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E4112

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

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For patient eligibility or treatment-related questions Contact the Study PI of the Lead Protocol Organization.		
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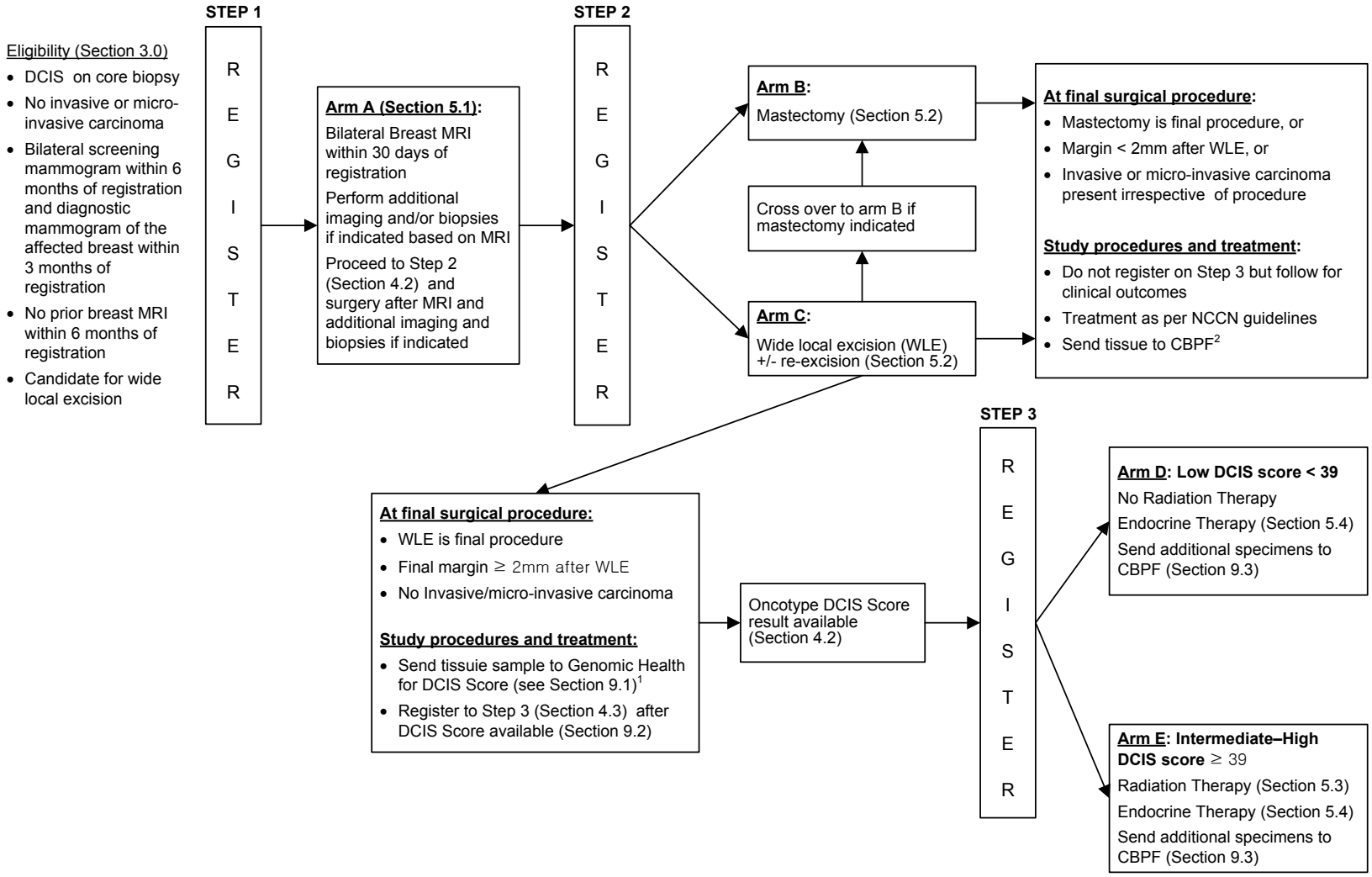
Schema



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.[1] 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[2], and the term "ductal intraepithelial neoplasia" (DIN) has been proposed as an alternative classification of this spectrum. [3] The frequency of DCIS diagnosis has increased up to 7-fold since mammography became routine[4], and now accounts for up to 28% of all breast carcinomas in the United States in 2012, or an estimated 63,300 new cases.[5] 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.[6]

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.[7] 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 ($P < 0.00001$).[8] 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).[9,10]

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[11]. 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.[1]

The ECOG-ACRIN research group proposes a prospective clinical trial that will address specific recommendations of an NIH State of the Science Conference[12], 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.[13]

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 Onco*type* 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).

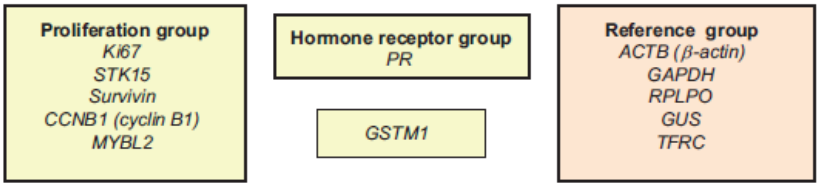


Figure 1. Panel of 12 genes included in the DCIS Score. Seven cancer-related genes: *Ki67* = MKI67; *STK15* = aurora kinase A; *survivin* = BIRC5; *CCNB1* = cyclin B1; *MYBL2* = v-myb myeloblastosis viral oncogene homolog (avian)-like 2; *PR* = progesterone receptor; and *GSTM1* = glutathione S-transferase 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$_{\mu}$ is calculated as: DCIS Score$_{\mu}$ = +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$_{\mu}$) + 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. [13] 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.[14] Eligible patients had either: low or intermediate grade DCIS with tumor size ≤ 2.5 cm (Cohort 1); or high grade DCIS with tumor size ≤ 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.[15 16] 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)[35]. 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 (≥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 [11]; 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-exicion procedures.

