

# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. DOI: [10.1056/NEJMoa1804710](https://doi.org/10.1056/NEJMoa1804710)

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

## **Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer**

This supplement contains the following items:

### **1. Original protocol (Version date 4/7/06 on protocol cover page), final protocol (Version date 4/25/14 on protocol cover page), summary of changes (described below).**

The study was activated for patient accrual on April 7, 2006, and was permanently closed to accrual after meeting its accrual goal on October 6, 2010. Between activation and the current date (August 20, 2015), there have been 10 protocol updates (including administrative changes only) and 8 protocol addenda (4 including only administrative changes) to the protocol. The only addenda reflecting major changes to the original version of the protocol include the following, of which only one is relevant (Addendum 4) to the current publication describing the low-risk registry:

- Addendum 4 (3/18/09) – Amendment of accrual goal and statistical analysis plan.
- Addendum 5 (1/13/10) – A quality of life sub-study was added on the last 1000 patients enrolled.
- Addendum 6 (2/29/12) – The DMC monitoring plan was amended as described below in summary of changes to statistical analysis plan.
- Addendum 7 (2/25/13) – A biospecimen collection sub-study (EL1112) was added for patients who had not relapsed in order to create a “Late Relapse Biospecimen Bank”.

### **2. Original statistical analysis plan, final statistical analysis plan, summary of changes**

#### **a. Original statistical analysis plan:**

The primary endpoint is disease-free survival (DFS), defined to be time from randomization to first event, where the first event is any of ipsilateral breast tumor recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers), or death without evidence of recurrence (as defined in reference 4). DFS is used for the primary endpoint rather than distant relapse-free interval (DRFI, as defined in Section 6), which was used as the primary endpoint in the development of the assay, because DFS is the standard endpoint for evaluating adjuvant treatments for breast cancer, and the important question here, as in other treatment studies, is whether chemotherapy results in an overall DFS benefit of sufficient magnitude to justify its use. Patients will be followed for distant failure following local recurrence. (Note: In various presentations, the primary endpoint of the analyses of the assay in the B-20 and B-14 studies was called DRFS, and it was called ‘distant recurrence’ in the NEJM paper, but the definition used is the same as DRFI here.) DRFI is a key secondary endpoint, and RFI and OS as defined in Section 6 will also be analyzed.

Patients being considered for this study will have their RS evaluated, most after pre-registration on this study, but RS evaluation prior to initial registration is also allowed. Patients with an RS of 11 – 25 will be randomized. The randomization will be stratified on tumor size ( $\leq 2$  cm vs.  $> 2$  cm), menopausal status (pre vs. post), planned chemotherapy (taxane containing or not), and planned radiation therapy [whole breast, no boost planned vs. whole breast, boost planned vs. partial breast irradiation planned vs. no planned radiation therapy (for patients who have had a mastectomy)], as described in Section 4.

The overall DFS hazard rate on the tamoxifen + CMF arm of B-20 was .025 / year, which under an exponential distribution, gives 5-year and 10-year DFS rates of approximately 88% and 78%. In the preliminary results, the 5-year and 10-year DRFIs in the RS 11 – 25 group on tamoxifen+chemo are 97% and 94%, and the 5-year and 10-year DFS rates are 91% and 76%. For purposes of the calculations here, we assume exponential failure distributions with 5-year and 10-year DFS rates of 90% and 81% and 5-year and 10 year DRFI rates of 97% and 94% with chemo+hormonal therapy for the RS 11 – 25 group.

This study uses a non-inferiority design to determine whether patients with Recurrence Score (RS) between 11 and 25 derive benefit from adjuvant chemotherapy. Studies have indicated that patients with a low RS receive little if any benefit from chemotherapy and patients with a high RS receive a substantial benefit. This is biologically plausible, since the RS is driven primarily by genes reflecting cell proliferation. The test of non-inferiority here uses a null hypothesis of no difference, as when testing for superiority, but with a larger type I error (one-sided 10%) and smaller type II error (5%) than usual. A decrease in the 5-year DFS rate from 90% with chemotherapy to 87.0% or lower on hormonal therapy alone would be considered unacceptable. This difference corresponds to a 32.2% increase in the DFS failure hazard rate from not giving chemotherapy (the hazard ratio for hormones alone / chemo + hormones is 1.322). DFS will be compared using a stratified log rank test, with the test stratified on the same factors used in the randomization. Patients not meeting the protocol eligibility criteria will be excluded from the primary comparison. The local lab's assessment of hormone receptor status and Her2 status will be used to determine eligibility.

It is possible that not all patients will comply with their assigned therapy. Since the primary analysis will compare the randomized treatment groups, non-compliance will dilute the treatment effect and reduce the power of this study. The design allows the sum of the non-compliance rates on the two arms to be up to 5%; that would occur, for example, if 2% of the patients assigned to hormonal therapy alone receive chemotherapy and if 3% of the patients assigned to chemo+hormonal therapy do not receive chemotherapy. To compensate for this level of non-compliance, the accrual and event numbers are inflated by 10.8% (based on the Lachin-Foulkes correction).

The design assumes randomization of 4,390 patients with RS of 11 – 25 over 3 years, of which it is assumed up to 5% may be ineligible for this study (so at least 4,172 eligible patients will be enrolled). Full information corresponds to 534 DFS events in the subset of eligible patients. This is expected to occur at a little over 7.1 years from activation (at a median follow-up of about 5.6 years) if the 5-year DFS rates are 90% and 87% in the two arms, and about 8 years after activation (at a median follow-up of about 6.5 years) if the 5-year DFS rates are 90% in both arms. Based on information provided by NSABP and GHI on the RS distribution in Her2 negative patients on NSABP B14, it is expected that 46% of the patients screened will have RS values of 11 – 25. It is assumed that at least 95% of these will agree to be randomized. Thus up to 10,046 patients may need to be screened to give the required number of randomizations. Patients with RS already evaluated, with RS values between 11 and 25, can enroll and proceed directly to randomization, so the total number of patients screened as part of this study should be lower than the estimated maximum value.

The sample size estimates for this trial are based upon distribution of RS data from the B14/B20 trials, which is likely to be representative of the distribution of RS observed in TAILORx. However, should the distribution of RS be more typical of that observed in the early post-marketing experience, it is anticipated that we will need to screen 6753 patients (if patients with Her2/neu positive disease are excluded), of whom 1080 patients will have a RS < 11, and 1283 will have a RS > 25.

This study will be monitored by the ECOG Data Monitoring Committee (DMC). The DMC meets twice each year. The first interim analysis will be performed at the first DMC meeting when at least 25% of the total planned number of DFS events (133 events in the primary analysis subset) has been reported. Interim analyses will be performed for each subsequent DMC meeting until either the criteria for early stopping are met or the total planned number of DFS events has been reported. At each interim analysis (and at the final analysis), the stratified log rank test statistic will be computed. The stopping boundary for rejecting non-inferiority will be based on a truncated version of the Lan-Demets error spending rate function corresponding to an O'Brien-Fleming shaped boundary with an overall one-sided type I error of 10%. At early analyses, the boundary will be truncated at a level corresponding to a one-sided nominal significance of 0.002. The boundary function will be computed to maintain the type I error rate adjusting for the effects of the truncation and the effects of the early stopping in favor of non-inferiority, discussed below. If the boundary is crossed at an interim analysis or at the final analysis, then the hypothesis of non-

inferiority will be rejected. If the criteria for rejecting the hypothesis of non-inferiority are not met, then it will be concluded that hormonal therapy alone is not inferior to combined chemo+hormonal therapy.

To allow for early stopping in favor of non-inferiority, this study will also be monitored using repeated confidence interval (RCI) methodology. At each interim analysis, the two-sided 95% RCI on the log hazard ratio (for hormones alone / chemo + hormones) will be computed. This RCI uses the critical value from the O'Brien-Fleming error spending rate function with an overall one-sided 2.5% error rate. If the upper limit of this RCI lies below the minimum unacceptable log ratio of  $\log(1.322)$  then the study will be stopped in favor of non-inferiority. This monitoring rule has deliberately been chosen to be conservative, since the results must be convincing that the conclusion of non-inferiority is based on an adequate amount of information rather than on an underpowered comparison.

Accrual rates, the distribution of Recurrence Scores, and compliance rates with the assigned treatments will be closely monitored throughout the study. If there are significant deviations from the assumptions stated above, then design modifications to ensure that adequate power will be available will be considered by the Steering Committee. If the modifications needed are not feasible, then early termination of this study will be discussed with the Steering Committee, the Breast Intergroup and CTEP. These rates will also be reported to the DMC at every DMC meeting while this study is ongoing, and the DMC may also recommend changes to the design or early termination of this study.

At the time of the final analysis, DRFI will also be compared using a stratified log rank test with one-sided type I error of 10%. Under the accrual, follow-up and compliance assumptions given above, the DRFI test will have 95% power to detect a difference in DRFI corresponding to 5-year DRFI rates of 97% on chemo+hormonal therapy vs. 95.2% on hormonal therapy alone. This analysis requires 182 DRFI failures in the subset of eligible patients. Note that in this analysis, patients who die without developing distant (breast cancer) metastases are censored at the time of death, and other intervening DFS events (eg local-regional recurrence) are ignored. While ideally this study would include an early stopping rule based on differences in DRFI, the expected number of events during the accrual period is too low to provide a meaningful stopping rule, and once accrual is completed, the release of results will be based on the primary endpoint.

Survival will also be compared. Overall survival rates are likely to be similar to the DRFI rates given above. Using a stratified log rank test with one-sided type I error of 10%, at a time when 284 deaths have been observed, there would be 95% power to detect a difference in survival corresponding to 5-year survival rates of 95% on chemo+hormonal therapy vs. 92.8% on hormonal therapy alone.

The interaction of the treatment effect with RS will also be examined for each of the endpoints. Smoothing spline methods (34) will be used to estimate the treatment hazard ratio as a function of RS and to test for treatment by RS interaction. One analysis will just analyze the patients in the randomized group (RS 11 – 25). A second analysis will be done estimating the failure rates as a function of RS separately in the chemo and no chemo groups. This analysis will use patients from Arms A and B to estimate the relationship without chemotherapy and patients from arms C and D to estimate the relationship with chemotherapy. This analysis should lead to more precise estimates of the relationships at the extremes of the intermediate group than the analysis limited to the RS 11 – 25 group. However, the question of whether there could be different patient selection in the three groups, potentially leading to biases in the second analysis, will also need to be considered.

Another secondary objective is to validate whether patients with Recurrence Scores <11 (Arm A) have failure rates that are low enough that adjuvant chemotherapy is unlikely to be of much absolute benefit. Depending on the distribution of RS values and on the total number of patients pre-registered for RS screening vs. entering with RS already evaluated, it is expected that 2400 – 2700 of the eligible patients enrolled on the pre-registration step will have  $RS \leq 10$  and will be followed for study endpoints. Based on data from NSABP B-20 and B-14, it is expected that the 10-year DRFI rate will be about 95% and the 10-year DFS rate will be between 80% and 85%.

The null hypothesis of a 10-year DRFI rate of 95% will be tested by fitting an exponential model and using the Wald test statistic for the log hazard rate. With at least 2,515 eligible patients entered over 3 years and 5 years of additional follow-up, a one-sided test with type I error 2.5% will have power of at least 80% for the alternative that the 10-year DRFI rate is 93.5%. Full information for this test is 108 distant recurrence failures.

All patients with an elevated Recurrence Score > 25 (Arm D) who are assigned to receive chemotherapy will also be followed for relapse and survival. This will provide an extremely valuable resource for further correlative studies, and will be required for achieving the second primary objective (2.1.2) of evaluating emerging "Cancer Clinical Tests" as they develop. Identifying patients with a high Recurrence Score (>25) who relapse despite adjuvant chemotherapy will be just as informative as identifying patients with a low RS (<11) who relapse without chemotherapy. The ability to evaluate emerging future "Cancer Clinical Tests" will only be possible if outcome data is collected for all patients enrolled in all arms (A-D) of the trial.

For objective 2.2.4, the prognostic significance of the genomic variables (overall RS and the individual gene group scores for proliferation, HER2, ER, invasion, and other genes) will be evaluated by fitting proportional hazards regression models containing standard factors such as tumor size, hormone receptor status and tumor grade in addition to the genomic variables. The endpoint for the primary analyses will be DRFI, and models where the log hazard ratio is linear in the genomic variables will be used for the primary test of significance. For each genomic variable, the model will be fit using the standard factors and the genomic variable and the significance of the genomic variable will be determined. Additional analyses will be done to explore the functional form of the relationships using penalized spline methods and other exploratory modeling techniques. Joint models combining the gene group variables will also be fit to evaluate whether the different gene groups are of independent prognostic significance.

ER, PgR and Her2 will be centrally evaluated. Study eligibility (and hence whether cases are included in the primary analysis) will be determined by the results from the local labs. Secondary analyses excluding cases that are ER and PR negative on central review and excluding cases that are Her2 positive on central review will be performed to examine the sensitivity of the results to possible misclassification of these factors by the local labs.

Another objective of this study is to compare the prognostic and predictive power of Adjuvant! with the GHI RS and to determine if the classical information reflected in Adjuvant! adds significantly to RS. The Adjuvant! continues to undergo refinement and enhancement, but roughly it begins by estimated 10-year breast cancer specific mortality (BCSM) from SEER data based on tumor size, grade, nodal status and ER status. The benefit of treatment is estimated from the Oxford overview, and the effects of competing risks are factored in based on age and co-morbidities. Following the methodology in John Bryant's presentation at St. Gallen (2005), the Adjuvant! 10-year BCSM will be used to rank the risk level of the patients enrolled in this study. The Adjuvant! risk rankings (ARR) will then be analyzed in a similar way to the GHI RS. In the group of patients who do not receive chemotherapy (both the randomized group and the  $RS \leq 10$  cohort), models for DFS and DRFI will be fit containing RS and ARR separately and together to compare the prognostic power of these variables separately and in combination with other factors. Models with both RS and ARR will be used to determine whether either adds significant prognostic information to the other. A similar analysis will be done in the cohort of chemotherapy treated patients. Within the randomized group, analyses examining interaction of the ARR and the effect of chemotherapy, similar to those for RS, will also be performed.

Return of Research Results: The results of correlative science studies, including genomic studies, will require mature clinical results with at least five years of clinical followup, or longer. Since the research results are not anticipated to have clinical relevance to either the patient or their family members, these results will not be disclosed to the patient. If, unexpectedly, results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting is required. Research data will not be shared with individual patients when the data are generated. Sharing of research data with individual patients may occur when data have been

validated by multiple studies, and testing done in CLIA-approved laboratories. The results of the research relative to objective 2.11 (the primary clinical objective) and 2.21 (a secondary clinical objective) will be released by the ECOG Data Monitoring Committee (DMC) in accordance with the ECOG DSMC Policies and Procedures and with the criteria stipulated in the statistical section of the protocol. Use of tissue and clinical information for objective 2.12 (specimen bank) will require review by the PACCT Correlative Science Committee (as described in Appendix VI). Release of data regarding secondary objectives (2.21, 2.22, and 2.23) will require that a sufficient amount of time elapsed to achieve the primary objective, that the data analysis and review has been completed, and that the ECOG statistician has written a technical report describing the results. Standard procedures described in the ECOG DSMC Policies and Procedures will be followed in order to safeguard against the inadvertent release of data.

Based on previous data from E2197, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	229	0	229
Not Hispanic or Latino	9817	0	9817
<b>Ethnic Category: Total of all subjects</b>	10046	0	10046
Racial Category			
American Indian or Alaskan Native	24	0	24
Asian	135	0	135
Black or African American	765	0	765
Native Hawaiian or other Pacific Islander	4	0	4
White	9118	0	9118
<b>Racial Category: Total of all subjects</b>	10046	0	10046

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

#### Study Monitoring

This study will be monitored by the ECOG Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG DMC Policy can be obtained from the ECOG Coordinating Center.

**b. Final statistical analysis plan:**

**Statistical Considerations**

This section incorporates major changes made to the statistical design in November 2008. The revised design parallels the original design, but the design was updated to reflect a substantially higher rate of non-adherence with the treatment assignment than allowed in the original design, leading to an increase in the accrual goal for the randomized cohort from 4,390 to 6,860 patients. The null and the alternative hypotheses and the type I error and the power are the same as in the original design. The assumptions on the distribution of OncoType DX Recurrence Scores (RS) and on the accrual rates were also updated to reflect the experience with the study so far. The difference that could be detected in the low RS stratum (arm A) was also modified to reflect lower accrual to this group than originally expected.

The primary endpoint is invasive disease-free survival (DFS), defined to be time from randomization to first event, where the first event is any of ipsilateral breast tumor recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers), or death without evidence of recurrence (as defined in reference 4). DFS is used for the primary endpoint rather than distant relapse-free interval (DRFI), which was used as the primary endpoint in the development of the assay, because DFS is the standard endpoint for evaluating adjuvant treatments for breast cancer, and the important question here, as in other treatment studies, is whether chemotherapy results in an overall DFS benefit of sufficient magnitude to justify its use. Patients will be followed for distant failure following local recurrence. (Note: In various presentations, the primary endpoint of the analyses of the assay in the B-20 and B-14 studies was called DRFS, and it was called 'distant recurrence' in the NEJM paper, but the definition used is the same as DRFI here.) DRFI is a key secondary endpoint, and RFI and OS will also be analyzed.

Patients being considered for this study will have their RS evaluated, either after pre-registration (most cases) or prior to initial registration. Patients with an RS of 11 – 25 will be randomized. The randomization will be stratified on tumor size ( $\leq 2$  cm vs.  $> 2$  cm), menopausal status (pre vs. post), planned chemotherapy (taxane containing or not), planned radiation therapy [whole breast, no boost planned vs. whole breast, boost planned vs. partial breast irradiation planned vs. no planned radiation therapy (for patients who have had a mastectomy)], and RS group (11-15 vs. 16-20 vs. 21-25, added mid-study).

