5. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
6. Results from the research may be placed in centralized storage systems called databases. It is possible that some of your genetic information and your health information may be placed in these databases. It is also possible that some of these databases may be public.

### **What are the possible risks in providing your samples for research?**

- There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
- There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

### **When my samples are used for research, how will information about me be kept private?**

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2. The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and ECOG-ACRIN staff with access to the list must sign an agreement to keep your identity confidential.
3. Researchers to whom ECOG-ACRIN sends your sample from the Biobank and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4. Information that identifies you will not be given to anyone, unless required by law.

5. If research results are published, your name and other personal information will not be used.

### **What are the Possible Benefits of allowing my samples to be used for research?**

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

### **Are there any costs or payments associated with providing my samples for research?**

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

### **What if I change my mind about allowing my samples to be used for research?**

If you decide you no longer want your samples to be used, you can call the study doctor, \_\_\_\_\_, *(insert name of study doctor for main trial)* at \_\_\_\_\_ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

### **What if I have more questions?**

If you have questions about the use of your samples for research, contact the study doctor, \_\_\_\_\_, *(insert name of study doctor for main trial)*, at \_\_\_\_\_ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

### **SAMPLES FOR FUTURE RESEARCH STUDIES:**

- May we keep any samples left over from the Oncotype DX Assay for DCIS and the research studies and have additional tissue from your surgery, if available, for research studies in the future?
- **My samples and related information may be kept in a Biobank for use in future health research.**

YES

NO

**THIS IS THE END OF THE SECTION ABOUT OPTIONAL STUDIES.**

## WHERE CAN I GET MORE INFORMATION?

You may visit the NCI Web site at <http://cancer.gov/> for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor \_\_\_\_\_ (insert name of study doctor[s]) at \_\_\_\_\_ (insert telephone number).

## MY SIGNATURE AGREEING TO TAKE PART IN THE MAIN STUDY

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'*.

Participant's signature \_\_\_\_\_

Date of signature \_\_\_\_\_

Signature of person(s) conducting the informed consent discussion

\_\_\_\_\_

Date of signature \_\_\_\_\_

# Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)

ECOG 4112

CONFIDENTIAL



## Statistical Analysis Plan

September 27, 2018

### Prepared by:

Constantine Gatsonis, PhD  
Justin Romanoff, MA  
Bradley S. Snyder, MS

Trial identifier # NCT02352883 @ [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

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## Summary

ECOG 4112 is a prospective multi-center study designed to determine the proportion of patients with ductal carcinoma in situ (DCIS) undergoing mastectomy after integrating magnetic resonance imaging (MRI) into their management who would otherwise be candidates for wide local excision (WLE) based on standard mammographic imaging, physical examination, and a diagnostic core needle biopsy demonstrating DCIS (without invasion or microinvasion). The study will enroll women aged 18 years or older with a diagnosis of DCIS within 4 months, diagnostic mammogram of the affected breast within 3 months, and two-view mammogram of both breasts within 6 months who had no prior MRI of the breast within 6 months and no prior ipsilateral invasive breast cancer or DCIS.

All eligible participants will undergo bilateral breast MRI within 30 days after enrollment (step 1). Additional imaging (MRI or ultrasound) and/or biopsies will be performed based on suspicious MRI findings. Patients will proceed to wide local excision and/or mastectomy based on clinician/patient decision after all imaging and biopsies (step 2). For patients with margins less than 2 mm after an initial attempt at WLE, re-excision(s) and/or a completion mastectomy will be performed. Patients who do not have a mastectomy, have adequate tumor free margins of at least 2 mm, and are without invasive/microinvasive disease will have tissue samples submitted for Oncotype DX Breast DCIS Score evaluation. Those with low DCIS Scores ( $< 39$ ) will be recommended to receive no radiation therapy, while those with an intermediate or high DCIS Score ( $\geq 39$ ) will be assigned to receive definitive breast radiation. A sample size of 350 participants was determined to be sufficient to ensure that the Wilson 95% confidence interval (CI) for the expected proportion of mastectomies would have length less than 0.08.