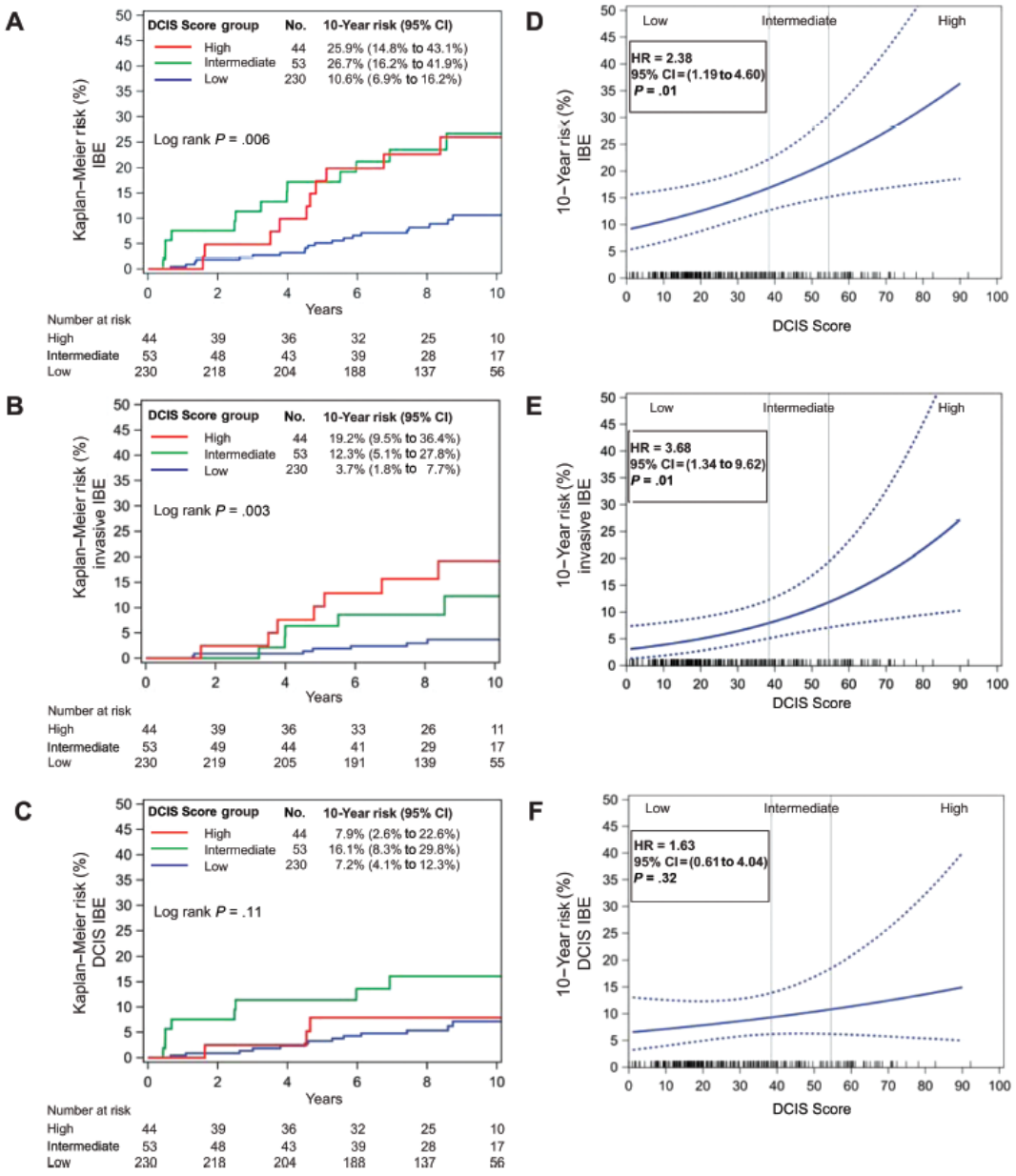


Figure 2. Kaplan–Meier plots and 10-year risk estimates with 95% confidence intervals (CIs) for developing an ipsilateral breast event (IBE), an invasive IBE, and a ductal carcinoma in situ (DCIS) IBE. The number of patients at risk are included below each plot for each prespecified risk group, based on the DCIS Score of low (< 39), intermediate (39–54), and high (≥ 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.[12] 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.[17] 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.[18] 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%). [19] 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.[19]. Instead, unique morphological features such as non-mass enhancement are more useful than kinetic features for diagnosis. [20-22] 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.[23] This suggests MRI may provide information regarding DCIS microenvironment such as basement membrane permeability.[24] 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. [25] 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.[26] Data on re-excision rates (postulated to be lower following MRI-based surgical planning) have shown no advantage for MRI-based DCIS excision.[27,28] 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%).[44] 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 [33] 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."[12] 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.[36] 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.[37] 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.[38] 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.[39, 40, 41] 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.[42] 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.[52] This tool has the potential to inform cost-effectiveness analyses.

1.6.2 Study hypotheses:

Primary PRO hypothesis:

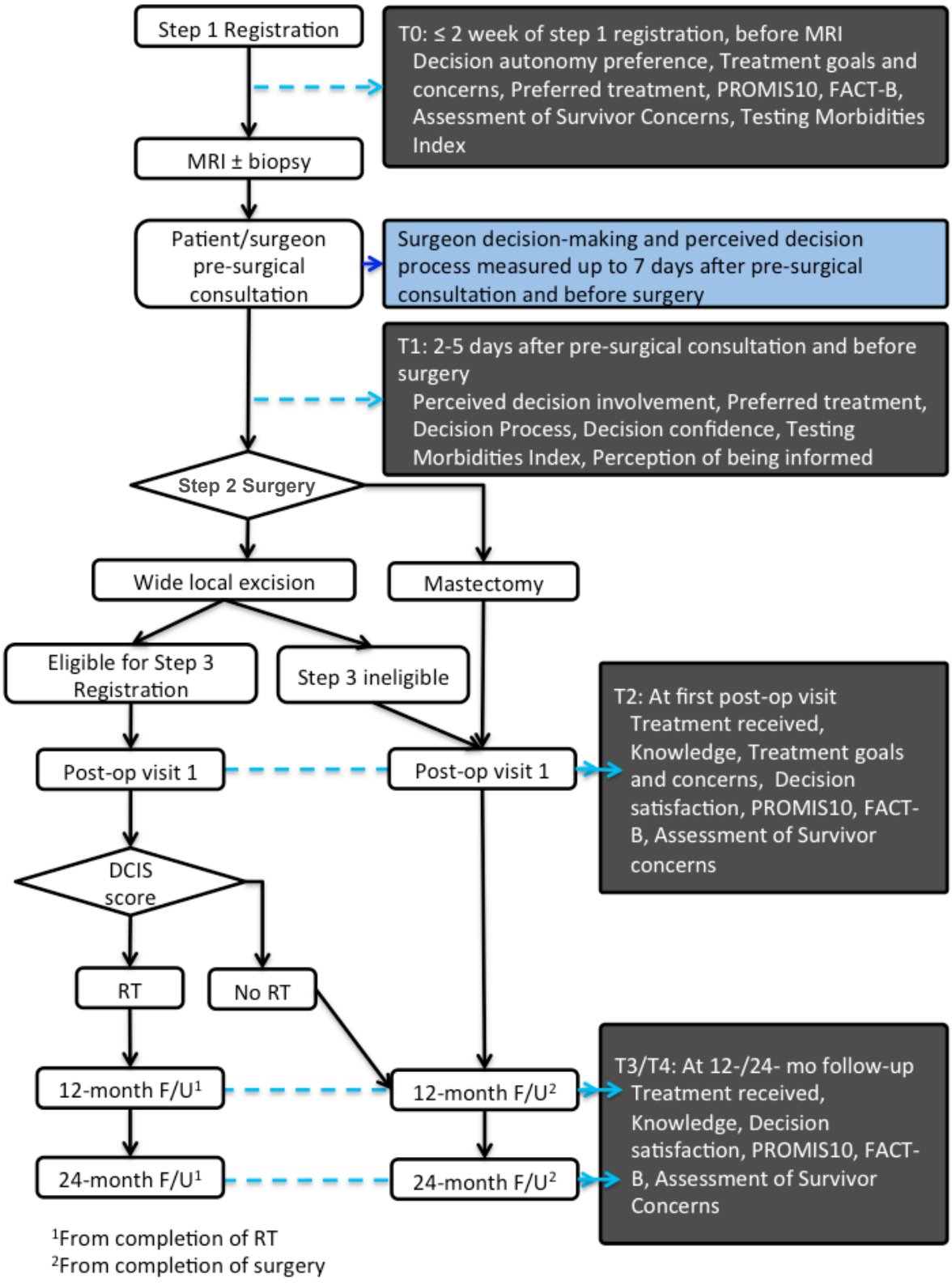
1. Women with DCIS receive treatment that is concordant with their treatment goals and concerns.