The overall DFS hazard rate on the tamoxifen + CMF arm of B-20 was .025 / year, which under an exponential distribution, gives 5-year and 10-year DFS rates of approximately 88% and 78%. In the preliminary results, the 5-year and 10-year DRFIs in the RS 11 – 25 group on tamoxifen+chemo are 97% and 94%, and the 5-year and 10-year DFS rates are 91% and 76%. For purposes of the calculations here, we assume exponential failure distributions with 5-year and 10-year DFS rates of 90% and 81% and 5-year and 10 year DRFI rates of 97% and 94% with chemo+hormonal therapy for the RS 11 – 25 group.

This study uses a non-inferiority design to determine whether patients with Recurrence Score (RS) between 11 and 25 derive benefit from adjuvant chemotherapy. Studies have indicated that patients with a low RS receive little if any benefit from chemotherapy



and patients with a high RS receive a substantial benefit. This is biologically plausible, since the RS is driven primarily by genes reflecting cell proliferation. The test of non-inferiority here uses a null hypothesis of no difference, as when testing for superiority, but with a larger type I error (one-sided 10%) and smaller type II error (5%) than usual. A decrease in the 5-year DFS rate from 90% with chemotherapy to 87.0% or lower on hormonal therapy alone would be considered unacceptable. This difference corresponds to a 32.2% increase in the DFS failure hazard rate from not giving chemotherapy (the hazard ratio for hormones alone / chemo + hormones is 1.322). DFS will be compared using a stratified log rank test, with the test stratified on the same factors used in the randomization (including on RS group 11-15 vs. 16-20 vs. 21-25, which was not added to the stratification until midway through the study). The primary analysis will compare treatment groups defined by the randomized treatment assignment. Patients not meeting the protocol eligibility criteria will be excluded from the primary comparison. The local lab's assessment of hormone receptor status and Her2 status will be used to determine eligibility. A secondary analysis comparing groups defined by treatment received will also be performed. Both the primary assigned treatment and secondary as treated comparisons need to be non-significant for a clear conclusion of non-inferiority of hormonal therapy alone.

It is possible that not all patients will receive their assigned therapy. Since the primary analysis will compare the randomized treatment groups, treatment non-adherence will dilute the treatment effect and reduce the power of this study. Based on data available as of October 30, 2008, it is estimated that 17% of the patients assigned to hormonal therapy plus chemotherapy are not receiving chemotherapy, and 7% of the patients randomized to hormonal therapy alone are receiving chemotherapy. To adjust the sample size to maintain adequate power for the primary comparison with these rates of non-adherence, an increase of 73% in the number of patients randomized relative to a design with 100% adherence is needed (based on the Lachin-Foulkes correction).

The design assumes randomization of 6,860 patients with RS of 11 – 25 over 3.81 years (1800/year), of which it is assumed up to 5% may be ineligible for this study (so at least 6,517 eligible patients will be enrolled). Full information corresponds to 835 DFS events in the subset of eligible patients. This is expected to occur in summer 2014 (at a median follow-up of about 5.8 years) if the 5-year DFS rates are 90% with chemotherapy and 87% without, and in spring/summer 2015 (at a median follow-up of about 6.7 years) if the 5-year DFS rates are 90% in both arms. These projections take into account a 2.5% early lost to follow-up rate (based on the number of patients withdrawing consent). Allowing time for data submission and review, actual analysis times could be as much as a year later. Based on information available on this study through October 7008, 61% of the pre-registered patients have RS 11-25 and are randomized, 13% have RS < 11 and are registered to arm A, 16% have RS > 25 and are registered to arm D, and 10% are not enrolled on any of the arms. Thus up to 11,246 patients may need to be screened to give the required number of randomizations.

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. The first interim analysis will be performed at the first DMC meeting when at least 25% of the total planned number of DFS events (209 events in the primary analysis subset) has been reported. Interim analyses will be performed for each subsequent DMC meeting until either the criteria for early stopping are met or the total planned number of DFS events has been reported, except that a scheduled interim analysis will not be performed if the increment in the information since the previous interim analysis is less than 10% of the total planned information. At each interim

analysis (and at the final analysis), the stratified log rank test statistic will be computed. The stopping boundary for rejecting non-inferiority will be based on a truncated version of the Lan- Demets error spending rate function corresponding to an O'Brien-Fleming shaped boundary with an overall one-sided type I error of 10%. At early analyses, the boundary will be truncated at a level corresponding to a one-sided nominal significance of 0.002. The boundary function will be computed to maintain the type I error rate adjusting for the effects of the truncation and the effects of the early stopping in favor of non-inferiority, discussed below. If the boundary is crossed at an interim analysis or at the final analysis, then the hypothesis of non-inferiority will be rejected. If the criteria for rejecting the hypothesis of non-inferiority are not met, then it will be concluded that hormonal therapy alone is not inferior to combined chemo+hormonal therapy.

To allow for early stopping in favor of non-inferiority, this study will also be monitored using conditional power for the primary assigned treatment comparison above and using repeated confidence interval (RCI) methodology. At each interim analysis, the conditional power of the logrank test for the primary comparison at a type I error rate of 10% (one-sided) will be computed using simulations (incorporating the estimated distribution of treatment non-adherence). The two-sided 95% RCI on the log hazard ratio (for received hormones alone vs. received chemo + hormones), will also be computed. Since ITT and as treated analyses have well-known potential biases in the presence of treatment non-adherence, the hazard ratio in the subpopulation that would receive the assigned treatment if assigned to either arm will be estimated using a full mixture likelihood approach (Cuzick et al, JRSSB, 69:565-588, 2007) and the RCI obtained by inverting the corresponding likelihood ratio test. The RCI will use the critical value from the O'Brien-Fleming error spending rate function with an overall one-sided 2.5% error rate. If the conditional power of the assigned treatment analysis is < 10% and the upper limit of the RCI lies below the minimum unacceptable log ratio of  $\log(1.322)$ , then the study will be stopped in favor of non-inferiority. This monitoring rule has deliberately been chosen to be conservative, since the results must be convincing that the conclusion of non-inferiority is based on an adequate amount of information rather than on an underpowered comparison.

Accrual rates, the distribution of Recurrence Scores and treatment adherence rates will continue to be closely monitored throughout the study. If there are significant deviations from the assumptions stated above, then design modifications to ensure that adequate power will be available will be considered by the Steering Committee. If the modifications needed are not feasible, then early termination of this study will be discussed with the Steering Committee, the Breast Intergroup and CTEP. These rates will also be reported to the DMC at every DMC meeting while this study is ongoing, and the DMC may also recommend changes to the design or early termination of this study.

At the time of the final analysis, DRFI will also be compared using a stratified log rank test with one-sided type I error of 10%. Under the accrual, follow-up and adherence assumptions given above, the DRFI test will have 95% power to detect a difference in DRFI corresponding to 5-year DRFI rates of 97% on chemo+hormonal therapy vs. 95.2% on hormonal therapy alone. This analysis requires 284 DRFI failures in the subset of eligible patients. Note that in this analysis, patients who die without developing distant (breast cancer) metastases are censored at the time of death, and other intervening DFS events (eg local-regional recurrence) are ignored. While ideally this study would include an early stopping rule based on differences in DRFI, the expected number of events during the accrual period is too low to provide a meaningful stopping

rule, and once accrual is completed, the release of results will be based on the primary endpoint.

Survival will also be compared. Using a stratified log rank test with one-sided type I error of 10%, at a time when 443 deaths have been observed, there would be 95% power to detect a difference in survival corresponding to 5-year survival rates of 95% on chemo+hormonal therapy vs. 92.8% on hormonal therapy alone.

Because of the high non-adherence with treatment assignment, estimated effects from the assigned treatment analyses will be biased towards no difference. Multiple analyses will be performed to estimate the actual effects of chemotherapy. These analyses will include comparing groups by treatment received (the as treated analysis), comparing treatments excluding the patients not receiving their assigned treatments (per protocol analysis), and newer statistical methods for estimating causal effects of treatment. Cox proportional hazards models stratified on the randomization stratification factors (including on RS group 11-15 vs. 16-20 vs. 21-25, which was not added to the stratification until midway through the study) will be used to estimate the treatment hazard ratios for the as treated and per protocol analyses. Details of the causal inference methods will be given in the statistical analysis plan for the study.

The interaction of the treatment effect with RS will also be examined for each of the endpoints within the various estimation methods. Smoothing spline methods (34) will be used to estimate the treatment hazard ratio as a function of RS and to test for treatment by RS interaction. One analysis will just analyze the patients in the randomized group (RS 11 – 25). A second analysis will be done estimating the failure rates as a function of RS separately in the chemo and no chemo groups. This analysis will use patients from Arms A and B to estimate the relationship without chemotherapy and patients from arms C and D to estimate the relationship with chemotherapy. This analysis should lead to more precise estimates of the relationships at the extremes of the intermediate group than the analysis limited to the RS 11 – 25 group. However, the question of whether there could be different patient selection in the three groups, potentially leading to biases in the second analysis, will also need to be considered.

Another secondary objective is to validate whether patients with Recurrence Scores <11 (Arm A) have failure rates that are low enough that adjuvant chemotherapy is unlikely to be of much absolute benefit. Based on experience through October 7008, 13% of the pre-registered entries are RS < 11 and are being enrolled for follow-up on arm A. Assuming 11,284 patients are pre-registered and 95% of the registered patients are eligible, then 1,394 eligible patients would be expected to be enrolled and followed on arm A. Based on data from NSABP B-20 and B-14, it is expected that the 10-year DRFI rate will be about 95% and the 10-year DFS rate will be between 80% and 85%. The null hypothesis of a 10-year DRFI rate of 95% will be tested by fitting an exponential model and using the Wald test statistic for the log hazard rate. With 1,394 eligible patients entered over 3.81 years and 3.5 years of additional follow-up, a one-sided test with type I error 2.5% will have power of at least 85% for the alternative that the 10-year DRFI rate is 93%. Full information for this test is 75 distant recurrence failures.

All patients with an elevated Recurrence Score > 25 (Arm D) who are assigned to receive chemotherapy will also be followed for relapse and survival. This will provide an extremely valuable resource for further correlative studies, and will be required for achieving the second primary objective (2.1.2) of evaluating emerging "Cancer Clinical Tests" as they develop. Identifying patients with a high Recurrence Score (>25) who relapse despite adjuvant chemotherapy will be just as informative as identifying patients

with a low RS (<11) who relapse without chemotherapy. The ability to evaluate emerging future "Cancer Clinical Tests" will only be possible if outcome data is collected for all patients enrolled in all arms (A-D) of the trial.

For objective 2.2.4, the prognostic significance of the genomic variables (overall RS and the individual gene group scores for proliferation, HER2, ER, invasion, and other genes) will be evaluated by fitting proportional hazards regression models containing standard factors such as tumor size, hormone receptor status and tumor grade in addition to the genomic variables. The endpoint for the primary analyses will be DRFI, and models where the log hazard ratio is linear in the genomic variables will be used for the primary test of significance. For each genomic variable, the model will be fit using the standard factors and the genomic variable and the significance of the genomic variable will be determined. Additional analyses will be done to explore the functional form of the relationships using penalized spline methods and other exploratory modeling techniques. Joint models combining the gene group variables will also be fit to evaluate whether the different gene groups are of independent prognostic significance.

ER, PgR and Her2 will be centrally evaluated. Study eligibility (and hence whether cases are included in the primary analysis) will be determined by the results from the local labs. Secondary analyses excluding cases that are ER and PR negative on central review and excluding cases that are Her2 positive on central review will be performed to examine the sensitivity of the results to possible misclassification of these factors by the local labs.

Another objective of this study is to compare the prognostic and predictive power of Adjuvant! with the GHI RS and to determine if the classical information reflected in Adjuvant! adds significantly to RS. The Adjuvant! continues to undergo refinement and enhancement, but roughly it begins by estimated 10-year breast cancer specific mortality (BCSM) from SEER data based on tumor size, grade, nodal status and ER status. The benefit of treatment is estimated from the Oxford overview, and the effects of competing risks are factored in based on age and co-morbidities. Following the methodology in John Bryant's presentation at St. Gallen (2005), the Adjuvant! 10-year BCSM will be used to rank the risk level of the patients enrolled in this study. The Adjuvant! risk rankings (ARR) will then be analyzed in a similar way to the GHI RS. In the group of patients who do not receive chemotherapy (both the randomized group and the  $RS \leq 10$  cohort), models for DFS and DRFI will be fit containing RS and ARR separately and together to compare the prognostic power of these variables separately and in combination with other factors. Models with both RS and ARR will be used to determine whether either adds significant prognostic information to the other. A similar analysis will be done in the cohort of chemotherapy treated patients. Within the randomized group, analyses examining interaction of the ARR and the effect of chemotherapy, similar to those for RS, will also be performed.

Return of Research Results: The results of correlative science studies, including genomic studies, will require mature clinical results with at least five years of clinical followup, or longer. Since the research results are not anticipated to have clinical relevance to either the patient or their family members, these results will not be disclosed to the patient. If, unexpectedly, results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting is required. Research data will not be shared with individual patients when the data are generated. Sharing of research data with individual patients may occur when data have been validated by multiple studies, and testing done in CLIA-approved laboratories. The

results of the research relative to objective 2.11 (the primary clinical objective) and 2.21 (a secondary clinical objective) will be released by the ECOG-ACRIN Data Monitoring Committee (DMC) in accordance with the ECOG-ACRIN DSMC Policies and Procedures and with the criteria stipulated in the statistical section of the protocol. Use of tissue and clinical information for objective 2.12 (specimen bank) will require review by the PACCT Correlative Science Committee.

Release of data regarding secondary objectives (2.21, 2.22, and 2.23) will require that sufficient amount of time elapsed to achieve the primary objective, that the data analysis and review has been completed, and that the ECOG-ACRIN statistician has written a technical report describing the results. Standard procedures described in the ECOG-ACRIN DSMC Policies and Procedures will be followed in order to safeguard against the inadvertent release of data.

Based on previous data from E2197, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	256	0	256
Not Hispanic or Latino	10992	0	10992
<b>Ethnic Category: Total of all subjects</b>	11248	0	11248
<b>Racial Category</b>			
American Indian or Alaskan Native	27	0	27
Asian	151	0	151
Black or African American	857	0	857
Native Hawaiian or other Pacific Islander	4	0	4
White	10209	0	10209
<b>Racial Category: Total of all subjects</b>	11248	0	11248

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Quality of Life Analysis Plan

Perceived cognitive function as assessed by the FACT-Cog Version 3 will be used as the primary quality of life endpoint. The primary question for the Quality of Life component is to assess differences in perceived cognitive impairment among women randomized to receive hormonal treatment alone (Arm B) versus chemotherapy + hormonal treatment (Arm C). Participants receiving treatment on Arms A and D will also complete the Quality of Life assessment. Secondary analyses will examine whether participants assigned to the Secondary Study Group are similar to participants receiving comparable treatment through the Primary Study Group with regard to patient-reported outcomes measures. We will allow total accrual of 1,000 participants to the Quality of Life component of this trial. To ensure that we have adequate power to examine differences between Arms B and C, we will monitor accrual to the Primary Study Group to ensure an adequate sample size. If needed, we will close the Quality of Life component to accrual from participants on Arms A and D if we do not achieve anticipated accrual to the Primary Study Group.

Primary endpoint:

- Comparison of FACT-Cog Perceived cognitive impairment scores between participants on Arm B and Arm C at 3 month assessment

Secondary endpoints:

- Comparison of FACT-Cog scores between Arms B and C at 3, 12, 18, 24 and 36 months
- Differences in FACT-Cog change scores from randomization to 3, 6, 12, 18, 24 and 36 months
- Differences between Arms B and C on other patient-reported outcomes measures
- Differences between participants receiving hormonal treatment alone (Arm B versus Arm A) on patient-reported outcomes measures
- Differences between participants receiving chemotherapy followed by hormonal treatment (Arm C versus Arm D) on patient-reported outcomes measures

FACT-Cog summary scores, Version 3 scoring

		N	Mean	SD	Median
<b>Pre-tx (n = 80)</b>	<b>FACT-Cog Perceived Cognitive Impairments (0-80)</b>	78	64.57	12.16	67.2
	<b>FACT-Cog Impact on QOL (0-16)</b>	78	13.95	3.58	16
	<b>FACT-Cog Comments from Others (0-16)</b>	78	14.85	1.85	16
	<b>FACT-Cog Perceived Cognitive Abilities (0-36)</b>	74	26.25	6.22	26.4
<b>Cycle 4 Day 1 (n = 79)</b>	<b>FACT-Cog Perceived Cognitive Impairments (0-80)</b>	77	57.56	16.18	62.2
	<b>FACT-Cog Impact on QOL (0-16)</b>	76	12.89	4.25	15
	<b>FACT-Cog Comments from Others (0-16)</b>	77	14.46	2.10	16
	<b>FACT-Cog Perceived Cognitive Abilities (0-36)</b>	75	26.04	7.07	27
<b>6 month post-T1 (n = 64)</b>	<b>FACT-Cog Perceived Cognitive Impairments (0-80)</b>	64	58.26	14.63	60.6
	<b>FACT-Cog Impact on QOL (0-16)</b>	64	13.48	3.83	15
	<b>FACT-Cog Comments from Others (0-16)</b>	63	14.24	2.76	16
	<b>FACT-Cog Perceived Cognitive Abilities (0-36)</b>	64	28.18	5.67	28.3

**NOTE:** Data not available for 5 newly created items (2 perceived cognitive function, 1 comments from others, 2 perceived cognitive

As of November 3, 2009, 5408 of the planned 6860 patients have been randomized, leaving 1452 remaining to be randomized to arms B (hormonal therapy alone) and C (chemo + hormonal therapy) in the TAILORx primary study group. At the current rate, the accrual goal should be reached in early August, 2010. During that period, it is projected that an additional 800 patients should be enrolled in the secondary study groups. The potential number of participants in the QOL evaluation will depend on how quickly the amendment is activated and approved by IRBs.