The statistical analysis plan is based on the February 17, 2016 version of the protocol (addendum #3), and addresses the primary objective, secondary objectives 1, 3, and 4, and additional exploratory analyses.

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## 1. Introduction

Ductal carcinoma in situ (DCIS) of the breast is a clonal proliferation of cells within the ductal lumen that does not invade beyond the epithelial basement membrane into the adjacent breast stroma, but which is a precursor to invasive ductal carcinoma.<sup>1</sup> The frequency of DCIS diagnosis has increased up to 7-fold since mammography became routine,<sup>2</sup> and now accounts for up to 28% of all breast carcinomas in the United States in 2012, or an estimated 63,300 new cases.<sup>3</sup> While this may be viewed as clear evidence for the benefit of screening mammography due to the low mortality rates associated with DCIS, another view is that detection of DCIS may be harmful because of “overdiagnosis” of disease that would never become evident if not detected by mammography.<sup>4</sup>

About 75% of women diagnosed with DCIS in the United States are treated with wide local excision (WLE) and 25% with mastectomy; of those treated with WLE, about 75% also receive irradiation.<sup>5</sup> For patients who are candidates of WLE, the primary objective of surgery is to achieve adequate surgical margins during the initial surgical resection while maintaining an acceptable cosmetic outcome.

Magnetic resonance imaging (MRI) has become the most accurate imaging modality for DCIS detection and characterization due to evolution of acquisition techniques to emphasize spatial resolution over temporal resolution, exceeding that of mammography or ultrasound.<sup>6-8</sup> Morphological features have been shown to be useful for DCIS diagnosis,<sup>9-11</sup> while it has been suggested that MRI may provide biomarkers of DCIS aggressiveness.<sup>12</sup> Advanced MRI presents an opportunity for better anatomic delineation of DCIS that would allow more complete excision, offering the possibility of lower recurrence after WLE, with or without radiation. However, despite the uniformly promising data on DCIS detection, there have been few attempts to translate them into improved short- or long-term outcomes for DCIS patients. Moreover, at this trial's inception, there were no studies that had compared the impact of pretreatment MRI on decision making quality and satisfaction, post-treatment concern, and overall quality of life (QOL).

The ECOG 4112 trial is designed to address current gaps in knowledge as specified by the 2009 National Institute of Health “State of the Science” meeting, regarding the challenges and opportunities in the diagnosis and management of DCIS.<sup>13</sup> The goals of the study are to determine the proportion of patients undergoing mastectomy after integrating MRI into the management of patients with DCIS who would otherwise be candidates for WLE; to correlate the MRI findings with a prognostic 12-gene Oncotype DX Breast DCIS Score;<sup>14</sup> to evaluate patient reported outcomes when managed with MRI in addition to standard care; and to estimate 5- and 10-year ipsilateral breast event (IBE) rates in patients treated with WLE for DCIS after MRI with a low DCIS Score treated without radiation, and an intermediate or high DCIS Score treated with radiation.

## **1.1 Objectives/Aims**

### **1.1.1 Primary Objective**

1. To estimate the proportion of patients with DCIS diagnosed on core needle biopsy (CNB) judged to be breast conservation candidates based upon standard imaging (mammography +/- sonography) and physical examination (a) who convert to mastectomy in step 1 based on MRI findings, and (b) who have a mastectomy as the final surgical procedure in step 2.