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.


Step 1 Registration
T0: ≤ 2 week of step 1 registration, before MRI
Decision autonomy preference, Treatment goals and concerns, Preferred treatment, PROMIS10, FACT-B, Assessment of Survivor Concerns, Testing Morbidities Index
MRI ± biopsy
Patient/surgeon pre-surgical consultation
Surgeon decision-making and perceived decision process measured up to 7 days after pre-surgical consultation and before surgery
T1: 2-5 days after pre-surgical consultation and before surgery
Perceived decision involvement, Preferred treatment, Decision Process, Decision confidence, Testing Morbidities Index, Perception of being informed
Step 2 Surgery
Wide local excision
Mastectomy
Eligible for Step 3 Registration
Step 3 ineligible
Post-op visit 1
Post-op visit 1
T2: At first post-op visit
Treatment received, Knowledge, Treatment goals and concerns, Decision satisfaction, PROMIS10, FACT-B, Assessment of Survivor concerns
DCIS score
RT
No RT
12-month F/U1
12-month F/U2
24-month F/U1
24-month F/U2
T3/T4: At 12-/24- mo follow-up
Treatment received, Knowledge, Decision satisfaction, PROMIS10, FACT-B, Assessment of Survivor Concerns
1From completion of RT
2From completion of surgery

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.[46,47] 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.[45]

Treatment Goals and Concerns will be measured using items adapted from the Breast Cancer Surgery Decision Quality Instrument Worksheet developed by Sepucha et al.[57,58] 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.[45] 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.[57] 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.[57]

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). [48,49]

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.[34]

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.[52] 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). [54-56]

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.[45]

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 (cancercare.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 using the web platform. At the start of the study, all participating surgeons will be asked to provide contact information. This information will be maintained in a dedicated SQL server independent of the main study database.

Surgeons 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 surgeon account. The web site will reference a study-specific toll-free phone number that surgeons can use to reach the OEAU staff should they have questions or need assistance. All data will be stored on a secure server. If surgeons 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 surgeon has been able to access the questionnaire on the web. If surgeons have still not responded within 5 working days of the original e-mail, the OEAU Research Associate will attempt to telephone the surgeon and administer the questionnaire by telephone. If questionnaires are telephone-administered, they will be marked as such.

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

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 ≥ 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. 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 bilateral screening mammogram within 6 months and diagnostic mammogram of the affected breast within 3 months prior to registration.

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 objects or implanted medical devices in body (i.e., cardiac pacemaker, aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, tattoos near the eye, or steel implants);

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 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^2 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.

All females of childbearing potential must have a blood test or urine study within 3 weeks 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.

_____ _____

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 (≥ 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.

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 Onco*type*DX 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. **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.

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.

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.

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.

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.

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 sugery as their final surgical procedure during step 2 with surgical margin status ≥ 2mm and have DCIS only, pathology materials are to be submitted to Genomic Health, Inc. for determination of Onco*type* 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 Onco*type*DX 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 < 2mm. 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
  - 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.

5. Treatment Plan

Step 1:

- All patients will undergo MRI within 30 days following registration to Step 1 and prior to surgery (see section 5.1 for guidelines for MRI imaging).
- 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); if initial biopsies are performed, patients will proceed to step 2 only if the biopsy reveals pure DCIS.
- Proceed to step 2 after MRI performed and clinical decision has been made regarding the planned surgical procedure (i.e., wide local excision or mastectomy).

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).
- If additional biopsies were performed after step 1, registration to step 2 will only take place if the biopsy reveals pure DCIS.
- 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.
- Registration to step 3 may take place after the DCIS Score report has been received by the site/treating physician.
- For patients who have undergone mastectomy and/or have invasive or microinvasive carcinoma during step 2, surgical tissue will NOT be submitted to GHI, but rather to the CBPF Patients with invasive or microinvasive carcinoma will be managed as clinically indicated in accordance with NCCN guidelines, and will be followed for clinical outcomes

Step 3:

- Only patients with pure DCIS treated with wide local excision and adequate negative margins (≥ 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:
- Low DCIS Score (< 39): No radiation therapy
- Intermediate-High DCIS Score (≥ 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.

5.1 Imaging

5.1.1 Magnetic Resonance Site Qualification

Prior to patient enrollment, all participating sites must be accredited for breast MRI.

Prior to patient enrollment, all participating sites must be ACRIN qualified for breast MRI.

Sites meeting ACR Breast MRI Accreditation Program Requirements are automatically eligible to participate. Documentation of accreditation should be submitted via CTSU.

If a site is not ACR accredited for breast MRI, sites must complete the Breast MRI Quality Assessment Form and related instructions for qualification and site activation.