The primary analysis will compare arms in the 'per-protocol' population, with cases not adhering to the chemo assignments excluded. Secondary analyses comparing all patients as treated and all patients as assigned (ITT) will also be examined. Current data suggest 17% of the patients assigned to chemo are not receiving it and 7% of the patients assigned to hormones alone are receiving chemo. Since enrollment and baseline assessment for the cognitive and QoL evaluations will occur before chemo adherence status is definitively known, the enrollment requirements will be increased by a factor of  $1/0.85=1.176$ . So far, 62% of the randomized participants are post-menopausal and 38% are pre-menopausal.

The primary analysis to determine the effects of chemotherapy will use linear mixed models (as implemented for example in SAS PROC MIXED) to perform repeated measures regression analysis of the follow-up evaluations, with the baseline evaluation included as a covariate. Initially, a model allowing separate means for each treatment at each assessment will be used, but more parsimonious models for the changes over assessments will be considered. One particular model that will be examined is a piecewise linear model allowing a change in slope at the end of chemo. The primary analysis will treat missing data as missing at random, but sensitivity analyses using selection models to

allow for various assumptions about the relationship between probability of missing data and cognitive function will also be analyzed. Power calculations will be based on ordinary t-tests without considering the adjustment for the baseline evaluation. This should give a conservative approximation to the analysis adjusting for baseline levels, if there is a reasonable degree of correlation between the baseline and follow-up levels and if missing follow-up information is missing at random.

The primary endpoint of cognitive function at 3 months will be evaluated using the FACT-COG. The primary FACT-COG evaluation will be the difference in the 3-month 'Perceived Cognitive Impairments' scale. In the pilot data in the table above, there was an average drop of 6-7 points from baseline to cycle 4 of chemotherapy and to 6 months, with an average population standard deviation of about 15. The correlation between the baseline and follow-up evaluations was also 0.5 to 0.6. With 235 patients per arm, a t-test comparing the 3-month evaluations will have 90% power for a mean difference of 4.5 points (0.3 standard deviations), allowing a two-sided type I error of 5%. Within the postmenopausal and premenopausal subsets, there will be 90% power to detect a mean difference of 5.7 and 7.35 points (0.38 and 0.49 standard deviations), respectively. Because of the correlation of the baseline and 3-month evaluations, the regression adjustment for the baseline evaluation should increase the power of these comparisons. We assume up to 10% of the cases may have incomplete information through the 3 month evaluation, so 522 patients are needed to give 235/arm analyzable. ECOG-ACRIN has demonstrated experience in E1Z03 in collecting a longitudinal data set with over 94% adherence with submitting data. This study took an active approach with sites being reminded in advance of scheduled assessment times.

Assuming there is significantly larger cognitive impairment or perceived cognitive impairment at 3 months for patients treated with chemo, a major secondary objective is investigating whether this difference persists, and if not, how long it takes to recover from the effects of chemo. Assuming an additional 5% drop out (giving 223/arm in the per-protocol analysis), a 5%-level two-sample t-test comparing the 12-months post randomization evaluations will have 90% power to detect mean differences in the FACT-COG Perceived Cognitive Impairment scale of 4.65, 5.85 and 7.50 points (0.31, 0.39, and 0.50 population standard deviations) in the overall, postmenopausal and premenopausal groups. The question of the duration of chemo-related impairment (or perceived impairment) will be investigated through modeling the assessments as a function of time in the repeated measures model. Simultaneous confidence intervals for differences over time will be determined from a model where the effects are allowed to vary smoothly over time which gives a reasonable fit to the data.

The impact of other variables, such as baseline characteristics and demographic factors will be evaluated by including them as covariates in the repeated measures regression analysis. The relationship of cognitive function to outcomes in other domains, such as symptoms of depression and anxiety (assessed by the Hospital Anxiety and Depression Scale) and fatigue (assessed by the FACT fatigue scale) will be evaluated by including the values as (time-dependent) covariates in the longitudinal models.

Allowing up to 15% of those participating in the cognitive and QOL components to be non-adherent with the chemotherapy assignment, and hence excluded from the primary per-protocol analysis, a total of 614 patients need to be enrolled from the primary study group. At current rates, it is expected that 64% of the patients entering the primary and secondary study groups will be randomized in the primary study group. Thus participation by a total of 1000 patients should be sufficient to meet the objectives of this project.

#### Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of

addenda to this protocol document. A complete copy of the ECOG-ACRIN DMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

**c. Summary of changes to statistical analysis plan.**

- Addendum 4 (3/18/09): The accrual goal was amended on 3/18/09 as part of Addendum 4, and monitoring plan on 2/29/12 as part of Addendum 6. The trial was amended to increase the accrual goal in the randomized group of patients with a RS 11-25 from 4390 to 6860 due to a higher than anticipated non-adherence rate to assigned therapy (endocrine therapy vs. chemoendocrine therapy). It was anticipated that 13% of patients would have a RS < 11 and be assigned to the low risk registry stratum described in this report (N=1394) - the actual proportion was 15.9% (N=1629). The low risk registry stratum described in this manuscript (updated protocol page 93) would be adequately powered to distinguish a 10 year distant relapse free interval (DRFI) rate of 95% (null hypothesis) vs. 93% (alternative hypothesis). The very low DRFI rate at 5 years observed in the low risk registry (99.3%, 95% CI 98.7, 99.6%) prompted the ECOG-ACRIN DMC to recommend release of the data from this stratum, and the TAILORx Steering Committee members to recommend the study be reported and published as quickly as feasible.
- Addendum 5 (1/13/10): Due to the addition of a quality of life sub-study in Addendum 5, an relevant statistical analysis plan was added to the statistical section (protocol pages 95-98).
- Addendum 6 (2/29/12): The DMC monitoring plan was amended (*in italics*) to indicate: "Interim analyses will be performed for each subsequent DMC meeting until either the criteria for early stopping are met or the total planned number of DFS events has been reported, *except that a scheduled interim analysis will not be performed if the increment in the information since the previous interim analysis is less than 10% of the total planned information.*"





# EASTERN COOPERATIVE ONCOLOGY GROUP

*and*

## THE BREAST CANCER INTERGROUP

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*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

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**Version Date: June 13, 2006**  
**NCI Update Date: April 7, 2006**

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### ACTIVATION DATE

**April 7, 2006**  
Update #1 – Incorporated Prior to Activation  
Addendum #1 – 6/06

Rev. 6/06 Institutions aligned with ECOG will enroll patients via ECOG. Institutions not aligned with ECOG will enroll patients via the NCI Cancer Trials Support Unit (CTSU).

Rev. 6/06 Data management activities will be performed by the Cancer Trials Support Unit (CTSU). All data, from ECOG and non-ECOG institutions alike, should be submitted to CTSU Data Operations unless otherwise specified in the CTSU logistical appendix.

Rev. 6/06 **NOTE:** This does not include Expedited Adverse Event Reporting; please follow instructions in section 5.3 for submission of AE data.

The CTSU will use the PACCT-1 number as required for reporting to ECOG and the NCI and when registering patients through ECOG.

CTSU participants and institutions will be instructed to use the PACCT-1 study number on all data forms, reports, and communications.

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## Cancer Trials Support Unit (CTSU) Address and Contact Information

### Data management activities for the study will be performed by CTSU

All sites, ECOG and non-ECOG alike, will submit data via the CTSU. For this reason, investigators and study support staff involved in the collection and reporting of study data must be registered members of the CTSU.

#### To submit site registration documents:

CTSU Regulatory Office  
1818 Market Street, Suite 1100  
Philadelphia, PA 19103  
Phone - 1-888-823-5923  
Fax – 215-569-0206

#### For patient enrollments:

For patient enrollments that must be completed within approximately one hour or for extenuating circumstances, call 301-704-2376.

For all other CTSU patient enrollments, please leave a voicemail at 1-888-462-3009.  
Fax enrollment documents to 1-888-691-8039

NOTE: No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.

#### For data submission:

Data management activities for PACCT-1 (TAILORx) will be performed by the CTSU for ECOG and non-ECOG sites alike. Sites pre-selected by ECOG will submit case report forms and manage discrepancies via CTSU's Remote Data Capture (RDC) system. All non-RDC sites will submit hard-copy case report forms and query responses to the following address:

CTSU Data Operations Center  
5615 Kirby Drive Suite 710  
Houston, TX 77005  
(ph) 1-800-856-1856

Rev. 6/06 **NOTE:** This does not include Expedited Adverse Event Reporting; please follow instructions in section 5.3 for submission of AE data.

#### For patient eligibility or treatment-related questions:

Rev. 6/06 Contact the ECOG Study Chair, the Study Chair Liaison, or the CTSU Help Desk.

#### All other questions (including forms-specific questions) should be communicated by phone or e-mail to the CTSU Help Desk at:

CTSU General Information Line – 1-888-823-5923, or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).  
All calls and correspondence will be triaged to the appropriate CTSU representative.

**The CTSU Public Web site is located at: [www.ctsu.org](http://www.ctsu.org)**

**The CTSU Registered Member Web site is located at <http://members.ctsu.org>**

CTSU logistical information is found in Appendix XI.

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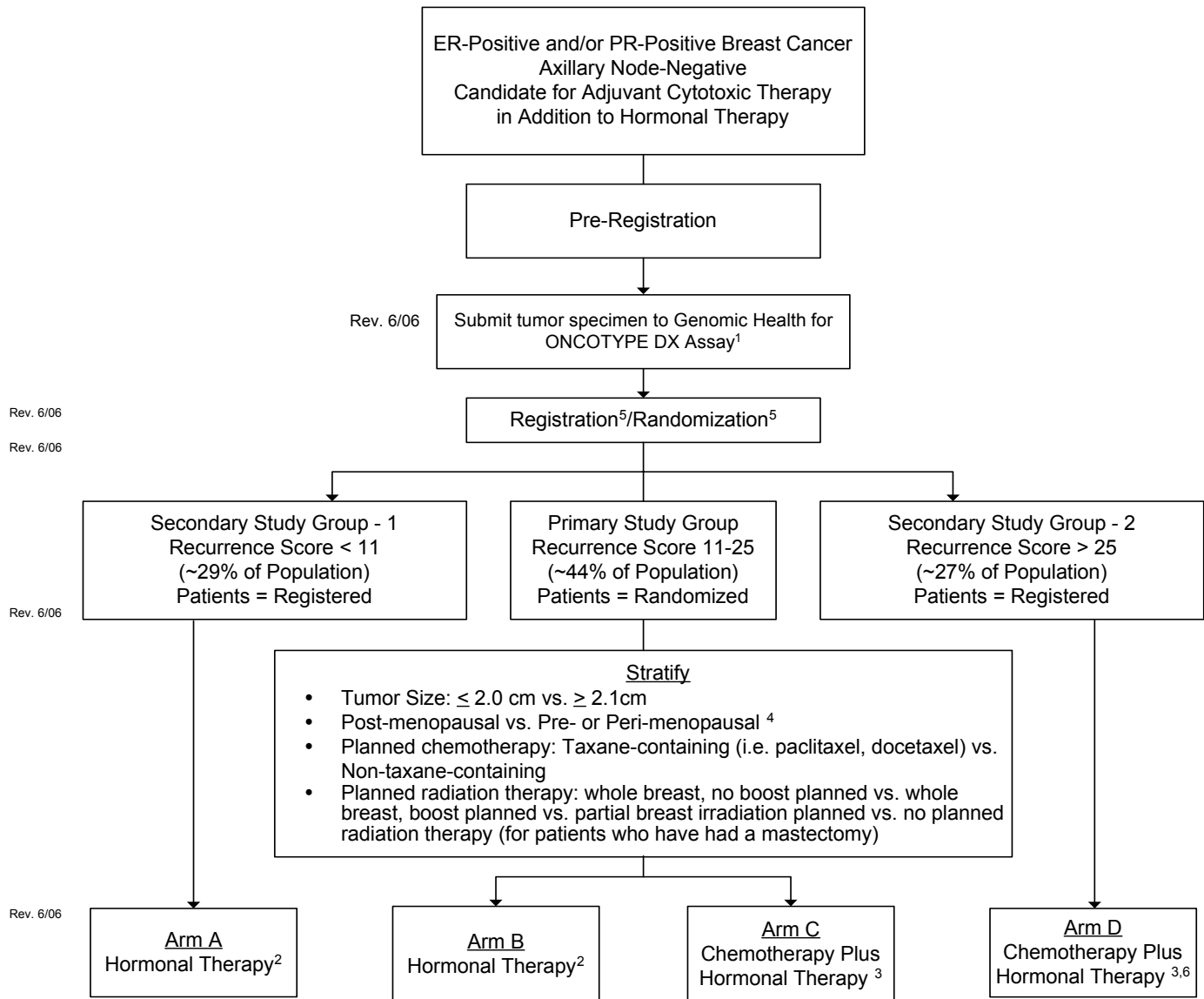
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**SCHEMA**



Accrual Goal =10,046 patients  
Patients who have had breast conservation surgery will also be treated with radiotherapy.  
Refer to Section 5.2 for RT guidelines

1. A tumor specimen MUST be sent to Genomic Health for the Oncotype DX assay (see Section 10 and Appendix V for details). Residual tumor tissue and RNA will be forwarded to the ECOG PCO-RL by Genomic Health, and will be retained by the ECOG PCO-RL for individuals who have consented to use of tissue for future research (or returned to the site if consent was not granted). Patients who have had the Oncotype DX assay performed prior to pre-registration may also enroll if the RS was 11-25, the patient has signed consent, and all eligibility criteria are met. In this case, tumor specimen must be sent directly to the ECOG PCO-RL.
2. Patients will receive hormonal therapy of the treating physician's choice (see Appendix III for details).
3. Patients will receive chemotherapy plus hormonal therapy of the treating physician's choice (see Appendices II & III for details).
4. See Appendix III for status definitions
5. See Section 10.2 for submission of samples to the ECOG-PCO.
6. For patients with a RS  $\geq 26$  who do not register on another CTSU study, the enrolling site is asked to provide baseline and follow-up information on a voluntary basis. Requested information will include the following: (1) a baseline case report form, (2) a report of disease relapse event (as defined in Section 6), and/or second primary cancer, and/or death (if any of these events occur), (3) and a report of disease and survival status 5 years after registration.

## 1. Introduction

### 1.1 Background

In 2004, it is projected that there will be 215,900 new cases of female breast cancer and 40,110 deaths due to the disease in the United States (1). Cancer is the leading cause of death in women between the ages of 40-79, with breast cancer being the most common cancer in this group, and the second leading cause of cancer death. Breast cancer mortality has declined over the past 10 years due largely to the earlier detection of cancer by mammographic screening, but also in part due to the increasing use of adjuvant hormonal therapy and chemotherapy (2,3). The selection of adjuvant hormonal therapy based upon expression of the estrogen receptor (ER) and/or progesterone receptor (PR) has remained consistent (about two-thirds of all cancers) over the past 30 years. However, indications for adjuvant chemotherapy have expanded considerably to now include even women at very low risk of systemic recurrence. For example, the addition of adjuvant chemotherapy to tamoxifen reduces the risk of relapse in patients with axillary node negative, estrogen receptor (ER)-positive disease by approximately 30% (4-7). Indeed, attention has now begun to focus on who should not rather than who should receive chemotherapy (8). Models have been developed that can assist physicians in estimating the absolute benefit for an individual patient, although such models are based purely on clinical data and have inherent limitations (9,10). An International Expert Consensus Panel (11) defined “minimal risk” and “average-risk” groups for “endocrine-responsive” disease, and suggested that adjuvant chemotherapy be considered for women in the “average risk” group (Table 1) who are less than 70 years of age; by definition, “average risk” does not include patients with pure tubular or colloid histology, histologic patterns associated with a very favorable prognosis. A limitation of these guidelines is their reliance on histologic and/or nuclear grade for risk classification, which some have reported to have great interobserver variability, even amongst expert pathologists (12). Another limitation is that a relatively small proportion of patients with axillary node-negative, ER-positive disease are classified as “minimal risk”. Evidence-based practice guidelines issued by the National Comprehensive Cancer Center Network ([www.nccn.org](http://www.nccn.org)) use a lower threshold for recommending adjuvant chemotherapy in addition to hormonal therapy (Table 1). Although the NCCN guidelines do not use the terms “minimal risk” or “average risk”, these terms have been used in Table 1 to draw comparisons between the two guidelines for groups who are advised to receive or not to receive adjuvant chemotherapy. Finally, the United States National Institute of Health Consensus Development Panel concluded, “On the basis of available data, it is accepted practice to offer cytotoxic chemotherapy to most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both lymph node-negative and lymph node-positive). For women with lymph node-negative cancers smaller than 1 cm in diameter, the decision to consider chemotherapy should be individualized. Similarly, in patients with small lymph node-negative breast cancers with favorable histologic subtypes, such as tubular and mucinous cancers, retrospective data support long-term survival following primary therapy without the need for adjuvant chemotherapy.” With regard to age, the panel concluded, “There are limited data to define the optimal use of adjuvant chemotherapy for women more than 70 years of age.... Increased participation of women over the age of 70 years in randomized clinical trials and studies specifically addressing the value and tolerance of adjuvant chemotherapy in these women are urgently needed” (13).