### **1.1.2 Secondary Objectives**

1. To assess the relation between baseline clinical covariates (e.g., tumor grade, necrosis, histologic type, mammographic lesion size), MRI morphologic and kinetic features, and the DCIS Score.
2. To assess the diagnostic accuracy of MRI in extent of disease evaluation in patients with DCIS.
3. To estimate the proportion of patients who require re-operation because of inadequate excision after MRI.
4. To estimate the proportion of patients who proceed to mastectomy after an initial attempt at WLE because of either inadequate tumor-free margins (< 2 mm), or other reasons.
5. To estimate the 5-year and 10-year IBE (in situ and invasive) rate among women with DCIS assessed with MRI preoperatively and treated with WLE without radiation therapy (if there is a low DCIS score) or with radiation therapy (if there is an intermediate-high DCIS score).
6. To estimate the proportion of women with DCIS who receive treatment that is concordant with their treatment goals and concerns.
7. To estimate the proportion of women with DCIS whose decision autonomy preference was concordant with perceived level of decision involvement.
8. To assess decision quality using knowledge score and decision process.
9. To assess concordance between decision autonomy preference and perceived level of decision involvement, knowledge, and decision process scores as independent predictors of decision satisfaction at the first post-operative visit.
10. To assess the relationship of patient-reported outcomes and disease-specific covariates, and QOL after treatment.
11. To assess the role of disease status, diagnostic test results, and surgeon recommendation as predictors of treatment received.
12. To compare the patient-reported diagnostic testing burden of bilateral mammography and MRI as measured by the Testing Morbidities Index (TMI).

## 2. Eligibility Criteria

- Age  $\geq$  18 years.
- Patients must be females. Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.
- Patients must have pathologically confirmed diagnosis of unilateral DCIS with no evidence of microinvasive or invasive disease obtained by CNB within 4 months of registration. If the core biopsy describes “suspicion of microinvasion”, patients remain eligible. Patients diagnosed by surgical excision are not eligible. Patients with synchronous bilateral disease (i.e., synchronous DCIS or invasive cancer) are not eligible.

Patients will be staged prior to registration according to the clinical staging criteria adapted from the American Joint Committee on Cancer (AJCC) Cancer Staging Data Forms of the AJCC Cancer Staging Manual, 7<sup>th</sup> Edition, 2009.

Note: for consistency purposes, AJCC 7<sup>th</sup> Edition will continue to be used throughout the entire study enrollment period.

- Required studies include a diagnostic mammogram of the affected breast within 3 months prior to registration, and a two-view (full view cranial-caudal and full view mediolateral oblique) mammogram of both breasts within 6 months of registration (if the patient has only one breast, a unilateral exam of the intact breast is required).
- Patients must not have previous ipsilateral invasive breast cancer or DCIS.
- Patients must not have known deleterious mutations in BRCA genes.
- Patients must not have received hormonal therapy (i.e., tamoxifen, raloxifene, and/or aromatase inhibitors) for prevention of breast cancer within 3 months of the biopsy documenting DCIS.
- Patients must not have history of chemotherapy for cancer within 6 months prior to registration.
- No prior history of breast radiotherapy that will prevent the use of radiotherapy for the present DCIS.
- Patients must be judged to be suitable to undergo MRI and receive the contrast agent gadolinium (exclusions follow):
  - No history of untreatable claustrophobia;
  - No presence of metallic implants that, in the opinion of the radiology, would make MRI a contraindication;
  - No history of sickle cell disease;
  - No contraindication to intravenous contrast administration;
  - No known allergy-like reaction to gadolinium or moderate or severe allergic reactions to one or more allergens as defined by the American

College of Radiology (ACR); patient may be eligible if willing to undergo pre-treatment as defined by the institution's policy and/or ACR guidance (see [www.acr.org/SecondaryMainMenuCategories/quality\\_safety/contrast\\_manual.aspx](http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx) for reaction definition and premedication guidance);

- No findings consistent with renal failure, as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m<sup>2</sup> based on a serum creatinine level obtained within 28 days prior to registration;
- Weight lower than that allowable by the MRI table.
- No prior MRI of the breasts within the 6 months prior to registration.
- Patients must be eligible for breast conservation treatment (BCT) based on clinical examination and mammography. If ultrasound is performed, findings must also be consistent with eligibility for BCT.
- Patients must not have multicentric disease scheduled to undergo multiple lumpectomies. Multifocal disease that can be encompassed in a single operative bed are eligible.
- Women must not be pregnant or breast-feeding.

All females of childbearing potential must have a blood test or urine study within 28 days prior to registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

- Women of childbearing potential must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

### 3. Imaging Procedures and Treatment

The study schema can be found in Figure 1.