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

MRI Test Imaging Requirements

For the pre-contrast and post-contrast T1-weighted series, the following parameters must be met:

Sequence	Slice Thickness	Gap	Maximum In Plane Pixel Dimension for Phase and Frequency
Sagittal, Axial and/or Coronal	< 3 mm	0 mm	<1 mm

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 whole body 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)
  - A 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
  - 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

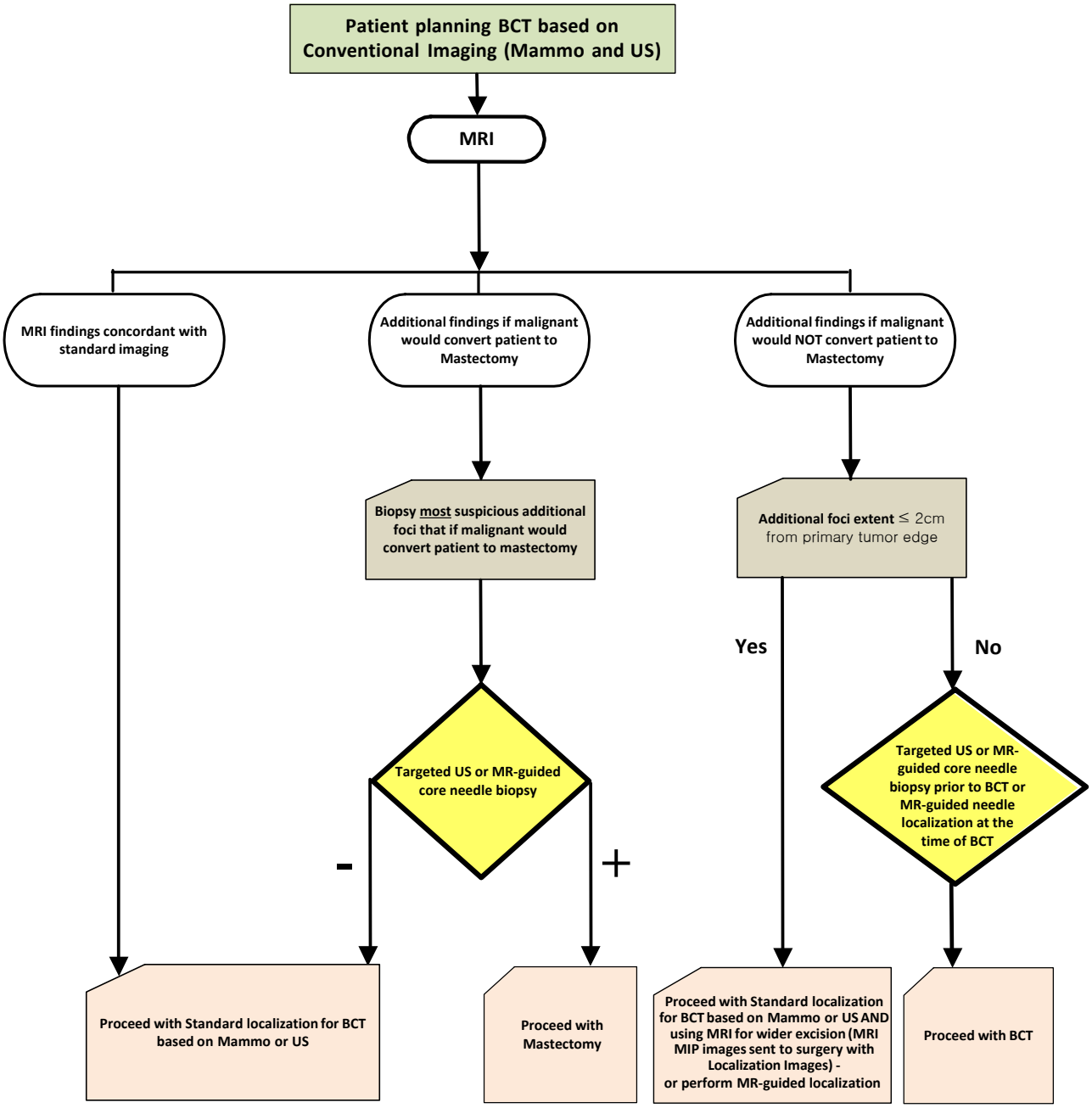
- Care should be taken to select the smallest FOV and slice coverage that completely encompasses both breasts and axilla

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 ≤ 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 ≤ 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: 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. ACRIN will provide installation 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 ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software.

For more information, contact:

TRIAD-support@phila.acr.org or call 215-940-8820

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.

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 should be performed for all mastectomy patients; for breast conserving procedures, sentinel node biopsy should not be performed.

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 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

≥ 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 ≥ 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.qarc.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).
- Copy of the ECOG-ACRIN E4112 Checklist for Submission of Radiation Oncology Quality Assurance Materials (located at 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

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 *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* 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 or by phone at 1-888-283-7457.

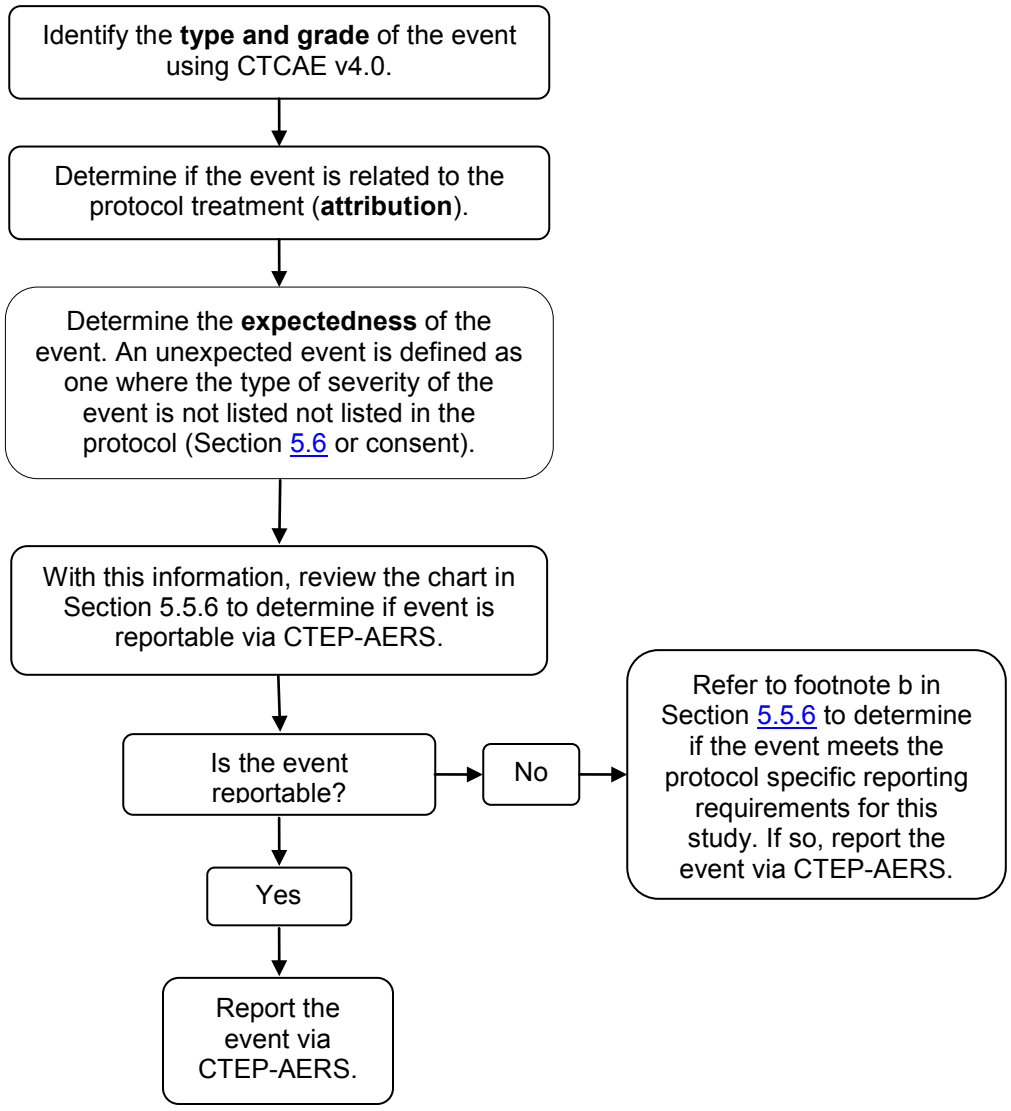
5.5.4 Determination of Reporting Requirements