**Table 1 - Recommendations for Adjuvant Therapy of Axillary Lymph Node-Negative, Endocrine Responsive Disease**

	Definition	Premenopausal	Postmenopausal
<b>International Consensus Guidelines (Goldhirsch, 2003)</b>	<b>Minimal Risk (*):</b> Tubular or colloid histology OR All of the following features (*): pT ≤ 2 cm, and Grade 1, and Age ≥ 35 years	Hormonal Therapy OR None	Hormonal Therapy OR None
<b>NCCN Guidelines (www.nccn.org)</b>	Tubular or colloid histology OR pT < 1 cm and no unfavorable features	Hormonal Therapy OR None	Hormonal Therapy OR None
<b>International Consensus Guidelines (Goldhirsch, 2003)</b>	<b>Average Risk:</b> ER and/or PR expressed, and at least one of the following features: pT > 2 cm, or Grade 2 or 3, or Age < 35 years	Chemotherapy ⇒ Hormonal Therapy OR Hormonal Therapy	Hormonal Therapy OR Chemotherapy ⇒ Hormonal Therapy
<b>NCCN Guidelines (www.nccn.org)</b>	pT > 1cm, AND Histology ductal (NOS), lobular, mixed, or metaplastic OR Tumor 0.6-1.0 cm with unfavorable features+	Chemotherapy ⇒ Hormonal Therapy	Chemotherapy ⇒ Hormonal Therapy OR Hormonal Therapy (if > 60 years of age)

Abbreviations and/or definitions: pT – pathologic tumor size, defined as size of invasive component of tumor; Grade – histologic and/or nuclear grade; ER – estrogen receptor; PR – progesterone receptor; unfavorable features (+) – for NCCN guidelines, defined as angiolymphatic invasion, poor nuclear grade, poor histologic grade, or Her2 overexpression

Minimal Risk (\*) – some panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal risk

1.2 Axillary Lymph Node Negative Breast Cancer and Indications for Chemotherapy

According to Surveillance and Epidemiology and End Results (SEER) data, approximately 25% of women present with “average risk” node-negative disease in the United States, accounting for about 54,000 women diagnosed with breast cancer each year (14). Although adjuvant chemotherapy is of clear benefit even in “average risk” populations, the majority of women are treated unnecessarily to benefit a few. Assuming a relative risk reduction of 30% from the addition of adjuvant chemotherapy to hormonal therapy, the absolute benefit derived from the addition of chemotherapy is low, even in individuals at higher risk for relapse. For example, using the ADJUVANT! decision analysis model, approximately 100 women must be treated in order to benefit only 3 or 4 patients (Table 2). A recent report indicated that this decision tool performed remarkably well when validated using an independent population based dataset including 4083 women with pT1-2, pN0-1 breast cancer, including patients with lymph node negative disease (15). The decision aid did overestimate prognosis, however, for ER-positive disease (10 year breast cancer specific survival projected 84.9% with ADJUVANT! vs. 83.0% in validation dataset) and for the benefit for adjuvant chemotherapy (projected 75.2% vs. actual 70.6%). Although such decision aids may be useful in estimating the benefit of chemotherapy, they are not sufficiently reliable to distinguish individuals who will not derive benefit from adjuvant chemotherapy.

**Table 2 - Absolute Improvement in 10-Year Disease Free Survival in Node-Negative Breast Cancer Treated by Addition of Chemotherapy to Tamoxifen (tam)**

St. Gallen Risk Group	Grade	Tumor size (cm)	Tam x 5 years	Tam x 5 years plus chemo	Absolute risk reduction by addition of chemo to tam
Minimal Risk	1	1.1-2.0	93%	94%	1%
Average Risk	2	1.1-2.0	81%	83%	2%
Average Risk	3	1.1-2.0	78%	81%	3%
Average Risk	1	2.1-3.0	75%	78%	3%
Average Risk	2	2.1-3.0	73%	76%	3%
Average Risk	3	2.1-3.0	68%	72%	4%

Calculations based upon Adjuvant Online model ([www.adjuvantonline.com](http://www.adjuvantonline.com)) (10).

Calculation based upon women age 55 in perfect health, ER-positive tumor, negative axillary lymph nodes; chemotherapy regimen is AC (doxorubicin 60 mg/m<sup>2</sup>, cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks x 4 cycles)

1.3 Genomic Profiling in Breast Cancer

Gene expression profiling of human breast cancer has been shown to be potentially useful in identifying breast tumor subtypes associated with distinct phenotypic characteristics that may have clinical implications. A series of studies have been reported over the past few years that have utilized expression profiling for the following purposes: (1) identifying distinct molecular subtypes of breast cancer, (2) identifying molecular signatures associated with a good vs. poor prognosis (i.e., prognostic factor), and (3) identifying molecular signatures that predict benefit from specific therapies (ie, predictive factor).

1.3.1 Identifying Molecular Subtypes of Breast Cancer

Perou initially reported variations in gene expression patterns in 40 breast tumors analyzed by cDNA microarrays and hierarchical clustering that classified tumors into a basal epithelial-like group, a luminal group, an ERBB2-overexpressing group, and a normal breast-like group (16). A subsequent report by the same group that included 78 cancers, 3 fibroadenomas, and 4 normal breast tissues indicated that the previously characterized luminal epithelial/ER-positive group could be divided into at least two subgroups with distinctive expression profiles, and that these subtypes were associated with differing prognoses when analyzed in a uniformly treated group of patients (17). Another report by the same group provided additional evidence supporting their original findings in two different data sets that included 115 patients with breast cancer treated with neoadjuvant chemotherapy; a favorable prognosis noted for the luminal A subgroup, unfavorable prognosis for the basal and Her2 group, and an intermediate prognosis was noted for the luminal B group (18). It is noteworthy that routine immunohistochemical markers for hormone receptor expression and Her2/neu expression may be used to approximate these genomic subtypes, with the basal type characterized by absence of ER/PR and Her2/neu expression, luminal types characterized by ER and/or PR expression without Her2/neu expression, and Her2 type characterized by presence of Her2/neu expression irrespective of ER/PR expression status.



1.3.2 Identifying Molecular Signatures Associated with Prognosis (ie, Prognostic Factor)

Other groups have evaluated gene expression profiles by performing supervised clustering analyses on the basis of clinical outcome (relapsers vs. non-relapsers) in order to identify specific gene expression profiles associated with prognosis. Some of these studies are summarized in Table 3, and discussed in further detail below. For the purposes of this discussion, the techniques may be broadly categorized as those that utilize routinely processed tissue (e.g., formalin-fixed, paraffin embedded tissue) and those that require specialized processing not routinely performed in clinical pathology laboratories (e.g., snap frozen fresh tissue).

**Table 3 - Characteristics and Performance of Selected Molecular Profiling Techniques**

	<u>Van de Vijver, 2002</u>	<u>Piccart, 2004</u>	<u>Wang V, Klijn JG, Zhang Y, et al., 2005</u>	<u>Paik, 2003</u>	<u>Esteva, 2003</u>
Tissue	Fresh frozen	Fresh frozen	Fresh frozen	Paraffin-embedded	Paraffin-embedded
Molecular technique	Rosetta Inpharmatics RNA expression	Rosetta Inpharmatics RNA expression	Affymetrix human U133a GeneChip RNA expression	Genomic Health RT-PCR RNA expression	Genomic Health RT-PCR RNA expression
Tissue processing	Thirty 30 micron sections	Thirty 30 micron sections	Thirty 30 micron sections	Three 10 micron sections	Three 10 micron sections
No. genes in panel	70 genes	70 genes	76 genes	16 genes (plus 5 reference genes)	16 genes (plus 5 reference genes)
Training/Validation	Validation	Validation	Training & validation	Training & validation	Validation
No. selected/evaluatable	295/295	301/291	286/286	2167/675	220/149
ER Expression	77%	67%	70%	100%	70%
Axillary Nodes					
Positive	51%	0%	0%	0%	0%
Negative	49%	100%	100%	100%	100%
Adjuvant therapy					
Tamoxifen	7%	0%	0%	100%	0%
Chemotherapy	31%	0%	0%	0%	0%
Both	7%	0%	0%	0%	0%
Median followup	6.7 years	10 years	8.4 years	10.9 years	Minimum of 5 years
Genetic signature					
Good	61%	63%	34%	51%	32%
Intermediate	Not applicable	Not applicable	Not applicable	22%	14%
Poor	39%	37%	64%	27%	54%

1.3.2.1 Frozen Tissue Specimens

A group from the Netherlands Cancer Institute in Amsterdam identified a 70 gene panel that was evaluated in a training set of 78 breast cancers measuring less than 5 cm in size associated with negative axillary nodes in patients less than 55 years of age, by characterizing the molecular signature of patients who did and did not have systemic relapse within five years (19). The “good” and “poor” signature profiles outperformed established clinical criteria. The technology involved use of an RNA expression profile in fresh frozen tissue (Rosetta Inpharmatics; 25,000 transcripts). This methodology was subsequently evaluated in a validation set of 295 consecutive patients with stage I or II breast cancer younger than 53 years old, of whom 151 had lymph-node–negative disease and 144 had lymph–positive disease (Table 3) (20). Adjuvant therapy was given to 44% of all patients, including 6% of the lymph node negative

group and 83% of the lymph node positive group; adjuvant therapy included chemotherapy in 31%, hormonal therapy in 7%, and both in 7%. Among the 295 patients, 180 had a good-prognosis signature (61%) and 115 had a poor-prognosis signature (39%). At 10 years, the probability of remaining free of distant metastases was 51% ( $\pm 5\%$ ) in the group with a poor-prognosis signature and 85% ( $\pm 4\%$ ) in the group with a good-prognosis signature. Multivariate Cox regression analysis showed that prognosis profile was a strong independent factor predicting disease outcome. For the lymph node negative group, the estimated 5-year distant disease free survival was 95% ( $\pm 3\%$ ) for the good signature group and 66% ( $\pm 5\%$ ) for the poor signature group. When comparing the expression profiling with established clinical criteria in lymph node negative disease, the expression profile assigned many more to the low-risk group (good-prognosis signature) than did the clinical criteria (40% vs. 15% for St. Gallen criteria and 7% for NIH criteria). In addition, low-risk patients identified by gene-expression profiling had a higher likelihood of metastasis-free survival than those classified according to the St. Gallen or NIH criteria, and high-risk patients identified by gene-expression profiling tended to have a higher rate of distant metastases than did the high-risk patients identified by the St. Gallen or NIH criteria. This result indicates that both sets of the currently used clinical criteria misclassify a substantial number of patients. Indeed, the high-risk group defined according to the NIH criteria included many patients who had a good-prognosis signature and a good outcome. Conversely, the low-risk group identified by the NIH criteria included patients with a poor-prognosis signature and poor outcome. Similar subgroups were identified within the high-risk and low-risk groups identified according to the St. Gallen criteria. Since both the St. Gallen and the NIH subgroups contain misclassified patients (who can be better identified through the prognosis signature), these patients would be either overtreated or undertreated in current clinical practice. An external validation study of the 70 gene profile was subsequently performed by the TRANSBIG Network, and a preliminary analysis of this study has been presented (21). This study included frozen tumor specimens from 301 patients with node-negative breast cancer who had primary treatment rendered at six non-Dutch centers in the United States and Europe, and who received no systemic adjuvant therapy. Sixty-three percent had high-risk profile (consistent with the 60% incidence for the original Dutch report), and this signature was associated with a 1.8-fold increased risk of systemic recurrence and 2.5-fold increased risk of death. However, there was significant heterogeneity between original Amsterdam and external validation samples, and the overall performance of the prognostic signature was inferior in the external validation set. Another group from the Erasmus Medical Center in Rotterdam reported their experience with RNA expression profiling using a different platform (Affymetrix Human U133a GeneChip; 23,000 transcripts), which included 286 node-negative breast cancer patients who received no adjuvant systemic therapy (including 115 patients in the training set and 171 in the validation set) (22). In the training group of 115 patients (80 ER-positive), a 76-gene signature (60 for ER-positive and 16 for ER-negative) was identified that was predictive of distance metastases within 5 years. A high-risk gene signature was associated with a significantly increased risk of distant metastases within 5 years when adjusted for known prognostic variables (hazard ratio [HR] 5.78;  $p < 0.00003$ ), including in subgroups of patients with tumors between 1-2 cm in size ( $N=79$ ; HR 14.1,  $p < 0.00003$ ), premenopausal women ( $n=84$ ; HR

9.6;  $p < 0.0002$ ), and postmenopausal women ( $N=87$ ; HR 4.04,  $p=0.0017$ ). In the subgroup of 42 ER-negative patients in the validation set, a 16 gene profile had strong predictive value (HR 8.74,  $p=0.012$ ).

### 1.3.2.2 Formalin-Fixed Paraffin Embedded Specimens

Another technique that utilizes a 21-gene panel RT-PCR assay that can be performed on formalin-fixed paraffin embedded tissue (FPET). The 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. It uses three specific reagents for each gene results in high specificity. The assay (Oncotype DX™ Breast Cancer Assay, Genomic Health, Redwood, CA; <http://www.genomichealth.com/oncotype>) is performed within 10-14 days, and has received CLIA approval in the United States. The training set that was used to develop this assay consisted of three studies involving 449 patients from three groups, including 224 patients treated with node-negative, ER-positive disease treated with tamoxifen (23), 79 patients with 10 or more positive axillary nodes (24), and 146 additional patients with operable breast cancer (25). Two hundred fifty candidate genes were selected from the literature for study in this training set. Univariate analysis of 185 cancer related genes indicated that 41 genes were associated with relapse free survival ( $p < 0.05$ ), including 22 with  $p < 0.01$ , 10 with  $p < 0.001$ . Expression of many genes were tightly correlated. A “Recurrence Score” (RS) was calculated using a weighted algorithm based upon gene expression profiles of groups of genes (e.g., proliferation, ER, Her2, and invasion-associated genes) and some individual genes that emerged as predictive in the training set (e.g., CD69, BAG-1, GSTM-1) (Table 4). Each group of genes receives a RS of up to 15, with each unit of RS equivalent to a two-fold increase in RNA expression level. The score for each gene group is weighted toward the proliferation, Her2, and ER-associated genes using the adjustment outlined in Table 4. In the training set, groups were identified that had a high ( $RS \geq 31$ ), low ( $RS < 18$ ), or intermediate ( $RS 18-30$ ) risk of systemic recurrence.

**Table 4: Genomic Health Recurrence Score (RS) Algorithm (Oncotype DX)**

<u>Group</u>	<u>Genes</u>	<u>Adjustment</u>
<b>Proliferation</b>	Ki67, STK15, survivin, cyclin B1, MYB2	+1.04
<b>Her2</b>	Her2, Grb7	+0.47
<b>ER</b>	ER, PR, BCL-2, SCUBE2	-0.34
<b>Invasion</b>	Stromelysin-3, CAT	+0.10
<b>CD68</b>	CD68	+0.05
<b>BAG-</b>	BAG-1	-0.07
<b>GSTM-1</b>	GSTM-1	-0.08

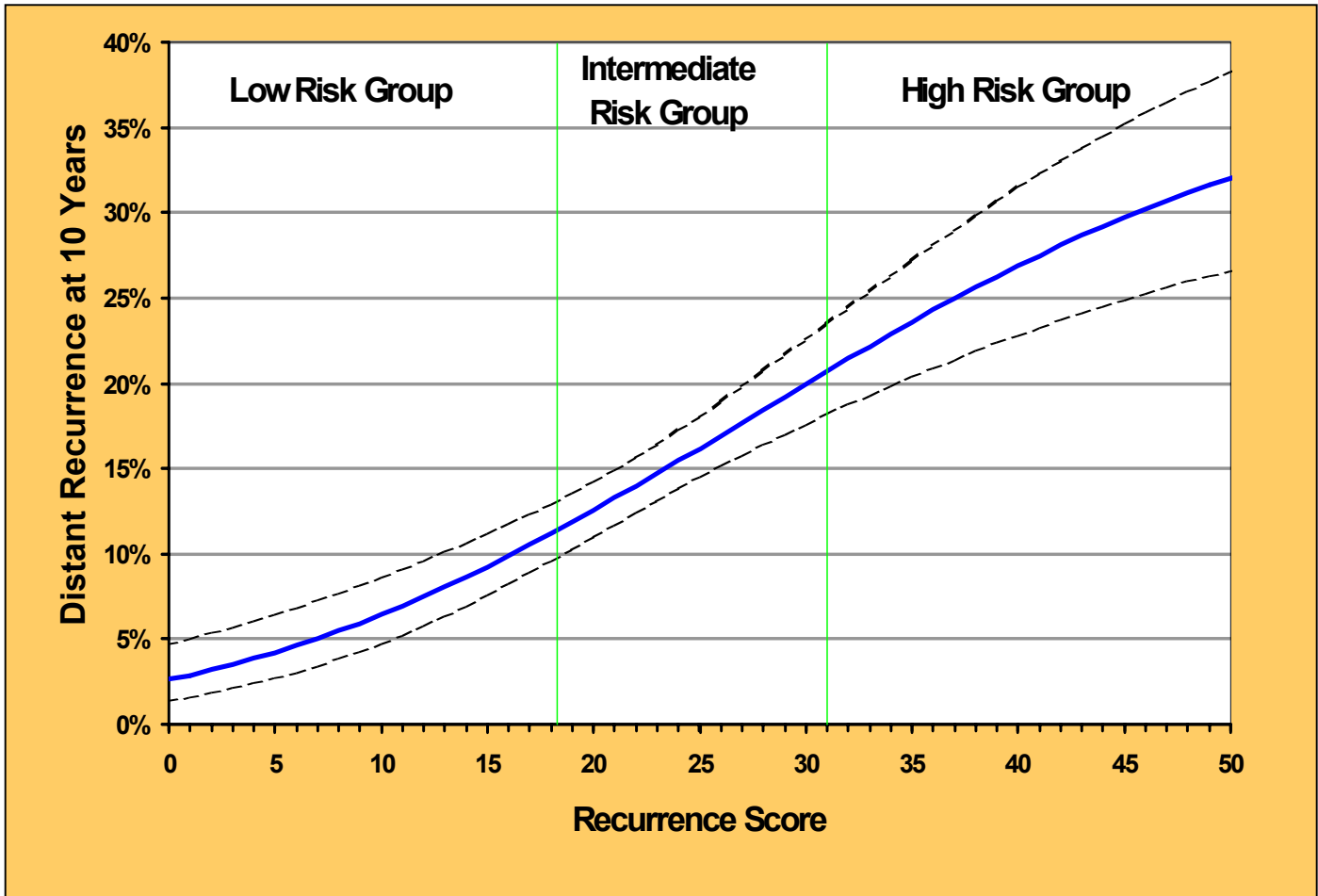
The Genomic Health RS was subsequently evaluated in a validation set that consisted of a subset of patients with ER-positive, node negative breast cancer enrolled on NSABP trial B-14 (23, 26). Of the 2167 patients enrolled on this trial who were either randomized or registered to receive tamoxifen, tumor blocks were available for 675 cases with at least 5% invasive cancer; there was no difference in patient characteristics or outcome for those who did or did not have blocks available for study. The

mean age of the study population was 52.4 years, mean tumor size was 2 cm, and median follow up was 10.9 years. The results of the analysis are contrasted with other studies in Table 3, and outlined in greater detail in Table 5. The primary study endpoint was distant recurrence free survival (DRFS) at 10 years; for the primary endpoint, patients were censored at the time of development of contralateral breast cancer, second non-breast cancer, or death without breast cancer recurrence.