All eligible participants will undergo bilateral breast MRI within 30 days after enrollment. The first two QOL questionnaires will be administered before the MRI, and between the MRI and first surgical procedure. MRI will be acquired on a 1.5 T or 3.0 T scanner with a dedicated breast radiofrequency coil. MRI examination will contain, at a minimum, a localization scan and a T2-weighted sequence followed by a single-dose gadolinium-based contrast contrast-enhanced T1-weighted series. An intravenous catheter will be inserted into the patient's arm or hand prior to the start of imaging. The contrast agent will be administered at a dose of 0.1 mmol/kg body weight and rate of 2 ml/s, followed by a 20 ml saline flush. Patients will be scanned in prone position.

The T2-weighted sequence will be performed before contrast with fat saturation (4-5 mm slice thickness), and the T1-weighted sequence will be performed once pre-contrast and multiple times post-injection using identical sequence parameters, with transmit and receive gain settings remaining constant. The in-plane pixel resolution for the T1-weighted sequences will be less than 1 mm in both the phase and frequency directions. Pre-contrast T1 images will be checked prior to contrast injection to confirm acceptable fat suppression, and post-contrast imaging continued for at least 8 minutes following contrast agent injection. Care will be taken to select the smallest FOV and slice coverage that completely encompassed both breasts and axilla.

Additional imaging (MRI or ultrasound) and/or biopsies will be performed based on suspicious MRI findings (Figure 2). Patients will proceed to WLE and/or mastectomy based on clinician/patient decision after all imaging and biopsies.

For patients with margins less than 2 mm after an initial attempt at WLE, re-excision(s) and/or a completion mastectomy will be performed. Patients who do not have a mastectomy, have adequate tumor free margins of at least 2 mm, and are without invasive/microinvasive disease will have tissue samples submitted for Oncotype DX Breast DCIS Score evaluation. Those with low DCIS Scores (< 39) will be recommended to receive no radiation therapy, while those with an intermediate or high DCIS Score ( $\geq 39$ ) will be assigned to receive definitive breast radiation starting within 8 weeks after their final surgery. Definitive breast radiation will initially include the whole breast, followed by a boost to the primary tumor bed.

Patients receiving radiotherapy will be treated with a linear accelerator with nominal photon energy 4-18 MV (typically 6 MV). Electron therapy will be permitted for the supplemental boost to the primary tumor bed. Co-60 is not allowed. The initial allowable dose for whole-breast radiation is 45-50.4 Gy using conventional fractions of 1.8-2.0 Gy per day, followed by a boost dose to the tumor bed of 10-16 Gy using conventional fractions of 1.8-2.0 Gy to bring the total dose of the tumor bed to 60-66 Gy. The initial allowable dose for accelerated whole-breast radiation is 42.56 Gy using 2.66 Gy daily fractions, followed by a boost dose to the tumor bed of 10 Gy using 2.0-2.5 Gy daily fractions. Patients will receive one treatment per day, five days per week (Monday through Friday). All fields will be treated each day. At least two fractions will be given during the first week of treatment.



All patients with estrogen receptor (ER) positive or progesterone receptor (PR) positive DCIS will be offered endocrine therapy for 5 years, irrespective of their DCIS Score.

## 4. Statistical Considerations

### 4.1 Design

Prior evidence suggests that about 8-12% of patients initially considered candidates for breast conservation surgery based on mammographic imaging would require mastectomy,<sup>15,16</sup> and the use of MRI in addition to mammography would increase the likelihood of requiring a mastectomy by about 1.5-fold.<sup>17</sup> Therefore, we assume that about 10% of patients that enroll on step 1 would require a mastectomy if they have never had an MRI, all of whom would have the mastectomy after an initial attempt at WLE. In addition, we assume that the integration of MRI may increase the likelihood of requiring mastectomy by about 1.5-fold, or to about 15%. Moreover, we anticipate that more mastectomies done after MRI and before WLE may result in fewer mastectomies done after WLE, and assume a 50:50 distribution (7.5% before WLE, 7.5% after WLE).