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[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last day of treatment regardless of attribution.

NOTE: Any death that occurs > 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 Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* 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 aemd@tech-res.com or 301-897-7497. Thjs will need to be discussed on a case-by-case basis.

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^2) 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.

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[1]	Follow-up[2]
History and Physical	X[3]				
Height, Weight, and ECOG Performance Status	X[3]				
Visit to monitor for ipsilateral breast event (IBE)					X[2]
Serum creatinine	X[4]				
Pregnancy test (for women of childbearing potential)	X[4]				
Mammogram (+/- ultrasound)[6]	X[5,6]				X[2]
Core needle biopsy documenting DCIS	X				
MRI		X[6]			
FFPE Tissue Submission[7]	X		X		
Patient and Surgeon Surveys	See Section 7.2				

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 7 days prior to registration to Step 1
4. Within 28 days prior to registration to Step 1
5. A diagnostic mammogram of the affected breast is required within 3 months prior to registration. A bilateral screening mammogram must have been done within 6 months prior to registration.
6. 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.
7. 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.

7.2 Patient and Surgeon Survey Schedule

	Baseline[1]	Prior to Surgery[2]	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 [33, 43], and the use of MRI in addition to mammography increases the likelihood of requiring a mastectomy by about 1.5-fold.[24] 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 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 (< 3mm), 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-Meir 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.[58] 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**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	4	0	0	4
Not Hispanic or Latino	346	0	0	346
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	**350**	**0**	**0**	**350**
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
Racial Category: Total of all subjects*	**350**			**350**

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 ≥3mm 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 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.

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:
• DCIS only • wide local excision • surgical margins ≥ 3mm	Surgical Tissue[1]	• Oncotype DX Requisition Form (example in Appendix II), select Breast Cancer Assay for Ductal Carcinoma in Situ **NOTE:** Pathology reports to be faxed to ECOG CBPF. Label with E4112, protocol specific patient ID#, and the GHI requisition number OncotypeDX Patient Report to be uploaded	Customer Service **Genomic Health, Inc.** 301 Penobscot Drive Redwood City, CA 94063 Telephone: 866-662-6897
All patients registered to Step 1	Pre-trial diagnostic tissue samples	• Pathology Report with immunologic studies, if available	**ECOG-ACRIN Central Biorepository and Pathology Facility** 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 **Fax forms to**: 713-563-6506
• Mastectomy is final procedure, or • Margin < 3mm after WLE, or • Invasive or micro-invasive carcinoma present irrespective of procedure	Surgical Tissue	• Pathology Report with immunologic studies, if available • Surgical Report • STS-generated Shipping Manifest	
All patients • Following Step 1 registration • Following Surgery		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.

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**
- **≥ 3mm surgical margins**

This section outlines the submission of surgical tissue for the Onco*type*DX 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 Onco*typeDX* Specimen Kit

Prior to pre-registration, contact Genomic Health Customer Service (866-662-6897) and request the "Onco*type* 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 Onco*type* 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 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. 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 Onco*typeDX* 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 Onco*type*DX 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) 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 < 3mm

Formalin paraffin-embedded DCIS/tumor tissue block

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

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

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 (>/= 3 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 2.21). 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 Onco*type* DX® 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 (Onco*type* DX™ Breast Cancer Assay, Genomic Health, Redwood, CA; http://www.genomichealth.com/oncotype) is performed within 10-14 days.

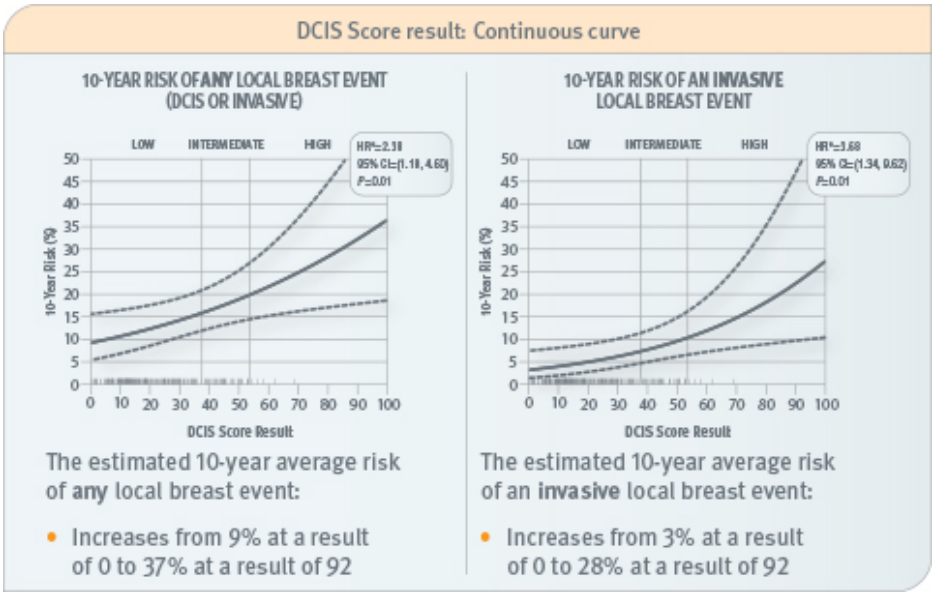
Using manually microdissected DCIS tissue the Onco*type* DX® Breast Cancer Assay is run which includes all 21 genes from the Recurrence Score. The DCIS Score result is generated from 12 of the 21 Recurrence Score, these genes specific to the calculation of the DCIS Score result, and they include 7 cancer-related 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 (Onco*type* DX)

Group	Genes
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.[35]



*HR=hazard ratio.