**Table 5. Genomic Health Recurrence Score in B-14 Trial (N=668)**

Recurrence Score (1–100)	Risk group	No. (%)	10-year distant recurrence rate (95% C.I.)	5-year distant recurrence rate (95% C.I.)
< 18	Low	338 (51%)	6.8 % (4–9.6%)	2.1% (0.6-3.7%)
18 –30	Intermediate	149 (22%)	14.3% (8.3–20.3%)	9.2% (4.4-14%)
>= 31	High	181 (27%)	30.5% (23.6–37.4%)	22.1% (15.9-28.2%)

Approximately 50% of patients were classified as having a low risk RS (<18), a group that experienced only a 6.8% distant recurrence rate at 10 years. There was a significantly inferior 10-year DRFS rate for those with a high RS compared to those with a low RS ( $p < 0.00001$ ). Cox proportional hazard model indicated that the only factor that emerged as significant variable at 10 years was the RS (hazard ratio [H.R.] 3.21, 95% confidence intervals [C.I.] 2.23, 4.61;  $p < 0.00001$ ). A continuous model was also developed that plots RS (X-axis) vs. 10-yr DRFS (Y-axis), and allows estimation of 10-year distant recurrence rate for specific RS. Information regarding 5-year distant recurrence rate is also provided in Table 5. These data illustrate that about one-third of distant relapses occurred between year 5 and 10 for patients with an intermediate or high RS tumor; in contrast, about two-thirds of relapses in the low RS group occurred between years 5 and 10.



**Figure 1. Genomic Health Recurrence Score as a Continuous Variable.**

Although the arbitrarily defined cut points as defined in Table 5 identified groups with disparate and substantially different risks of relapse that are clinically relevant, other analysis indicates that the RS also predicts relapse as a continuous variable (Figure 1). This point has relevance for the risk groups defined in this trial as described in Section 1.4.

The Genomic Health RS was also evaluated in 149 evaluable patients with node-negative breast cancer who were referred to MD Anderson Cancer Center over a 20-year period and who did not receive adjuvant chemotherapy (27). Tumor blocks were available for only 149 of the 220 patients who met these criteria during this time period. The characteristics of the study population are contrasted with the B-14 validation set in Table 3. In this study, RS was not predictive of distant relapse. An unusual feature of this study was that patients with good nuclear grade had a worse outcome compared with patients with intermediate or high nuclear grade. This study points out that the distinct assays may need to be developed for ER-positive and ER-negative cancers. The *Oncotype DX* assay is CLIA-approved only for patients with ER-positive, node negative breast cancer.

Finally, the reliability of the Genomic Health RS was also validated in a population-based case-control study (28). The study included patients with

node-negative breast cancer treated at 19 Kaiser Permanent hospitals between 1985 and 1995 who were less than 75 years of age and received no adjuvant chemotherapy. Of the 4964 patients identified, there were 227 eligible cases who died of breast cancer and 446 eligible controls who did not die of breast cancer and were matched for clinical characteristics. The results indicated that RS score was the strongest predictor of breast cancer death in multivariate analysis (odds ratio for death 6.5,  $p=0.002$ ), that RS significantly predicted breast cancer death in patients treated with or without tamoxifen, and that the risk of breast cancer death at 10 years was similar in this population as in the B-14 population.

1.3.3 Identifying Molecular Signatures Associated with Response to Treatment (ie, Predictive Factor)

A follow up report by the NSABP and Genomic Health provided further information regarding the predictive value the 21 gene *Oncotype DX* panel. The study included 357 of 373 patients with ER-positive node negative breast cancer in the placebo arm of the B-14 trial, and 424 of 430 patients treated with tamoxifen plus CMF (or MF in trial B-20) (29). In the B-20 trial, the addition of CMF chemotherapy to tamoxifen significantly improved 5-year disease free survival (DFS; 89% vs. 85%;  $p=0.001$ ) and distant disease free survival (DDFS; 91% vs. 87%;  $p=0.006$ ). Similar results were evident for MF chemotherapy. Overall, the addition of CMF to tamoxifen reduced the event rate by 35% for DFS, and 33% for DDFS (4). When the data were analyzed by RS risk group, there was a significant interaction between RS and benefit from chemotherapy (interaction  $p=0.0368$ ); chemotherapy significantly reduced the risk of recurrence in the high RS group (hazard ratio 0.258), but not in the intermediate or low risk groups. In addition, when evaluating the effect of tamoxifen by RS group in patients treated with tamoxifen only or a placebo, there was a significant interaction between tamoxifen benefit and RS ( $p<0.001$ ); RS was found to be an independent prognostic factor in the placebo arm, and tamoxifen reduced the risk of recurrence only in patients with a low or intermediate recurrence score.

The predictive accuracy of the RS in the tamoxifen alone arm of this analysis does not provide an independent validation set and must be interpreted with caution, as the tamoxifen arm of the B20 trial was used as the training set for development of the RS. Nevertheless, the analysis suggests that RS may be used to identify individuals who are more likely to derive benefit from chemotherapy.

**Table 6. Genomic Health Recurrence Score and Response to Chemotherapy in B-20 Trial (N=651)**

Risk group (RS ranges)	No. Patients	10-year DDFS Tam	10-year DDFS Tam + Chemotherapy	Hazard Rate (and 95% C.I.) for Recurrence in Patients Treated with Chemotherapy	P-Value
Low (< 18)	353 (54%)	97%	96%	1.312 (0.456, 3.777)	0.76
Intermediate (18-30)	134 (21%)	91%	89%	0.613 (0.236, 1.59)	0.71
High (> 30)	164 (25%)	61%	88%	0.258 (0.126, 0.528)	0.001

#### 1.4 Rationale for the Proposed Study

Clinical breast cancer research over the past 30 years has focused on expanding indications for adjuvant chemotherapy, and has been successful in establishing that even patients expected to have a very good prognosis with hormonal therapy alone derive some small absolute benefit from adjuvant chemotherapy (13). Previous attempts to refine prognostic and predictive factors using standard histopathologic criteria (e.g., tumor grade), indices of proliferation (S-phase fraction, Ki-67) or genomic instability (e.g., DNA ploidy), or single gene/protein expression profiles (e.g., Her2/neu, p53 expression) have not been sufficiently reliable to merit routine clinical use in patients with low to moderate-risk disease (12, 30).

Although several distinct molecular signatures identified by differing methodologies have been developed that may serve as useful prognostic markers, we have chosen to utilize Oncotype DX Breast Cancer Assay in this trial for the following reasons: (1) it is a standardized, multi-gene RT-PCR-based molecular technique performed in a single laboratory, (2) it may be applied to tissue specimens routinely processed in clinical pathology laboratories, (3) it has received CLIA approval in the United States to "...assess the likelihood that a women's breast cancer will...recur..." ([www.genomichealth.com](http://www.genomichealth.com)), (4) it more reliably predicts prognosis than standard clinical criteria in patients with ER-positive, node-negative disease than standard clinical criteria, including tumor size, histologic grade, and age, (5) it's performance has been validated in a large population-based study, (6) preliminary data indicates that it predicts benefit from adjuvant chemotherapy. Patients with ER-positive, axillary node negative breast cancer account for nearly one-half of all breast cancer diagnosed in the United States, and is the group in which more patients unnecessarily receive adjuvant chemotherapy.

Patients with ER and/or PR-positive, axillary lymph node negative breast cancer who meet standard clinical criteria for adjuvant chemotherapy, who are medically suitable candidates for chemotherapy, will be eligible to participate in this trial. Although these patients meet established clinical criteria for chemotherapy, the typical patient may be expected on average to derive a 3% improvement in 10-year DFS from such treatment. In this trial, the Oncotype DX Breast Cancer Assay will be utilized to prospectively guide treatment decisions for low risk and high risk tumors. In addition, the trial will attempt to refine the precision of the test in individuals who have intermediate risk tumors where the assay result is indeterminate in its ability to identify whether chemotherapy is beneficial. Patients will be assigned to treatment according to the schema indicated below. The definitions of low, intermediate, and high risk utilized in this trial are slightly different than those previously defined.

- **"Secondary Study Group-1"** (RS  $\leq$  10): Patients will be assigned to receive hormonal therapy alone. A RS of  $\leq$  10 was selected as the threshold for low risk because it is associated with a 10 year distant recurrence rate on average of  $\leq$  5% if treated with tamoxifen alone, and because no benefit from chemotherapy has been demonstrated in this group.
- **"Primary Study Group"** (RS 11-25) Patients will be randomly assigned to receive chemohormonal therapy vs. hormonal therapy alone. The risk of distant recurrence if treated with tamoxifen alone is sufficiently high to recommend chemotherapy (approximately 10% for the entire group), but chemotherapy has not been established to be clearly beneficial in this specific group.
- **"Secondary Study Group-2"** (RS  $\geq$  26): Patients will be assigned to receive chemotherapy plus hormonal therapy. A RS of  $\geq$  26 was selected as the threshold for high risk because it is associated with a 10 year distant recurrence rate of on average of 20% or more, and because chemotherapy has been shown to be beneficial in this group.

The primary clinical endpoint will be disease-free survival in patients in the “Primary Study Group.” co-primary endpoints will include distant disease-free survival, relapse free survival, and overall survival (as defined in Section 6). The trial will be adequately powered to determine whether hormonal therapy is not inferior to chemotherapy plus hormonal therapy in patients in the “Primary Study Group.” Should hormonal therapy be shown not to be inferior to chemohormonal therapy, it will spare the need for chemotherapy in up to 40% of women with ER-positive, axillary node negative breast cancer. In addition, all patients identified to have a non-elevated RS in this trial will be spared the need for adjuvant chemotherapy.

This study will include only patients with Her2/neu negative disease. Only 8% of patients enrolled in the B14 validation study had Her2/neu positive disease, and < 1% with a RS of < 26 demonstrated Her2/neu amplification. The outcomes for the Recurrence Score categories used in the PACCT trial for distant disease free survival (DDFS) and disease free survival (DFS) are shown in Table 7 (10-year outcomes) and Table 8 (5 year outcomes) (29).

Table 7:  
Genomic Health Recurrence Score and Response to Chemotherapy in B20 Trial (N=651) by RS Distribution in PACCT Trial (10 year outcomes)

RS	No. Patients	Tam 10-year DDFS	Tam + Chemo 10-year DDFS	H.R. (& 95% CI) For Recurrence by Addition of Chemo	P-Value	Tam 10-year DFS	Tam + Chemo 10-year DFS	H.R. (& 95% CI) For Recurrence by Addition of Chemo	P-Value
< 11	177 (27%)	98%	95%	1.788 (0.360, 8.868)	0.471	77%	85%	0.605 (0.317,1.153)	0.124
11-25	279 (43%)	95%	94%	0.755 (0.313, 1.824)	0.531	81%	76%	1.106 (0.671,1.823)	0.691
> 25	195 (30%)	63%	88%	0.285 (0.148, 0.551)	<0.0001	53%	75%	0.446 (0.270, 0.738)	0.0012

Abbreviations: H.R. - hazard ratio; CI - confidence intervals; DDFS - distant disease free survival; DFS - disease free survival; Tam - tamoxifen; chemo - chemotherapy (which included cyclophosphamide, methotrexate, 5-fluorouracil or methotrexate/5-fluorouracil).

Table 8:  
Genomic Health Recurrence Score and Response to Chemotherapy in B20 Trial (N=651) by RS Distribution in PACCT Trial (5-year outcomes)

RS	No. Patients	Tam 5-year DDFS	Tam + Chemo 5-year DDFS	H.R. (& 95% CI) For Recurrence by Addition of Chemo	P-Value	Tam 5-year DFS	Tam + Chemo 5-year DFS	H.R. (& 95% CI) For Recurrence by Addition of Chemo	P-Value
< 11	177 (27%)	98%	99%	1.788 (0.360, 8.868)	0.471	92%	95%	0.605 (0.317,1.153)	0.124
11-25	279 (43%)	97%	97%	0.755 (0.313, 1.824)	0.531	94%	91%	1.106 (0.671,1.823)	0.691
> 25	195 (30%)	69%	94%	0.285 (0.148, 0.551)	<0.0001	63%	85%	0.446 (0.270, 0.738)	0.0012

NSABP data indicates the following incidence of Her2/neu amplification in 668 patients evaluated in the B14 validation study: positive 55 (8%), missing 8 (1%), negative 605 (91%). The proportion of patients with Her2/neu amplification by RS as categorized in the B14 validation study is as follows: RS < 18 - 0/334; RS 18-31 – 5/147 (3%); RS > 31 – 50/179 (28%). The distribution for the RS groups as defined in the PACCT trial for the B14 validation study is as follows: RS < 11 – 0/159, RS 11-25 – 2/283 (<1%); RS > 25 – 53/218 (24%). For this reason, we have altered eligibility to include only patients with Her2/neu negative disease, which will serve to reduce the number of patients screened in order to identify patients with a RS of 11-25 from 11,553 to 10,046.



1.5 Correlative Science

Although the purpose of PACCT-1 is to validate the utility of the Genomic Health Recurrence Score, tumor RNA will be banked in addition to FPET tissue microarrays, plasma, and germline DNA. By virtue of the chemotherapy vs. no chemotherapy comparison in patients in the primary study group, we will be able to assess the utility of other “Clinical Cancer Tests” as they evolve (e.g., other genomic and/or epigenomic technologies, tumor and/or serum proteomic patterns, single nucleotide polymorphisms in drug and/or estrogen metabolizing enzymes, etc). Toward this end, all patients participating in this trial will be asked to donate specimens of tumor, lymphocytes, and serum for banking. As previous experience indicates that about 90% of patients who donate biological specimens consent to unspecified future research, it is anticipated that a number of additional studies will be planned in the future as technology evolves and as the trial matures. The background and rationale for selecting these biological specimens for long-term storage is provided in Appendix VIII, as well as the process required for utilizing these specimens for future research.

1.6 Gender and Ethnicity

Entry to this study is restricted to female patients. Study entry is open to patients of all ethnic backgrounds. Historically, approximately 15% of patients enrolled on ECOG breast cancer studies are members of minority ethnic groups. It is anticipated that a similar proportion of patients on this study will be members of ethnic minorities. Based on current data, ECOG believes that interactions between ethnicity and genomic profiling are not expected, and accrual will not be increased to meet subgroup targets.

## 2. Objectives

In women with ER-positive and/or PR-positive, axillary node-negative breast cancer who meet standard clinical criteria for adjuvant chemotherapy in addition to hormonal therapy, the objectives of this trial are:

### 2.1 Primary:

- 2.1.1 To determine whether adjuvant hormonal therapy is not inferior to adjuvant chemohormonal in women whose tumors meet established clinical guidelines for adjuvant chemotherapy and fall in the “primary study group” category (Oncotype DX Recurrence Score 11-25). The primary study endpoint is disease-free survival; other co-primary endpoints include distant recurrence free interval, recurrence free interval, and overall survival as defined in Section 6.
- 2.1.2 To create a tissue and specimen bank for patients enrolled in this trial, including formalin fixed paraffin embedded tumor specimens, tissue microarrays, plasma, and DNA obtained from peripheral blood. This resource will be critical for evaluating emerging Clinical Cancer Tests.