A sample size of 350 participants would be sufficient to ensure a Wilson 95% confidence interval of expected length 0.08 if the actual proportion was, conservatively, as high as 16% for the end point of interest, and we assumed that complete data would be available on at least 95% of participants. Computations were performed using the PASS 11 software.<sup>18</sup>

### 4.2 Randomization/Treatment Assignment

This study will not randomize participants.

### 4.3 Analysis

The *evaluable* patient set will be defined as all eligible patients who underwent a pre-operative MRI for whom final surgery is known.

Demographic, radiographic, and pathologic characteristics will be summarized and compared for all enrolled patients, evaluable patients, and patients who received a radiotherapy recommendation based on their DCIS Score.

#### 4.3.1 Primary Objective

*To estimate the proportion of patients with DCIS diagnosed on core needle biopsy (CNB) judged to be breast conservation candidates based upon standard imaging (mammography +/- sonography) and physical examination (a) who convert to mastectomy in step 1 based on MRI findings, and (b) who have a mastectomy as the final surgical procedure in step 2.*

The primary endpoint, the overall proportion of patients who converted to mastectomy, will be estimated as a binomial proportion with a corresponding 95% Wilson CI for all evaluable patients. In addition, the proportion of patients who converted to mastectomy based on MRI findings out of all patients who converted to mastectomy, and the proportion of patients who had a mastectomy as the final surgical procedure out of

those that underwent at least one WLE, will be estimated with corresponding 95% Wilson CIs.

#### **4.3.2 Secondary Objectives #1, 3, 4 (covered in this analysis)**

##### **Secondary Objective 1**

*To assess the relation between baseline clinical covariates (e.g., tumor grade, necrosis, histologic type, mammographic lesion size), MRI morphologic and kinetic features, and the DCIS Score.*

Patients who do not have a mastectomy, have adequate tumor free margins of at least 2 mm, and are without invasive/microinvasive disease are required to have tissue samples submitted for DCIS Score evaluation. Patients with available DCIS Scores will be categorized as having a low DCIS Score (< 39) or an intermediate-high DCIS Score ( $\geq 39$ ). Age, diagnostic mammogram longest diameter, tumor grade, ER/PR positivity, radiotherapy course, and endocrine treatment will be compared between the two DCIS Score groups using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for independence for categorical variables.

##### **Secondary Objective 3**

*To estimate the proportion of patients who require re-operation because of inadequate excision after MRI.*

The proportion of patients requiring reoperation will be calculated as the number of evaluable patients who had multiple WLEs out of the number of evaluable patients who had at least one WLE.

##### **Secondary Objective 4**

*To estimate the proportion of patients who proceed to mastectomy after an initial attempt at WLE because of either inadequate tumor-free margins (< 2 mm), or other reasons.*

Of the patients who had at least one WLE, the proportion of patients who proceeded to mastectomy will be calculated.

#### **4.3.3 Exploratory Objectives**

*To estimate the proportion of patients who have an additional biopsy after MRI and before surgery, and characteristics of the biopsy (breast biopsied, type of biopsy performed, imaging guidance used, histologic findings); to evaluate patient preference for surgery before and after MRI; to evaluate patient reasons for conversion to mastectomy; to estimate the proportion of patients who undergo mastectomy as the first surgical procedure and to evaluate the reasons for initial mastectomy; to evaluate the proportions of patients who have a WLE as their first or final surgical procedure; and to evaluate the proportion of patients diagnosed with invasive breast cancer.*

For evaluable participants that undergo an additional biopsy after MRI and before their first surgery, the breast biopsied relative to the known DCIS, the type of biopsy performed, the imaging guidance used for the biopsy, and the most severe histologic finding will be summarized. For patients with additional biopsy findings of DCIS or invasive breast cancer, the laterality of those findings relative to the original known DCIS will be summarized.

For evaluable patients who complete the first QOL questionnaire, patient surgical preference will be summarized by counts and percentages. Similarly, patient preference for surgery will be summarized for patients who completed the second QOL questionnaire.

The reasons for conversion to mastectomy for evaluable patients who receive a mastectomy at any time will be summarized by counts and percentages. In addition, the proportion of evaluable patients who underwent mastectomy as the first surgical procedure will be estimated along with its 95% Wilson CI, and the reasons for conversion to mastectomy among those patients will be summarized.