Table 2. Genomic DCIS Score, Results from Validation Study[35]

Recurrence Score (1–100)	Risk group	No. (%)	10-year risk of any local breast event (95% C.I.)	10-year risk of an invasive local breast event (95% C.I.)
< 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.

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).

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.

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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 ≥ 3mm 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

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

9/12/14

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

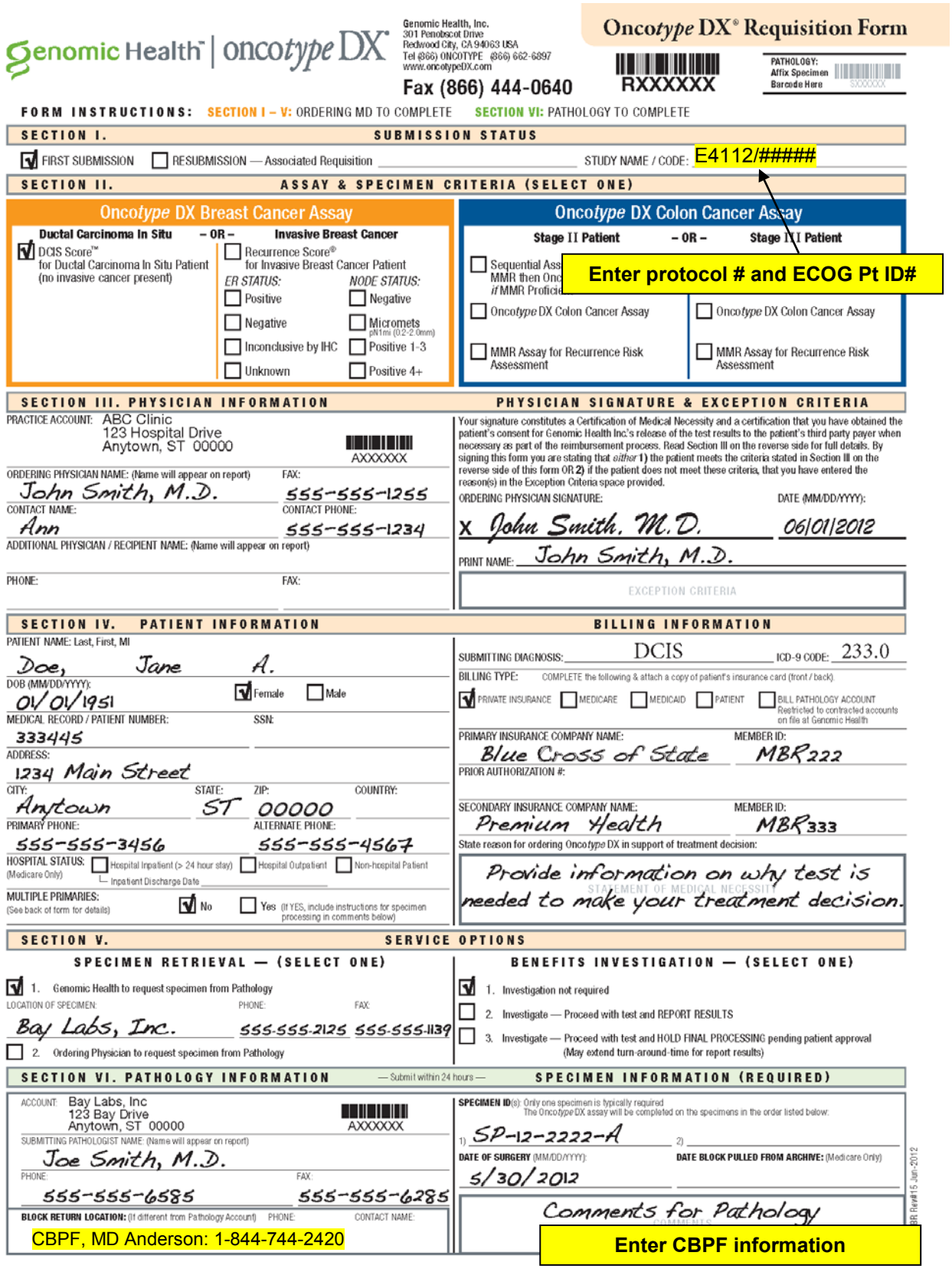
Appendix II

Sample Genomic Health Oncotype DX® Requisition Form

From patients who have DCIS only, have undergone wide local excision with surgical margins ≥ 3mm 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.



Genomic Health | oncotype DX

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Tel (866) ONCOTYPE (866) 662-6897
www.oncotypeDX.com
Fax (866) 444-0640

Oncotype DX® Requisition Form

RXXXXXX

PATHOLOGY: Affix Specimen Barcode Here SXXXXXX

FORM INSTRUCTIONS: SECTION I – V: ORDERING MD TO COMPLETE SECTION VI: PATHOLOGY TO COMPLETE

ORDERING PHYSICIAN to Complete

SECTION I. SUBMISSION STATUS

☑ FIRST SUBMISSION ☐ RESUBMISSION — Associated Requisition _____ STUDY NAME / CODE: E4112/#####

SECTION II. ASSAY & SPECIMEN CRITERIA (SELECT ONE)

Oncotype DX Breast Cancer Assay

Ductal Carcinoma In Situ – OR – Invasive Breast Cancer

☑ DCIS Score™ for Ductal Carcinoma In Situ Patient (no invasive cancer present)

☐ Recurrence Score® for Invasive Breast Cancer Patient

ER STATUS: ☐ Positive ☐ Negative ☐ Inconclusive by IHC ☐ Unknown

NODE STATUS: ☐ Negative ☐ Micromets pN1mi (0.2-2.0mm) ☐ Positive 1-3 ☐ Positive 4+

Oncotype DX Colon Cancer Assay

Stage II Patient – OR – Stage III Patient

☐ Sequential Ass… MMR then Onc… if MMR Proficie…

☐ Oncotype DX Colon Cancer Assay ☐ Oncotype DX Colon Cancer Assay

☐ MMR Assay for Recurrence Risk Assessment ☐ MMR Assay for Recurrence Risk Assessment

Enter protocol # and ECOG Pt ID#

SECTION III. PHYSICIAN INFORMATION

PRACTICE ACCOUNT: ABC Clinic
123 Hospital Drive
Anytown, ST 00000
AXXXXXX

ORDERING PHYSICIAN NAME: (Name will appear on report) John Smith, M.D.
FAX: 555-555-1255
CONTACT NAME: Ann
CONTACT PHONE: 555-555-1234
ADDITIONAL PHYSICIAN / RECIPIENT NAME: (Name will appear on report)
PHONE:
FAX:

PHYSICIAN SIGNATURE & EXCEPTION CRITERIA

Your signature constitutes a Certification of Medical Necessity and a certification that you have obtained the patient's consent for Genomic Health Inc.'s release of the test results to the patient's third party payer when necessary as part of the reimbursement process. Read Section III on the reverse side for full details. By signing this form you are stating that *either* **1)** the patient meets the criteria stated in Section III on the reverse side of this form OR **2)** if the patient does not meet these criteria, that you have entered the reason(s) in the Exception Criteria space provided.