### 2.2 Secondary:

- 2.2.1 To determine whether adjuvant hormonal therapy is sufficient treatment (i.e. 10 year distant disease-free survival of at least 95%) for women whose tumors meet established clinical guidelines for adjuvant chemotherapy and who fall into the "Secondary Study Group-1" category (Oncotype DX Recurrence Score  $\leq 10$ ). The primary study endpoint is disease-free survival; other co-primary endpoints include distant recurrence free interval, recurrence free interval, and overall survival as defined in Section 6.
- 2.2.2 To compare the outcomes projected at 10 years by Adjuvant! (with outcomes projected using classical pathologic information including tumor size, hormone receptor status, and histologic grade) with those made by the Genomic Health Oncotype DX test. Classical pathologic information and outcome results will also be used to create and refine models that would use classical information instead of or in combination with genomic tests.
- 2.2.3 To estimate failure rates as a function of RS separately in the chemotherapy (arms C, D) and no chemotherapy (arms A, B) groups. The purpose of the analysis is to develop more precise estimates of the relationship between recurrence score and chemotherapy treatment effect, if any, at the upper range of the RS 11 – 25 group.
- 2.2.4 To determine the prognostic significance of the Oncotype DX recurrence score and of the individual RS gene groups (proliferation gene group, HER2 gene group, ER gene group, invasion gene group, and other genes).

**3. Selection of Patients**

Each of the criteria in the following section must be met in order for a patient to be considered eligible for this study. Use the spaces provided to confirm a patient's eligibility. For each patient, this section should be photocopied, completed and maintained in the patient's chart.

Rev. 6/06 **NOTE:** This study involves a pre-registration and a registration/randomization (see Section 4). All time frames for prestudy scan and lab values and other requirements will be based on the date of pre-registration.

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

Rev. 6/06 **NOTE:** Questions regarding eligibility should be directed to the ECOG Study Chair, Joseph Sparano, M.D., at (718) 904-2555, the Study Chair Liaison, Una Hopkins, at (718)-405-8522 or the CTSU Help Desk at 1-888-823-5923.

**NOTE:** Patients enrolled on the PACCT-1 trial may be enrolled on other CTSU trials under the following conditions: (1) the patient has already registered on the PACCT-1 trial, (2) the treatment options in the other trials are consistent with PACCT-1-specified treatment assignment (ie, chemohormonal therapy or hormonal therapy alone).

**NOTE:** Pre-registration requires a previously determined Recurrence Score (from GHI) or tissue available for submission for Oncotype DX assay. See Appendix IV for submission of forms and samples associated with Recurrence Score status.

Rev. 6/06 **NOTE:** If the **Oncotype DX Recurrence Score was previously performed by Genomic Health and the RS is 11-25, eligible patients may proceed from the pre-registration process to randomization within 24 to 72 hours after submission of the Oncotype DX Assay report to the ECOG Coordinating Center (see Sections 3.1.3, 3.1.10 and 4.2). Pre-registration may NOT be bypassed.**

**ECOG Patient No.** \_\_\_\_\_

**Patient's Initials (Last, First, Middle)** \_\_\_\_\_

3.1 Pre-Registration

\_\_\_\_\_ 3.1.1 Patients with operable histologically confirmed adenocarcinoma of the female breast who have completed primary surgical treatment and meet the following criteria

\_\_\_\_\_ 3.1.1.1 **ER and/or PR-positive:**

Estrogen and/or progesterone receptor positive disease (as defined by local pathology laboratory).

ER Status: Positive / Negative / Indeterminate Date \_\_\_\_\_  
(please circle one)

PR Status: Positive / Negative / Indeterminate Date \_\_\_\_\_  
(please circle one)

\_\_\_\_\_ 3.1.1.2 **Negative axillary nodes:**

As assessed by a sentinel lymph node biopsy, an axillary dissection, or both procedures.

**NOTE:** As per the AJCC staging criteria (Sixth Edition), lymph nodes are characterized as positive or negative for metastases on the basis of conventional H&E staining; lymph nodes that are negative by H&E staining and positive by immunohistochemistry (I+) or molecular techniques [mol+] are considered negative (NO).

\_\_\_\_\_ 3.1.1.3 **Tumor size 1.1–5.0cm (or 5 mm-1.0 cm plus unfavorable histological features):**

Unfavorable features defined as intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion.

**NOTE:** Definition of tumor size: The tumor size used for determination of eligibility is the pathologic tumor size, which is usually determined by the size of the tumor as measured by inspection of the gross specimen. If the tumor size is measured microscopically and the tumor includes ductal carcinoma in-situ, the measurement should include only the invasive component of the tumor.

\_\_\_\_\_ 3.1.1.4 The tumor must be Her2/neu negative by either fluorescent in-situ hybridiation (FISH) or immunohistochemistry (e.g. 0 or 1+ by DAKO Herceptest).

\_\_\_\_\_ 3.1.2 The patient and physician must be agreeable to initiate standard chemotherapy and hormonal therapy as adjuvant therapy. The standard chemotherapy and hormonal therapy options permitted are described in Appendix II and Appendix III.

\_\_\_\_\_ 3.1.3 A tissue specimen from the primary breast cancer has been located and is ready to be shipped to the appropriate laboratory after consent is obtained and within 3 days following pre-registration as indicated in Section 10.

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**NOTE:** For determination of the Oncotype Recurrence Score, tissue must be shipped to Genomic Health. If the Oncotype DX Recurrence Score was previously performed by Genomic Health (prior to pre-registration), tissue must be submitted to the ECOG Pathology Coordinating Office upon randomization.

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\_\_\_\_\_ 3.1.4 Patients must be  $\geq 18$  years and  $\leq 75$  years. Patients must be less than 76 years of age because patients will be followed for up to 20 years, and because the primary study endpoints are based upon a 10 year endpoint.

\_\_\_\_\_ 3.1.5 Patients must have adequate organ function, including the following within 4 weeks prior to pre-registration:

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- Leukocyte count  $\geq 3500/ \text{mm}^3$  and platelets  $\geq 100,000/\text{mm}^3$ .

Leukocyte count: \_\_\_\_\_ Date of test: \_\_\_\_\_

Platelet Count: \_\_\_\_\_ Date of test: \_\_\_\_\_

- Serum creatinine  $\leq 1.5\text{mg/dL}$ .

Creatinine: \_\_\_\_\_ Date of test: \_\_\_\_\_

- Serum aspartate transaminase (AST) that is  $\leq 3$ -fold the upper institutional limits of normal.

AST: \_\_\_\_\_ Date of test: \_\_\_\_\_

Institutional limits of normal \_\_\_\_\_

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- \_\_\_\_\_ 3.1.6 Patients must be disease-free of prior invasive malignancies for  $\geq 5$  years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix. Patients with a previous ipsilateral or contralateral invasive breast cancer, or with bilateral synchronous cancers, are not eligible. Patients with previous ipsilateral or contralateral DCIS are not eligible.
- Rev. 6/06 \_\_\_\_\_ 3.1.7 Prior Treatment
- \_\_\_\_\_ 3.1.7.1 Mandatory prior surgery criteria:
- Rev. 6/06 \_\_\_\_\_ 3.1.7.1.1 Patient must pre-register within 84 days from the final surgical procedure required to adequately treat the primary tumor.
- \_\_\_\_\_ 3.1.7.1.2 All tumors should be removed by either a modified radical mastectomy or local excision plus an acceptable axillary procedure (i.e., sentinel lymph node biopsy, axillary dissection, or both). There must be adequate (at least 1 mm, i.e.  $> 1$  mm, if margin width specified) tumor-free margins of resection (for invasive and ductal carcinoma in-situ) in order for the patients to be eligible. Patients with lobular carcinoma in-situ involving the resection margins are eligible.
- \_\_\_\_\_ 3.1.7.2 Criteria re: other prior treatments:
- \_\_\_\_\_ 3.1.7.2.1 No prior chemotherapy for this malignancy.
- \_\_\_\_\_ 3.1.7.2.2 No prior radiation therapy for this malignancy.
- \_\_\_\_\_ 3.1.7.2.3 Hormonal therapy: Patients who develop breast cancer while receiving a selective estrogen-receptor modulator (SERM; e.g., tamoxifen, toremifene, raloxifene) or an aromatase inhibitor (e.g., anastrozole, letrozole, exemestane) for breast cancer prevention or a SERM for other indications (e.g., raloxifene for osteoporosis) are **not** eligible. However, patients may have received up to 8 weeks of a SERM or aromatase inhibitor for this malignancy and still be eligible for study entry.
- \_\_\_\_\_ 3.1.8 Patients must have an anticipated life expectancy of at least 10 years. Patients with the following medical conditions should not be enrolled on the study:
- \_\_\_\_\_ 3.1.8.1 Chronic obstructive pulmonary disease requiring treatment.
- \_\_\_\_\_ 3.1.8.2 Chronic liver disease (e.g., cirrhosis, chronic active hepatitis)
- \_\_\_\_\_ 3.1.8.3 Previous history of a cerebrovascular accident.
- \_\_\_\_\_ 3.1.8.4 History of congestive heart failure or other cardiac disease that would represent a contraindication to the use of an anthracycline (e.g., doxorubicin or epirubicin).
- \_\_\_\_\_ 3.1.8.5 Chronic psychiatric condition or other condition that would impair compliance with the treatment regimen.

\_\_\_\_\_ 3.1.9 Women must not be pregnant or breast-feeding due to the potential use of cytotoxic chemotherapy for patients participating in this trial, which is contraindicated due to the potential for chemotherapy to cause harm to the fetus or infant. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to pre-registration to rule out pregnancy.

Female of childbearing potential? \_\_\_\_\_ (Yes or No)

Date of negative blood or urine pregnancy test: \_\_\_\_\_

\_\_\_\_\_ 3.1.9.1 Women of childbearing potential must be strongly advised to utilize an accepted and effective form of non-hormonal contraception (e.g. intrauterine device, condoms, diaphragm, abstinence).

\_\_\_\_\_ 3.1.10 Patients must not have previously had the *Oncotype* DX Assay performed, with the exception of patients who have had the assay performed and have a Recurrence Score of 11-25.

**NOTE:** A copy of the “*Oncotype* DX Patient Report” is to be faxed to the ECOG Coordinating Center (Fax: 617-582-8578, Attn: Pre-registration/PACCT-1) upon receipt of the report, or, if *Oncotype* DX Assay was previously performed, immediately following pre-registration. The protocol number (PACCT-1), and **pre-registration sequence number** MUST be indicated on the report.

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3.2 Registration/randomization (24 to 72 hours after submission of the *Oncotype* DX Assay report to the ECOG Coordinating Center)

\_\_\_\_\_ 3.2.1 At the time of registration/randomization, information that will be required for proper stratification (as indicated in Section 4.2.5) will include:

- Tumor Size ( $\leq 2.0$  cm vs.  $\geq 2.1$  cm): \_\_\_\_\_
- Menopausal Status [Post-menopausal vs. Pre- or peri-menopausal (see Appendix III for status definitions)]: \_\_\_\_\_
- Planned Chemotherapy (Taxane-Containing vs. Non-Taxane Containing):  
\_\_\_\_\_
- Planned Radiation Therapy [Whole breast, no boost planned vs. Whole breast, boost planned vs. Partial breast irradiation planned vs. No planned radiation therapy (for patients who have had a mastectomy)]:  
\_\_\_\_\_

Research associates may need to contact the treating physician prior to registration regarding what type of adjuvant chemotherapy is planned if that information is not available in the medical record.

\_\_\_\_\_ 3.2.2 *Oncotype* DX Assay result:

Pre-registration #: \_\_\_\_\_

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

Physician's Signature: \_\_\_\_\_

Date: \_\_\_\_\_

#### 4. Pre-registration and Registration/Randomization Procedures

Data management activities for the PACCT-1 study will be performed jointly by the Cancer Trials Support Unit (CTSU) and the Eastern Cooperative Oncology Group (ECOG). All sites (ECOG and non-ECOG alike) will submit study data to the CTSU (with the exception of Expedited Adverse Event Reporting; please follow instructions in section 5.3 for submission of AE data), therefore, **all PACCT-1 investigators and support staff (ECOG and non-ECOG alike) must be registered members of the CTSU.** Please see the CTSU website ([www.ctsu.org](http://www.ctsu.org)) for details on registering as a CTSU member.

**NOTE: This study involves both a pre-registration and a registration. Please read these instructions carefully.**

**NOTE:** Pre-registration is required for low risk patients and for high risk patients who will be followed in the voluntary registry.

##### Submitting Regulatory Documents

Before an ECOG 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. HHS 310 Form.  
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 link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed [http://www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail [CTSUContact@westat.com](mailto:CTSUContact@westat.com). **Monday through Friday, 9:00am - 6:00pm.**

**Patients must not start protocol treatment prior to pre-registration and registration/randomization.**

#### 4.1 Pre-Registration

**ECOG Member Sites** will pre-register patients directly by using the Web-based Patient Registration Program (<https://webreg.ecog.org>).

**Non-ECOG sites** will pre-register patients through the CTSU registrar, as described in Appendix XI.

Institutions may pre-register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (<https://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday through Friday 9:00am – 5:00pm Eastern Time. Please note that a password is required to use this program. The following information will be requested for pre-registration:

##### 4.1.1 Protocol Number

##### 4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator's name

##### 4.1.3 Patient Identification

4.1.3.1 Patient's initials (Last, First, Middle) and chart number

4.1.3.2 Patient's Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Sex

4.1.3.3.2 Birth date (mm/yyyy)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

##### 4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility worksheet has been appended to the protocol. A confirmation of pre-registration will be forwarded by the ECOG Coordinating Center.

##### 4.1.5 Additional Requirements

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

4.1.5.2 Pathology blocks are to be submitted as follows:

- For determination of *Oncotype* DX Recurrence Score, materials **must** be submitted no later than 3 days after pre-registration as outlined in Section 10.1. Kits for tissue submission may be ordered prior to pre-registration.

**NOTE:** If sections, rather than blocks, are submitted for the RS assessment, additional materials are required for central review of ER/PR status as indicated in Section 10.2.



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- If the *Oncotype DX Recurrence Score* was previously determined by Genomic Health and the score is 11-25, blocks are to be submitted for central review after randomization as indicated in Section 10.2.

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4.1.5.3 Prior to registration, the institution must Fax a redacted copy of the “*Oncotype DX Patient Report*” to the ECOG Coordinating Center (617-582-8578, ATTN: Pre-Registration/PACCT-1). Indicate on the report the protocol number (PACCT-1), and patient’s ECOG **pre-registration** sequence number.

- If patient is having an *Oncotype DX Assay* performed by Genomic Health, Genomic Health will notify the submitting institution of the results of the *Oncotype DX Assay* within 14 working days of receipt of the sample.
- If patient has previously had an *Oncotype DX Recurrence Score* performed by Genomic Health, and the RS is 11-25, the “*Oncotype DX Patient Report*” should be FAXed to the ECOG Coordinating Center within 24 hours following pre-registration.
- 24 hours (72 hours if a weekend or holiday) after submission of the *Oncotype DX Patient Report* to ECOG, the institution may proceed to registering/randomizing the patient as outlined in Section 4.2.

#### 4.2 Registration/Randomization

**ECOG Member Sites** will register and randomize patients directly by using the Web-based Patient Registration Program (<https://webreg.ecog.org>).

**Non-ECOG sites** will register patients through the CTSU registrar, as described in Appendix XI.

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Institutions may register eligible patients to this study 24 hours (72 hours if weekend or holiday) after institution has Faxed a redacted copy of the “*Oncotype DX Patient Report*” to the ECOG Coordinating Center (617-582-8578, ATTN: Pre-Registration/PACCT-1) as outlined in Section 4.1.5.3.

**Patients must not start protocol treatment prior to registration/randomization.**

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**Treatments should begin within 14 days after registration/randomization.**

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ECOG institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (<https://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday through Friday 9:00am – 5:00pm Eastern Time. Please note that a password is required to use this program. The following information will be requested:

##### 4.2.1 Protocol Number

##### 4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name

4.2.2.2 Investigator’s name

##### 4.2.3 Patient Identification

4.2.3.1 Patient’s initials (Last, First, Middle) and chart number

4.2.3.2 Patient’s Social Security number

- 4.2.3.3 Patient demographics
  - 4.2.3.3.1 Sex
  - 4.2.3.3.2 Birth date (mm/yyyy)
  - 4.2.3.3.3 Race
  - 4.2.3.3.4 Ethnicity
  - 4.2.3.3.5 Nine-digit ZIP code
  - 4.2.3.3.6 Method of payment
- 4.2.3.4 Patient's sequence number from pre-registration (Step 1).
- 4.2.4 Classification factor  
Recurrence Score (RS)
- 4.2.5 Stratification factors
  - 4.2.5.1 Tumor Size
    - ≤ 2.0 cm
    - ≥ 2.1 cm
  - 4.2.5.2 Menopausal Status
    - Post-menopausal
    - Pre- or peri-menopausal
    - (See Appendix III for status definitions)
  - 4.2.5.3 Planned Chemotherapy
    - Taxane-containing (i.e., paclitaxel, docetaxel)
    - Non-taxane containing
  - 4.2.5.4 Planned radiation therapy
    - Whole breast, no boost planned
    - Whole breast, boost planned
    - Partial breast irradiation planned
    - No planned radiation therapy (for patients who have had a mastectomy)
- 4.2.6 Additional Requirements
  - 4.2.6.1 Tumor tissue must be submitted for correlative studies and banking as outlined in Section 10.  
**NOTE:** If tissue was submitted at pre-registration for Oncotype DX RS assessment, additional materials are requested for correlative studies and banking.
  - 4.2.6.2 Peripheral blood to be retained for possible future use should be submitted as outlined in Section 10.  
**NOTE:** Institutions outside the United States and Canada are not required to submit fresh samples because of the costs and problems associated with international shipping.
- 4.3 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 according to the instructions in the PACCT-1 Forms Packet. Document the reason for not starting protocol treatment on one of the baseline forms. Also report the date and *type* of the first non-protocol treatment that the patient receives.

## 5. Treatment Plan

**NOTE:** All questions regarding treatment or dose modifications should be directed to the ECOG Study Chair.

**NOTE:** Systemic treatment (chemotherapy or hormonal therapy) should be initiated within 14 days after registration/randomization. For patients randomized or assigned to receive chemotherapy, chemotherapy should be administered first; hormonal therapy should begin within 4 weeks after the last dose of chemotherapy, and should not be given concurrently with chemotherapy.