The proportion of evaluable patients who have at least one WLE and its 95% Wilson CI will be calculated. Of the patients who have at least one WLE, the proportion of patients who have WLE as their final surgery and its 95% Wilson CI will be calculated.

The proportion of patients diagnosed with invasive breast cancer at any time after study enrollment will be estimated with its corresponding 95% Wilson CI, and the final surgical procedure for those patients will be reported.

#### **4.4 Reference Standard (for Imaging Studies)**

Not applicable.

## 5. References

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## 6. Figures

### Eligibility (Section 3.0)

- DCIS on core biopsy
- No invasive or micro-invasive carcinoma
- Diagnostic mammogram of the affected breast within 3 months prior to registration and a two-view (full view CC and a full view MLO) mammogram of both breasts within 6 months of registration (if the patient has only one breast, a unilateral exam of the intact breast is required).
- No prior breast MRI within 6 months of registration
- Candidate for wide local excision

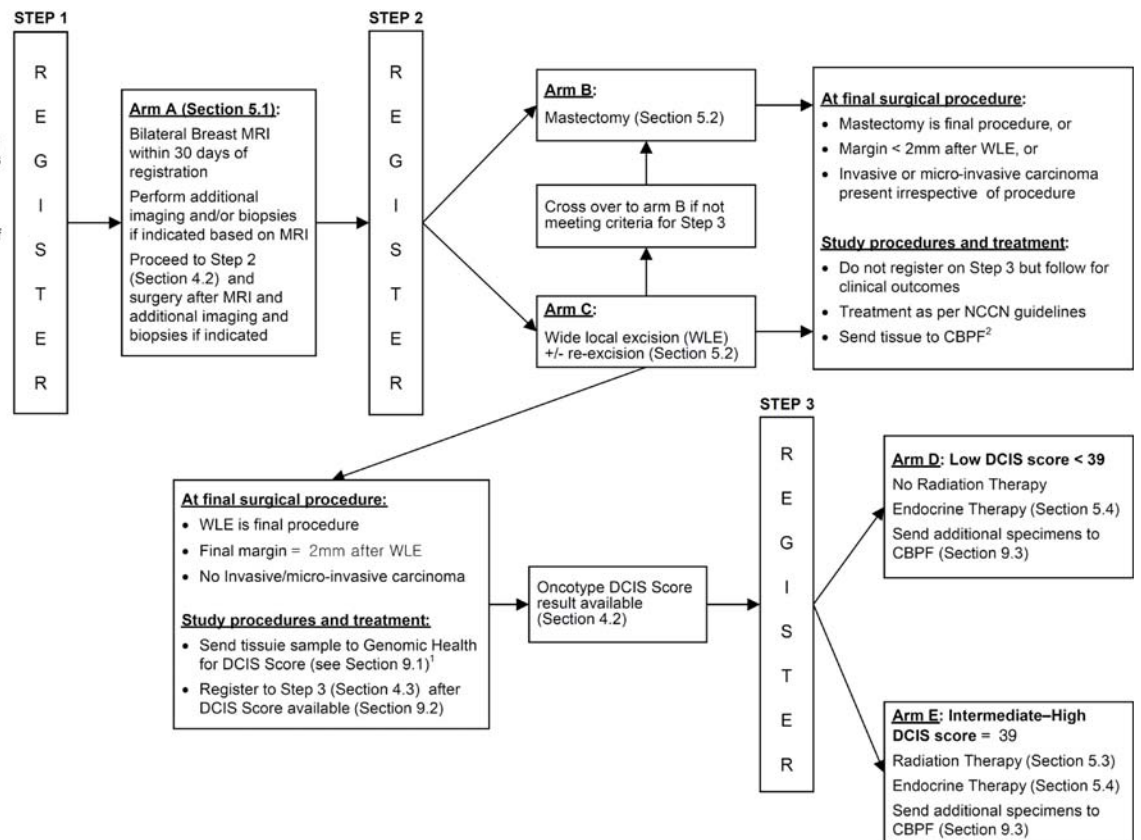


Figure 1 – Study schema

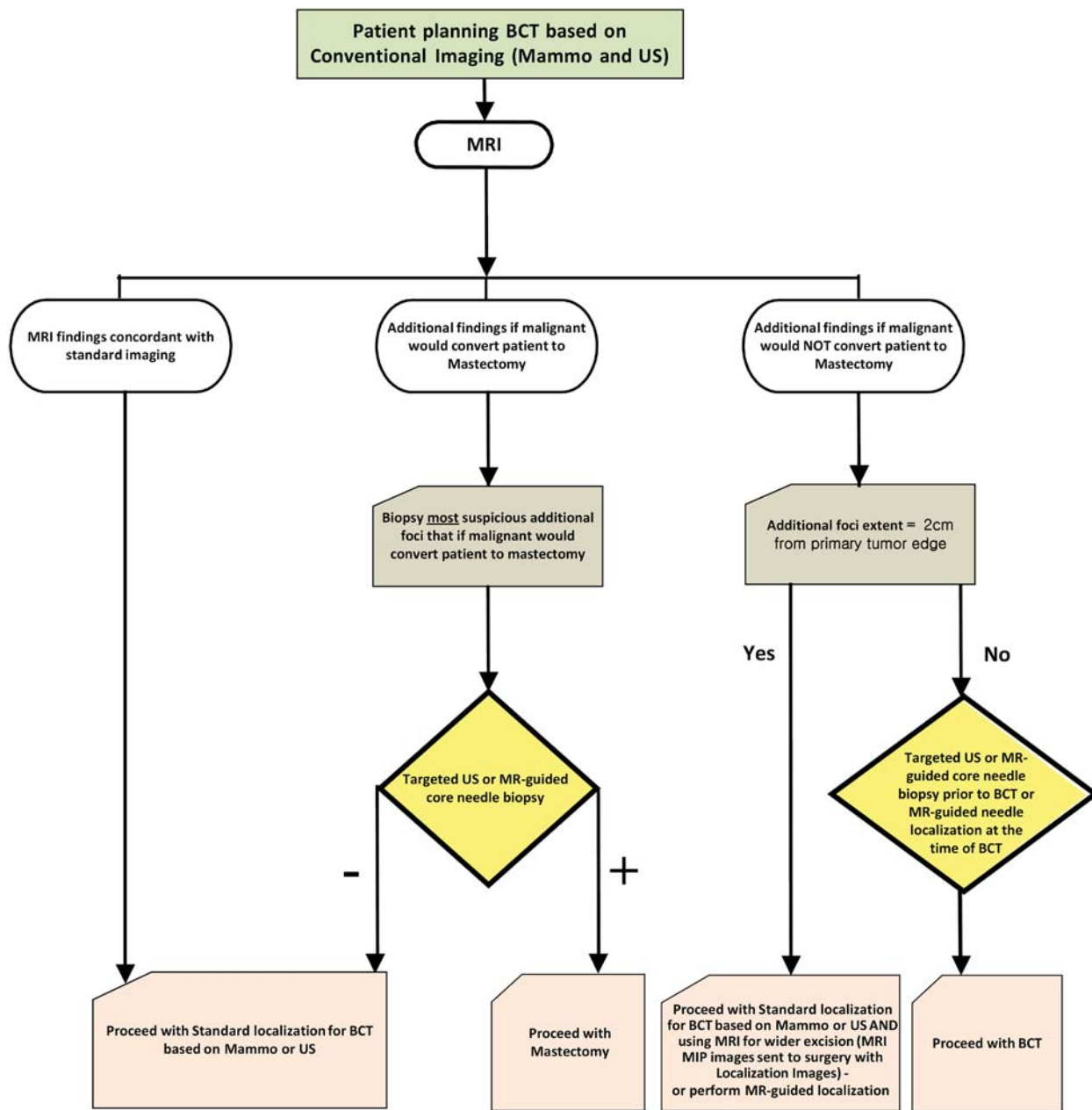


Figure 2 – MRI findings management flow chart