ORDERING PHYSICIAN SIGNATURE: X John Smith, M.D.
DATE (MM/DD/YYYY): 06/01/2012
PRINT NAME: John Smith, M.D.
EXCEPTION CRITERIA

SECTION IV. PATIENT INFORMATION

PATIENT NAME: Last, First, MI: Doe, Jane A.
DOB (MM/DD/YYYY): 01/01/1951
☑ Female ☐ Male
MEDICAL RECORD / PATIENT NUMBER: 333445
SSN:
ADDRESS: 1234 Main Street
CITY: Anytown
STATE: ST
ZIP: 00000
COUNTRY:
PRIMARY PHONE: 555-555-3456
ALTERNATE PHONE: 555-555-4567
HOSPITAL STATUS: (Medicare Only) ☐ Hospital Inpatient (> 24 hour stay) ☐ Hospital Outpatient ☐ Non-hospital Patient
└ Inpatient Discharge Date _____
MULTIPLE PRIMARIES: (See back of form for details) ☑ No ☐ Yes (If YES, include instructions for specimen processing in comments below)

BILLING INFORMATION

SUBMITTING DIAGNOSIS: DCIS
ICD-9 CODE: 233.0
BILLING TYPE: COMPLETE the following & attach a copy of patient's insurance card (front / back)
☑ PRIVATE INSURANCE ☐ MEDICARE ☐ MEDICAID ☐ PATIENT ☐ BILL PATHOLOGY ACCOUNT Restricted to contracted accounts on file at Genomic Health
PRIMARY INSURANCE COMPANY NAME: Blue Cross of State
MEMBER ID: MBR222
PRIOR AUTHORIZATION #:
SECONDARY INSURANCE COMPANY NAME: Premium Health
MEMBER ID: MBR333
State reason for ordering Oncotype DX in support of treatment decision:
STATEMENT OF MEDICAL NECESSITY
Provide information on why test is needed to make your treatment decision.

SECTION V. SERVICE OPTIONS

SPECIMEN RETRIEVAL — (SELECT ONE)

☑ 1. Genomic Health to request specimen from Pathology
LOCATION OF SPECIMEN: Bay Labs, Inc.
PHONE: 555-555-2125
FAX: 555-555-1139
☐ 2. Ordering Physician to request specimen from Pathology

BENEFITS INVESTIGATION — (SELECT ONE)

☑ 1. Investigation not required
☐ 2. Investigate — Proceed with test and REPORT RESULTS
☐ 3. Investigate — Proceed with test and HOLD FINAL PROCESSING pending patient approval (May extend turn-around-time for report results)

PATHOLOGY to Complete

SECTION VI. PATHOLOGY INFORMATION — Submit within 24 hours —

ACCOUNT: Bay Labs, Inc
123 Bay Drive
Anytown, ST 00000
AXXXXXX
SUBMITTING PATHOLOGIST NAME: (Name will appear on report) Joe Smith, M.D.
PHONE: 555-555-6585
FAX: 555-555-6285
BLOCK RETURN LOCATION: (If different from Pathology Account) PHONE: CONTACT NAME:
CBPF, MD Anderson: 1-844-744-2420

SPECIMEN INFORMATION (REQUIRED)

SPECIMEN ID(s): Only one specimen is typically required. The Oncotype DX assay will be completed on the specimens in the order listed below.
1) SP-12-2222-A
2)
DATE OF SURGERY (MM/DD/YYYY): 5/30/2012
DATE BLOCK PULLED FROM ARCHIVE: (Medicare Only)
Comments for Pathology
COMMENTS

Enter CBPF information

BR Rev#15 Jun-2012

Genomic Health™ oncotype DX® Breast Cancer Assay oncotype DX® Colon Cancer Assay

BREAST & COLON PATHOLOGY GUIDELINES

SELECTING THE MOST REPRESENTATIVE BREAST OR COLON TUMOR BLOCK

A. Choose the one block with the greatest amount/area of the highest grade carcinoma, morphologically consistent with the submitting diagnosis.

B. Neutral buffered formalin is the preferred fixative. Alternative fixatives are not recommended.

C. Hemorrhage, necrosis, and adipose tissue do not need to be minimized. They contain little RNA and thus do not significantly impact this assay.

D. For breast carcinoma submissions, microinvasive carcinomas (one or more foci < 0.1 cm) are not acceptable samples.

E. For DCIS submissions, total mastectomy specimens are not appropriate samples.

SPECIMEN PREPARATION INSTRUCTIONS

BLOCKS

1. Follow your laboratory's standard practice guidelines for the processing of fixed paraffin embedded (FPE) tissue.
2. Apply one S barcode label, obtained from the inner top lid of the Oncotype DX® Specimen Kit, to each block. (See photo, left).
3. Place the tumor block in the small plastic bag and seal the bag.
4. *Do not* submit an H&E slide when you are submitting tumor blocks. Genomic Health® will prepare an H&E slide on site.
5. Secure the specimen in the foam insert inside the Oncotype DX Specimen Kit.
6. 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.

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

   B. Hand number the serially sectioned unstained slides (1-15) to indicate the order in which they were cut.
3. 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.
4. Seal the large secondary containment bag and close the box using the tab.

SHIPPING INSTRUCTIONS

MATERIALS AND EQUIPMENT:

1. Oncotype DX Requisition Form
2. Copy of Pathology Report
3. Oncotype DX Specimen Kit containing the patient specimen
4. FedEx® US Airbill pre-printed with Genomic Health shipping information
5. FedEx® Clinical Pak, Large — a plastic "over wrap" used to ship the specimen to Genomic Health
6. FedEx® adhesive airbill pouch for the FedEx® Airbill

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

REQUISITION FORM AND SUPPORTING MATERIALS:

1. 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.
2. Before shipping, make a copy of the Oncotype DX Requisition Form and retain it for your records.
3. 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 Penobscot Drive | Redwood City CA 94063 USA | www.oncotypeDX.com

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

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	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.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	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)

Appendix V

Oncotype DX Patient Report

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

To order the "Onco*type* 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 "Onco*type* DX Requisition Form" and instructions on how the requisition form MUST be completed

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

After receipt of the patient report, **fax** a redacted copy of the first page of the "Onco*type* DX Patient Report" (labeled with protocol number (E4112), patient initials and case number) to the ECOG-ACRIN Operations Office (FAX: 617-582-8578, Attn: Pre-registration/E4112).