### 5.1 Treatment Arms

**NOTE:** Patients may be enrolled on a separate CTSU trial under the following conditions: (1) the patient already registered on the PACCT-1 trial and, (2) the treatment option in the other trial is consistent with PACCT-1 specific treatment assignment (i.e., chemotherapy/hormonal therapy or hormonal therapy alone).

5.1.1 Secondary Study Group-1 (RS  $\leq$  10): Patients will receive hormonal therapy of the treating physician's choice (see Appendix III for guidelines)

5.1.2 Primary Study Group (RS 11-25): Patients will be randomized at the time of registration to receive chemotherapy plus hormonal therapy or hormonal therapy alone (see Appendix II and III for guidelines).

5.1.3 Secondary Study Group-2 (RS  $\geq$  26): Patients will receive chemotherapy (see Appendix II) and hormonal therapy (see Appendix III) of the treating physician's choice.

For patients with a RS  $\geq$  26 who do not register on another CTSU study, the enrolling site is asked to provide baseline and follow-up information on a voluntary basis. Requested information will include the following: (1) a baseline case report form, (2) a report of disease relapse event (as defined in Section 6), and/or second primary cancer, and/or death (if any of these events occur), (3) and a report of disease and survival status 5 years after registration.

### 5.2 Radiotherapy

Patients who have had breast conservation surgery will be treated with radiotherapy. Guidelines for radiation therapy are as follows:

- Irradiation should begin with 4 weeks of registration for patients receiving hormonal therapy alone or within 4-8 weeks after completion of chemotherapy (or sooner if the patient has adequately recovered from chemotherapy-associated toxicity).
- External beam irradiation to the whole breast is advised to a dose of 45-50 Gy. A boost dose to the primary tumor bed may be delivered at the discretion of the treating physician to bring the total dose to 60-66 Gy. Patients may receive partial breast radiation if they are participating in NSABP and /or RTOG partial irradiation trial(s).
- Concurrent treatment: Irradiation should not be given concurrently with chemotherapy. Irradiation will be given concurrently with hormonal therapy. Hormonal therapy should not be delayed until the completion of irradiation.

**5.3 Adverse Event Reporting Requirements**

Identify the type of event and grade using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

**5.3.1 Reporting methods**

- **Arm A, B, C and D** – This study requires that expedited adverse event reporting use the NCI’s Adverse Expedited Reporting System (AdEERS). The NCI’s guidelines for AdEERS can be found at <http://ctep.cancer.gov>. For questions regarding the use of the AdEERS application, please contact the NCI Technical Help Desk: 301-840-8202.

An AdEERS report must be submitted to ECOG and the appropriate regulatory agencies by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at <http://ctep.cancer.gov>  
or
- Fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents paper template located at <http://ctep.cancer.gov> to ECOG (617-632-2990), Attention: AE and the NCI (301-230-0159).

**NOTE: Paper copies of AdEERS reports will only be accepted if the AdEERS system is down. Once the system is restored, a report submitted on a paper template must be entered into the AdEERS system by the original submitter of the report at the site.**

Any supporting or follow up documentation must be faxed to ECOG (617-632-2990), Attention: AE. In addition, supporting or follow up documentation must be faxed to the NCI (301) 230-0159.

**5.3.2 Other recipients of adverse event reports**

ECOG will forward AdEERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

Adverse events determined to be reportable 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.

**5.3.3 Expedited reporting for PACCT-1 protocol**

Attribution	Grade 5 <sup>a</sup>	
	Unexpected	Expected
Possible, Probable, Definite	7 calendar days	7 calendar days
<b>7 Calendar Days:</b> Indicates a full AdEERS report is to be submitted within 7 calendar days of learning of the event.		
<b>a</b> This includes all deaths within 30 days of the last dose of treatment regardless of attribution. <b>NOTE: Any death that occurs &gt; 30 days after the last dose 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>		

**5.3.4 Reporting secondary AML/MDS/ALL**

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to ECOG. Submit the following information within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on NCI-sponsored trials:

- a completed NCI/CTEP Secondary AML/MDS/ALL Report Form (*do not use AdEERS*);
- a copy of the pathology report confirming the AML/MDS/ALL; and
- a copy of the cytogenetics report (if available).

ECOG will forward copies to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP).

**NOTE:** If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS/ALL Report Form must be submitted for the most recent trial. ECOG must be provided with a copy of the report even if ECOG was not the patient's most recent trial.

**5.3.5 Reporting of other second primary cancers**

All cases of new primary cancers that occur on this protocol during or after protocol must be reported to CTSU or ECOG, according to the follow up schedule outlined in the PACCT-1 Forms Packet, on the ECOG Second Primary Form within 30 days of diagnosis, regardless of relationship to protocol treatment. This form is not for use for reporting recurrence or development of metastatic disease. A copy of the pathology report should be sent, if available.

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted, including the NCI AML/MDS/ALL form and ECOG Second Primary Form.

Submit Second Primary information to:

Westat, CTSU Data Management  
5615 Kirby Drive, Suite 710  
Houston, TX 77005

**NOTE:** A CTSU Data Transmittal Form should accompany all forms and reports submitted to the CTSU.

Submit AML/MDS/ALL information to:

ECOG Coordinating Center  
FSTRF  
900 Commonwealth Avenue  
Boston, MA 02215

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## 6. Measurement of Effect

**NOTE:** Recurrence must be documented by biopsy and/or evidence of disease on radiologic studies. Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Whenever possible, histologic proof of recurrence should be obtained.

### 6.1 Ipsilateral Breast Tumor Recurrence (IBTR)

Recurrence occurring within the ipsilateral breast in a patient who has had prior breast conserving therapy (ie, lumpectomy). Patients who develop an IBTR must continue to be followed for other sites of recurrence, which must be reported if they occur. Development of invasive disease in the ipsilateral breast should be reported as IBTR, not as a new primary cancer. New sites of ductal carcinoma in situ (DCIS) should be reported, but will not be considered an IBTR and follow-up for IBTR should continue.

### 6.2 Local/Regional Recurrence (LRR)

One or both of the following: (a) nodal relapse: recurrence in regional lymph nodes (e.g., ipsilateral axillary, supraclavicular, or internal mammary lymph nodes), and/or (b) recurrence in the skin and/or chest wall in a patient who has had a prior mastectomy or breast conserving surgery. Patients who develop an LRR must continue to be followed for other sites of recurrence, which must be reported if they occur.

### 6.3 Distant Recurrence (DR)

The development of a distant recurrence of breast cancer, including distant organs (eg, brain, liver, lungs, bone, etc) and/or non-regional lymph nodes (eg, mediastinal, cervical, contralateral axilla, etc). Patients who develop a distant recurrence must continue to be followed for survival; other sites of recurrence/progression do not need to be reported.

### 6.4 Second Primary Breast Cancer

Evidence of invasive breast cancer in the contralateral breast. Histologic confirmation of second primary breast cancers is required. New sites of DCIS should be reported, but do not be considered an event for purposes of analysis, and patients with DCIS should continue to be followed for development of invasive disease. Patients who develop a second primary breast cancer must continue to be followed for other sites of breast cancer recurrence, which must be reported if it occurs.

### 6.5 Second Primary Cancer (non-breast)

Any non-breast invasive cancer except squamous or basal cell carcinoma of the skin. New in situ cancers at any site (except breast) should not be reported. Patients who develop a second primary cancer must continue to be followed for breast cancer recurrence, which must be reported if it occurs.

### 6.6 Disease-Free Survival (DFS)

Date of randomization or registration to the date of ipsilateral breast tumor recurrence, local/regional recurrence, distant recurrence, second primary cancer (breast or non-breast), or death from any cause.

### 6.7 Distant Recurrence-Free Interval (DRFI)

Date of randomization or registration to the date of distant recurrence of breast cancer, as defined in Section 6.3, or of death with distant recurrence, if death is the first manifestation of distant recurrence.

### 6.8 Recurrence-Free Interval (RFI)

Date of randomization or registration to the date of first recurrence of breast cancer (IBTR, LRR, or DR) or to the date of death with recurrence, if death is the first manifestation of recurrence.

### 6.9 Overall Survival

Date of randomization or registration to date of death from any cause.

### 6.10 Cause-specific Survival

Date of randomization or registration to date of death from breast cancer.

## 7. Study Parameters

### 7.1 Therapeutic Parameters

Prestudy CBC (with differential and platelet count) and all required prestudy chemistries (as outlined in Section 3) should be done  $\leq$  4 weeks before pre-registration.

**NOTE:** When recording prestudy results on the ECOG Baseline Data Form, please make sure that ALL relevant dates are clearly given. Do **not** put all the results under the date for Day 1 of protocol treatment unless they were actually done that day. *Record the actual dates.*

	<u>Pre-Registration</u>	<u>Follow-up<sup>4</sup></u>
History & Physical Examination	X	Between every 3- 6 months x 5 years, then annually thereafter
Disease and survival status		X <sup>1</sup>
Height	X	
Weight	X	
Complete Blood Count (including leukocyte and platelet count)	X <sup>2</sup>	
Serum creatinine and AST (aspartate transaminase)	X <sup>2</sup>	
Mammography	X <sup>3</sup>	Annual
Oncotype DX assay (RS score) <sup>5</sup>	X	
BIOLOGICAL MATERIAL SUBMISSIONS and related documents: See Section 7.2 and Appendix IV		

1 The following events must be reported to ECOG within 30 days that they are known to have occurred: death from any cause, recurrence (ipsilateral breast tumor recurrence, local/regional recurrence, or distant recurrence, as defined in Section 6), or second primary cancer; if these events have not occurred, follow-up at the time points indicated for history and physical exam is required to confirm that they have not occurred.

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2 Obtained within 4 weeks prior to pre-registration

3 Mammogram obtained as part of the original diagnosis, biopsy and surgical treatment will suffice and need not be repeated.

4 Follow-up for up to 20 years

5 Oncotype DX assay (RS score) is performed by Genomic Health (see Sections 4 and 10 and Appendices IV and V). Fax a redacted copy of the "Oncotype DX Patient Report" to the ECOG Coordinating Center (617-582-8578, ATTN: Pre-Registration/PACCT-1). Registration/randomization may proceed 24 hours and up to 72 hours (if weekend or holiday) after submission of the Oncotype DX Patient Report to ECOG.

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7.2 Submission of Biological Materials

1. Submission of primary tumor tissue is mandatory.
2. Materials submitted for banking for possible future use are to be submitted after randomization/registration, prior to start of therapy. Submit only from patients who have given written consent for banking.

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	Pre-registration	Registration/ Randomization
Primary Tumor Tissue <sup>1,2</sup> (MANDATORY)	X <sup>1</sup>	X <sup>2</sup>
Frozen Tumor Tissue (if available)		X <sup>4</sup>
Serum, SST red marbled top <sup>3</sup>		X <sup>3</sup>
Peripheral Blood, CPT citrate (blue/black top) <sup>3</sup>		X <sup>3</sup>
Plasma, EDTA purple top <sup>3</sup>		X <sup>3</sup>
Peripheral blood PAXgene DNA <sup>3</sup>		X <sup>3</sup>

1. **MANDATORY: For the determination of Oncotype DX Recurrence Score**, one tumor tissue block must be submitted to Genomic Health (see Section 10 and Appendix IV). Kits for tissue submission and *Oncotype DX* Recurrence Score assessments must be ordered within one day after pre-registration (call Genomic Health, 866-662-6897). Samples are to be submitted within 3 days following pre-registration. Pathology report and ECOG Pathology Material Submission Form (#638 v04.2) must be completed and copies distributed to both Genomic Health (with the samples and requisition form) and the ECOG PCO-RL.

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**NOTE:** If additional material is available, at least one tumor block is to be forwarded to the ECOG PCO-RL for correlative studies and banking.

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2. MANDATORY submission to ECOG PCO from patients with *Oncotype DX* Recurrence Score determined prior to pre-registration, or if sections were submitted to Genomic Health at pre-registration; REQUESTED from patients if blocks were submitted to Genomic Health at pre-registration. Submit within two weeks of registration/randomization. See Section 10.2.

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3. Samples are to be collected/submitted after registration/randomization prior to start of the treatment. Submit to ECOG PCO from patients who have given written consent to allow banking of samples for possible future use as outlined in Section 10.2. Collection and shipping kits ordered by Faxing *PACCT-1 Peripheral Blood Collection and Shipping Kit Order Form* (Appendix VI) to Zerotak-International at 800-815-4675.

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4. Frozen tumor tissue that has been collected at the local institution, if not submitted after registration/randomization, will be considered part of the "Virtual Tumor Bank" if the patient has provided consent for future research [see Question 1 of 'Making Your Choice' in the Consent (App I, pg 11 of 13)]. This tissue may remain at the local site until requested by the ECOG Pathology Coordinator Office.



## 8. Drug Formulation and Procurement

### 8.1 Cyclophosphamide

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

#### 8.1.1 Other Names

Cytoxan, Neosar, CTX, CPM, NSC #261037.

#### 8.1.2 Classification

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

#### 8.1.3 Mode of Action

Cyclophosphamide metabolites are thought to disrupt cell division primarily by cross-linking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

#### 8.1.4 Storage and Stability

Tablets and injectable powder are stored at room temperature 25°C (77°F). The temperature is not to exceed 30°C (90 F°). Reconstituted parenteral solutions are stable for 24 hours at room temperature for 6-14 days if refrigerated.

#### 8.1.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

##### 8.1.5.1 Dosage in Renal or Hepatic Failure

Cyclophosphamide dosage adjustment for patients with renal or hepatic failure has not been adequately evaluated.

#### 8.1.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

#### 8.1.7 Administration

May be given orally, IV push, or by IV infusion.

#### 8.1.8 Compatibilities

Numerous compatibility studies have been published. For specific details refer to handbook on injectable drugs by Lawrence A. Trissel.

#### 8.1.9 Availability

Cyclophosphamide is commercially available as 25 mg and 50 mg tablets and for parenteral injection as 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.

8.1.10 Side Effects

Side effects vary significantly based on the specific dose and duration of cyclophosphamide.

8.1.10.1 Incidence More Frequent (>5%)

1. Anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills)
2. Thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising; black tarry stools; blood in urine or stools; pinpoint red spots on skin). Nadir counts usually occur 7 to 12 days after administration and recovery usually complete by day 17 to 21.
3. Alopecia
4. Anorexia, nausea and vomiting
5. Gonadal suppression (azoospermia, missed menstrual periods) resulting in infertility. Return of normal gonadal function and fertility occurs with time in many younger men and women.
6. Hemorrhagic cystitis

8.1.10.2 Incidence Less Frequent (1-5%)

1. Stomatitis

8.1.10.3 Incidence Rare (1%)

1. Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat)
2. Flushing or redness of face
3. Diarrhea
4. Skin rash
5. Pneumonitis or interstitial pulmonary fibrosis
6. Syndrome of inappropriate antidiuretic hormone (siadh)
7. Chemical phlebitis (redness, swelling or pain at site of injection)
8. Secondary malignancies
9. Blurred vision, cardiac toxicity presenting as congestive heart failure
10. Hemorrhagic myocarditis
11. Cardiac necrosis
12. Pericarditis (seen with high dose regimens used with bone marrow transplantation)

8.1.11 Drug Interactions

8.1.11.1 Digoxin

Several studies conducted in lymphoma patients receiving combination chemotherapy including cyclophosphamide revealed a 20–50% reduction in digoxin absorption when digoxin tablets were administered. When digoxin capsules were administered no significant decrease in digoxin absorption occurred. To avoid decreased serum digoxin levels the use of digoxin in liquid form (liquid or capsules containing liquid digoxin) instead of tablets is recommended.

8.1.11.2 Pentostatin

Two case reports describe fatal cardiac toxicity in patients receiving CTX 6.4 g/m<sup>2</sup> over 4 days and pentostatin 4 mg/m<sup>2</sup> over 4 hours on day 3. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

8.1.11.3 Succinylcholine

Cyclophosphamide may prolong the effects of succinylcholine by irreversibly inhibiting the enzyme pseudocholinesterase. Limited clinical observations and *in vitro* studies suggest that prolonged apnea might result when succinylcholine is administered to some patients also receiving cyclophosphamide. Management options include avoiding concurrent therapy or if concurrent therapy can not be avoided, to monitor for prolonged succinylcholine effect in patients receiving both drugs. If cyclophosphamide has been administered within 10 days of succinylcholine, extreme caution should be used after succinylcholine administration. The anesthesiologist should be informed of the potential for succinylcholine-induced apnea and appropriate precautions and monitoring should be implemented.

8.1.11.4 Trastuzumab

In early clinical trials the concurrent administration of cyclophosphamide and trastuzumab increased the incidence and severity of cardiac dysfunction. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

8.1.12 Nursing Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm<sup>3</sup> and increased risk of bleeding with platelet counts less than 20,000 cells/mm<sup>3</sup>. Advise patients to call the clinic if they develop a fever above 101°F or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters above normal intake for 72 hours after administration. Instruct patients to void more frequently to minimize occurrence of hemorrhagic cystitis. For high-dose therapy MESNA may be used.
4. Premedicate with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.1.13 References

American Hospital Formulary Service 99 – Drug Information; 832-837.

Cytosan Package Insert, Princeton, NJ: Mead Johnson Oncology Products 1998; July Micromedex Inc. Vol. 101; 1999.

USPDI Volume 1 1999; 1128-1134.

Trissel L.A, Handbook on injectable drugs (8<sup>th</sup> Ed), Bethesda, MD: American Society of Hospital Pharmacists, 1994, Pp. 287-295.