Registration to step 2, for patients diagnosed with DCIS only and have undergone excisional surgery only with margin status ≥ 3mm, 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.

genomic health | oncotype DX Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2000
www.oncotypeDX.com

Page 1 of 2

PATIENT REPORT

Patient/ID: Doe, Jane **E4112/##### - D,J**
Sex: Female
Date of Birth: 01-Jan-1950
Medical Record/Patient #: 556877771
Date of Surgery: 25-Sep-2008
Specimen Type/ID: Breast/SURG-0001

Requisition: R00003G
Specimen Received: 05-May-2009
Date Reported: 15-May-2009
Client: Community Medical Center
Ordering Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Recipient: Dr. Sally M Jones

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

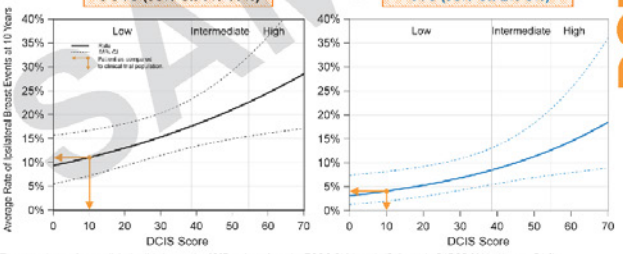
DCIS Score = 10 The findings summarized in the Clinic
patient population. It is unknown whet

CLINICAL EXPERIENCE: PROGNOSIS FOR D

The Clinical Validation study included female patients with DCIS treated with local excision without irradiation, and required clear surgical margins ≥ 3 mm and a lesion size of ≤ 2.5 cm. Approximately a third of patients were treated with tamoxifen.
The average 10 year rate for ipsilateral breast events for patients who had a DCIS Score of 10 was:

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

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



DCIS

These results are from a clinical validation study of 327 patients from the ECOG 5194 study (Solin et al., SABCS 2011. Abstract S4-6).

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1019272

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 advisable to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

OSR-8001 Rev001

3. ADD PROTOCOL# AND CASE: E4112/#####

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

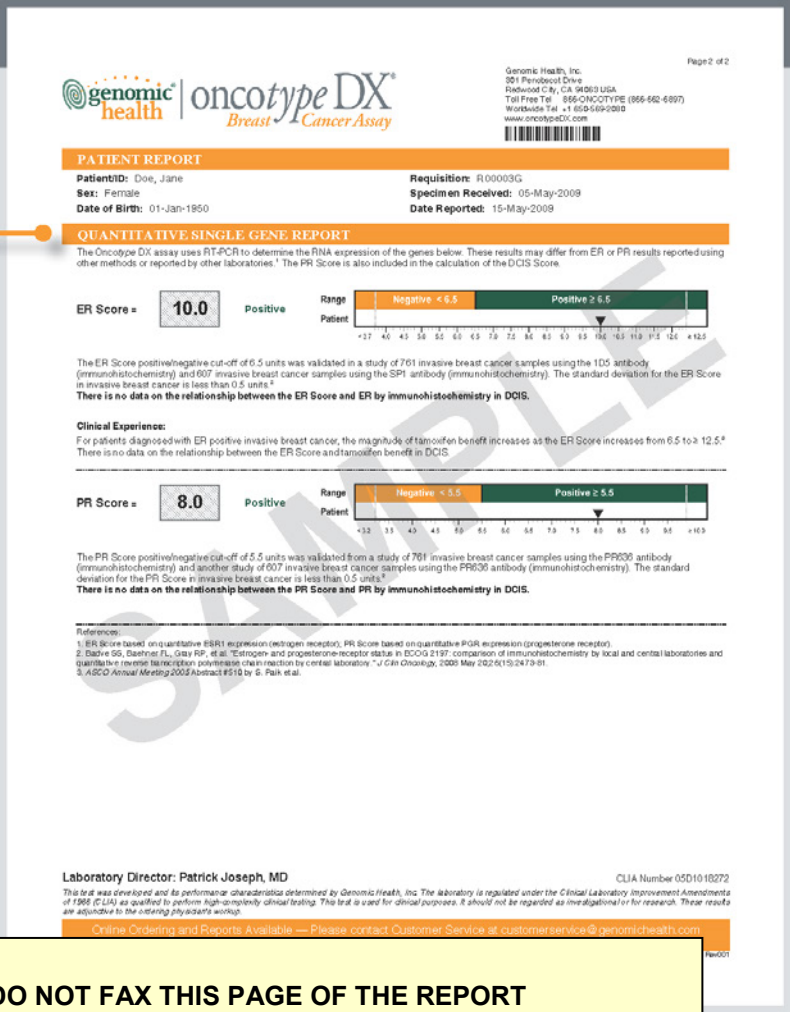
*In the clinical val ... e intervals are wide.

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

Oncotype DX® 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.



genomic health | oncotype DX® Breast Cancer Assay

Page 2 of 2

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2000
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
Date of Birth: 01-Jan-1950
Requisition: R00003G
Specimen Received: 05-May-2009
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.[1] The PR Score is also included in the calculation of the DCIS Score.

ER Score = 10.0 **Positive**

Range: Negative < 6.5 | Positive ≥ 6.5
Patient

The ER Score positive/negative cut-off of 6.5 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 SP1 antibody (immunohistochemistry). The standard deviation for the ER Score in invasive breast cancer is less than 0.5 units.[2]
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 6.5 to ≥ 12.5.[3]
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
Patient

The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 invasive breast cancer samples using the PR636 antibody (immunohistochemistry) and another study of 607 invasive breast cancer samples using the PR636 antibody (immunohistochemistry). The standard deviation for the PR Score in invasive breast cancer is less than 0.5 units.[2]
There is no data on the relationship between the PR Score and PR by immunohistochemistry in DCIS.

References:
1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor).
2. Badve SS, Baehner FL, Gray RP, et al. "Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory." *J Clin Oncology*; 2008 May 20;26(15):2473-81.
3. *ASCO Annual Meeting 2005* Abstract #510 by S. Paik et al.

SAMPLE

Laboratory Director: Patrick Joseph, MD CLIA Number 05D1018272

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 adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

Rev001

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.

GHI10054_1111