Cazin B, Gorin NC, Laporte JP. Cardiac complications after bone marrow transplantation: A report of a series of 63 consecutive transplants. *Cancer* 1986; 57:2061-2069.

Gryn *et. al.* Pentostatin increases the acute toxicity of high dose cyclophosphamide. *Bone Marrow Transplantation* 1993; 12:217-220.

Pedersen-Bjergaard J, Ersboll J, Sorenson HM. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for Non-Hodgkin's lymphoma. *Ann Intern Med* 1985; 103:195-200.

Stillwell TJ, Benson RJ. Cyclophosphamide-induced hemorrhagic cystitis: A review of 100 patients. *Cancer* 1988; 61:451-457.

Zuccherro FJ, Ed. Evaluation of drug interactions. St. Louis: Professional Drug Systems, 1997; 2/35, 12/21.

Hansten Pd, Ed. Drug interactions analysis and management. Applied Therapeutics, Inc., Vancouver, WA 1998; 185-186.

Trastuzumab Package Insert, South

## 8.2 Methotrexate

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

### 8.2.1 Other Names

#### 8.2.1.1 Chemical Name

N-[4-[[[(2,4-Diamino-6-pteridiny)]methyl]] methylamino]benzoyl]-L-glutamic acid

#### 8.2.1.2 Synonyms

Methotrexate sodium, MTX, Mexate, Mexate-AQ, Folex, Folex PFS, Abitrexate, Rheumatrex, Amethopterin, NSC #740

### 8.2.2 Classification

Antimetabolite

### 8.2.3 Mode of Action

Methotrexate inhibits the enzyme dihydrofolate reductase, thereby blocking the conversion of folic acid to its active form, tetrahydrofolic acid. Inhibition of this enzyme reduces purine synthesis and the conversion of deoxyuridylate to thymidylate which inhibits the synthesis of DNA, RNA and proteins.

### 8.2.4 Storage And Stability

Store at room temperature protected from light. Reconstituted solutions are stable at room temperature for at least 1 week. Solutions (50 mg/100 mL) in PVC bags of 5% dextrose may be frozen at -20°C for at least 30 days when thawed in 2 minutes by microwave radiation. There is no loss of potency after 5 freeze-thaw cycles.

### 8.2.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

8.2.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

8.2.7 Administration

Usually administered by IV bolus (< 100 mg), or slow IV infusion over 30 minutes or longer (> 100 mg). Has also been given intrathecally, intra- muscularly, orally, intra-arterially, intraperitoneally and intravesicularly.

8.2.8 Compatibilities

Compatible with sodium bicarbonate, cytarabine, cephalothin, mercaptopurine, vincristine sulfate, hydrocortisone, leucovorin, furosemide, and amino acids. At the "Y-site," compatible with fluorouracil, cisplatin and heparin.

8.2.9 Incompatibilities

Incompatible in solution with bleomycin, fluorouracil, prednisolone sodium phosphate, droperidol, metoclopramide, and ranitidine. Aspirin, probenecid, and nonsteroidal anti-inflammatory drugs may prolong methotrexate clearance and increase toxicity. They should not be given to patients receiving larger doses of methotrexate (for 48 hours after a dose).

8.2.10 Availability

Commercially available as a lyophilized powder for injection (20, 50, 100, 250, and 1000 mg/vial), as a 25 mg/mL preservative free isotonic solution for injection (50, 100, 200 and 250 mg/vial), as a 2.5 mg/mL (5 mg vial) and 25 mg/mL (50 and 250 mg vials) preservative protected isotonic solution for injection and as a 2.5 mg tablet.

8.2.11 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia: dose-related, more likely with prolonged drug exposure; anemia.
2. Dermatologic: Skin erythema and/or rash, sometimes pruritic; alopecia; photosensitivity; furunculosis; depigmentation or hyperpigmentation; acne; telangiectasia; skin desquamation (exfoliative dermatitis) and bullae formation; folliculitis.
3. Gastrointestinal: Nausea and vomiting, uncommon with conventional doses, and usually mild; stomatitis, common, dose- and infusion duration- related and highly variable; diarrhea; anorexia; hematemesis; melena.
4. Genitourinary: Renal dysfunction: dose-related, more likely to occur in patients with already compromised renal function, dehydration, or on other nephrotoxic drugs, manifested by increased creatinine, hematuria.
5. Hepatic: Increased SGOT, mild and transient; hepatic fibrosis and cirrhosis, more likely to occur in patients receiving long-term continuous or daily methotrexate treatment.
6. Neurologic: Encephalopathy, more commonly with multiple intrathecal doses and in patients who have received cranial irradiation; tiredness, weakness, confusion, ataxia, tremors, irritability, seizures, coma. Acute side effects of intrathecal methotrexate may include: dizziness, blurred vision, headache, back pain, nuchal rigidity, seizures, paralysis, hemiparesis.

7. Allergic: Fever and chills; rash; urticaria; anaphylaxis.
8. Ocular: Conjunctivitis; excessive lacrimation; cortical blindness has occurred with high doses.
9. Pulmonary: Pneumonitis, pulmonary fibrosis, cough, dyspnea.
10. Other: Malaise; osteoporosis (aseptic necrosis of the femoral head); hyperuricemia; reversible oligospermia.

#### 8.2.12 Nursing Implications

1. Administer antiemetics as indicated.
2. Monitor for hematologic toxicity.
3. Observe for gastrointestinal toxicity (stomatitis, diarrhea); offer symptomatic care.
4. For patients who are to begin methotrexate therapy at a dose of 1 g/m<sup>2</sup> or greater: Proper functioning of kidneys must be documented. Proper hydration and alkalinization of urine must be maintained.
5. Instruct patient to use sunscreen lotion or cream when exposed to the sun.
6. Scheduling for methotrexate serum levels may be necessary in high dose situations.
7. Time of administration of infusions may be critical - should be carefully monitored. An infusion pump may be necessary.
8. High dose methotrexate (see route of administration) must be given with leucovorin rescue. Educate patient and significant other about importance of compliance with medication schedule. There may be financial implications due to the high cost of the drug.

#### 8.2.13 References

- Alkins SA, Byrd JC, Morgan SK *et al.* Anaphylactoid reactions to methotrexate. *Cancer* 1996; 77:2123-2126.
- Anon: Drugs of choice for cancer chemotherapy. *Med Lett Drugs Ther* 1997; 39:21-28.
- Anon: NCI Investigational Drugs Pharmaceutical Data. National Cancer Institute, Bethesda, MD, 1988.
- Athanikar N, Boyer B, Deamer R *et al.* Visual compatibility of 30 additives with a parenteral nutrient solution. *Am J Hosp Pharm* 1979; 36:511-513.
- Benvenuto JA, Anderson RW, Kerkof K *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; 38:1914-1918.
- Bleyer WA: The clinical pharmacology of methotrexate. *Cancer* 1978; 41:36.
- Evans WE, Crom WR, Abromowitch M *et al.* Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. *N Engl J Med* 1986; 314(8):471-477.
- Jolivet J, *et al.* The pharmacology and clinical use of methotrexate. *N Engl J Med* 1983; 309: 1094-1104.

McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. Am J Hosp Pharm 1976; 33: 1010-13.

Product Information: Methotrexate. Immunex Corporation, Seattle, WA, 1998.

Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. Clin Pharmacokinet 1978; 3: 1-13.

### 8.3 Fluorouracil (Infusional)

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

#### 8.3.1 Other Names

5-Fluorouracil, 5-FU, Adrucil, Efudex. NSC #19893.

#### 8.3.2 Classification

Antimetabolite.

#### 8.3.3 Mode of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

#### 8.3.4 Storage and Stability

Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

#### 8.3.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

#### 8.3.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

#### 8.3.7 Administration

The drug will be given by protracted venous infusion.

#### 8.3.8 Incompatibilities

Incompatible with doxorubicin and other anthracyclines. When giving doxorubicin IV push or through a running IV, flush line before giving fluorouracil. May form precipitate with fluorouracil in some concentrations.

8.3.9 Availability

Commercially available in 500 mg/10 mL ampules and vials, and 1 g/20 mL, 2.5 g/50 mL, and 5 g/100 mL vials.

8.3.10 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, anemia, can be dose limiting; less common with continuous infusion.
2. Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.
3. Gastrointestinal: Nausea, vomiting, anorexia, diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.
4. Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia).
5. Cardiac: Angina, noted with continuous infusion.
6. Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.
7. Hepatic: Hepatitis with hepatic infusion.

8.3.11 Nursing Implications

1. Monitor CBC, platelet counts.
2. Administer antiemetics as indicated.
3. Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.
4. Assess for stomatitis - oral care recommendations as indicated.
5. Monitor for neurologic symptoms (headache, ataxia).
6. Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.
7. Inform patient of potential alopecia.

8.3.12 References

Hansen R, Quebbeman E, Ausman R, et al. Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. J Surg Oncol 40:177-181, 1989.

Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 61:36-45, 1988.

8.4 Doxorubicin

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.4.1 Other Names

Adriamycin, Rubex, Adriamycin RDF, Adriamycin PFS, hydroxydaunorubicin, hydroxydaunomycin, ADR, NSC #123127.



8.4.2 Classification

Anthracycline antibiotic.

8.4.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.4.4 Storage and Stability

Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

8.4.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

8.4.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

8.4.7 Administration

Intravenously, either as a bolus injection or as a continuous infusion through a central venous line.

8.4.8 Incompatibilities

Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

8.4.9 Compatibilities

Stable with vincristine in normal saline for 5 days at room temperature protected from light. Also compatible in solution with cyclophosphamide.

8.4.10 Availability

Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/mL solution for injection in 10, 20, 50, and 200 mg vials.

8.4.11 Side Effects

1. Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.
2. Dermatologic: Alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.
3. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule.
4. Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with total doses > 550 mg/m<sup>2</sup>, mediastinal irradiation pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.
5. Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity.
6. Local effects: Vesicant if extravasated; flush along vein, facial flush.

8.4.12 Nursing Implications

1. Monitor CBC, platelet counts.
2. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
3. Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete.
4. Advise patient of red discoloration of urine for 24 hours after administration of the drug.
5. Administer antiemetics as indicated.
6. Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection.
7. Be aware of "Adria" flare - most common reaction consists of an erythematous streak up the vein. It is associated with urticaria and pruritus. Occasionally the use of corticosteroids and/or antihistamines has been useful.
8. Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

8.4.13 References

Speth PA. Clinical pharmacokinetics of doxorubicin. Clin Pharmacokinetics 1988; 15:51-31.

Von Hoff DD, *et al.* Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91:710-717.

Lum BL, *et al.* Doxorubicin: Alteration of dose scheduling as a means of reducing cardiotoxicity. Drug Intell Clin Pharm 1985; 19:259-264.

8.5 Paclitaxel

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.5.1 Other Names

Taxol, Onxol, Nov-Onxol, Paclitaxel Novaplus, NSC# 125973

8.5.2 Classification

Antimicrotubule agent.

8.5.3 Mode of Action

Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

8.5.4 Storage and Stability

The intact vials may be stored under refrigeration or at room temperature. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/mL in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.

8.5.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

8.5.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

8.5.7 Administration

Usually administered as an intravenous infusion over 3 to 24 hours with an in-line 0.22 micron filter. One-hour intravenous bolus infusions have been used in Phase I studies.

8.5.8 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole may inhibit paclitaxel metabolism, based on *in vitro* data.

8.5.9 Availability

A concentrated solution of 6 mg/mL in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% is commercially available in 5 mL vials. 100 mg/16.7 mL and 300 mg/50 mL vials are also available.

8.5.10 Side Effects

1. Hematologic: Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia).
2. Hypersensitivity: Thought to be caused by the Cremophor vehicle. Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and tachycardia. More severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.
3. Cardiovascular: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication -- Dexamethasone) may also occur.
4. Neurologic: Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).
5. Dermatologic: Alopecia (universal, complete and often sudden, between days 14-21); injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.
6. Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhilitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
7. Hepatic: Increased AST, ALT, bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.
8. Other: Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

8.5.11 Nursing Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and stomatitis.
3. Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.
4. Advise patients of possible hair loss.
5. Cardiac monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.
6. Monitor liver function tests.

7. Advise patient of possible arthralgias and myalgias which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.
9. Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorsEL vehicle for this drug can cause tissue damage.
10. In-line filtration with a 0.22 micron filter should be used.

#### 8.5.12 References

Rowinsky EK, Casenave LA, Donehower RC. Taxol: A novel investigational microtubule agent. J Natl Cancer Inst 1990; 82:1247-1259.

Gregory RE, DeLisa AF. Paclitaxel: A new antineoplastic agent for refractory ovarian cancer. Clin Pharm 1993; 12:401-415.

Rowinsky EK, Eisenhauer EA, Chaudry V, *et al.* Clinical toxicities encountered with paclitaxel. Semin Oncology 1993; 20:1-15.

Walker FE. Paclitaxel: Side effects and patient education issues. Semin Oncology Nurs 1993; 9 (suppl 2):6-10.

#### 8.6 Epirubicin

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

##### 8.6.1 Other Names

Ellence®, 4'epidoxorubicin hydrochloride, IMI-28, ADR 143, NSC #256942

##### 8.6.2 Classification

Anthracycline antibiotic.

##### 8.6.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Epirubicin also inhibits topoisomerase II.

##### 8.6.4 Storage and Stability

This product is available as a solution and should be stored under refrigeration.

##### 8.6.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

8.6.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

8.6.7 Administration

Intravenously into the side arm of a freely flowing solution of normal saline or D5W over 3-5 minutes. If the patient has a venous access device, epirubicin may be diluted further for infusion.

8.6.8 Incompatibilities

Heparin and dexamethasone are incompatible. Alkaline solutions (pH > 8) cause decomposition of epirubicin and result in a color change of the drug from red to blue-purple.

8.6.9 Availability

Commercially available in 50 mg /25 mL and 200 mg/100 mL vials for injection from Pfizer Oncology.

8.6.10 Side Effects

1. Hematologic: Severe myelosuppression, dose limiting, with nadir of WBC about 12-15 days after treatment; modest thrombocytopenia with nadir 8-11 days after treatment.
2. Gastrointestinal: Significant nausea and vomiting, diarrhea, mucositis, anorexia.
3. Dermatological: Alopecia, regional phlebitis, nail pigmentation (rare), vesicant.
4. Cardiovascular: Previous radiation of marrow-producing bones and/or preventive chemotherapy with anthracene or anthracycline drugs lowers the cumulative dose that may cause the development of CHF. Cardiotoxicity, manifested as tachycardia, premature ventricular beats, or flattening T-waves, may occur with cumulative doses > 700 mg/m<sup>2</sup>. With cumulative doses > 1000 mg/m<sup>2</sup>, left ventricular failure may occur (clinical CHF).
5. Neurological: Asthenia (rare).
6. Other: Fever, development of secondary AML or MDS.

8.6.11 Nursing Implications

1. Check CBC, differential, and platelets, and bilirubin before treatment.
2. Give supportive care for nausea and vomiting; administer antiemetic therapy.
3. Monitor for development of congestive heart failure (basilar rales, S<sup>3</sup>, gallop dyspnea).
4. Advise patient regarding risk of infection and bleeding.
5. If extravasation occurs, treat with ice for 30 minutes 3-4 times daily.

8.6.12 References

Cersosimo RJ, Hong WK. Epirubicin: A review of the pharmacology, clinical activity and adverse effects of an Adriamycin analogue. *J Clin Oncol* 1986; 4:425.

Ganzina F. 4'-epi-doxorubicin, a new analogue of doxorubicin: A preliminary overview of preclinical and clinical data. *Cancer Treat Rev* 1983; 10:1-22.

Robustelli D, Cuna G, *et al.* Clinical evaluation of 4'-epi-doxorubicin in advanced solid tumors. *Invest New Drugs* 1983; 1:349-353.

Walde D, *et al.* High dose epirubicin in previously untreated patients with advanced metastatic cancer: A phase I study. *Proc Am Soc Clin Oncol* 1988; 7:73.

8.7 Docetaxel

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.7.1 Other Names

Taxotere, RP 56976, NSC #628503.

8.7.2 Classification

Antimicrotubule agent.

8.7.3 Mode of Action

Docetaxel, a semisynthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

8.7.4 Storage and Stability

Docetaxel is stored at 4°C protected from light. The solvent vials may be stored at room temperature or at 4°C. The premix solution is stable for 8 hours at room temperature (15°- 25°C) or refrigerated (at 2°- 8°C). The final dilution is also stable for 8 hours. (Please note that the company is no longer recommending that the final product be placed in PVC bags).

8.7.5 Dose Specifics

Please refer to Appendix II for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix II, please contact study chair.

8.7.6 Preparation

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 15 seconds. Allow to stand for 5 minutes at room temperature, and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Please note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in D5W or NS. The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.9 mg/mL. Non-PVC-containing

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intravenous infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

8.7.7 Administration

Docetaxel has been administered as a 1 to 24 hour infusion. A peristaltic infusion pump is recommended.

8.7.8 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexyl] phthalate). No further information available.

8.7.9 Availability

Docetaxel is commercially available in single-dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) docetaxel (anhydrous).

8.7.10 Side Effects

1. Cardiac: arrhythmias, pericardial effusions, palpitations.
2. Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, hypernatemia.
3. Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.
4. Neurologic: reversible dyesthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.
5. Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
6. Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.
7. Hepatic: increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction.
8. Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions.
9. Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites, flu-like symptoms, fever.

8.7.11 Nursing Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and mucositis.
3. Advise patients of possible hair loss.
4. Monitor for signs and symptoms of hypersensitivity reactions. Insure that recommended premedications are given.
5. Monitor liver function tests.
6. Evaluate site regularly for signs of infiltration.
7. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs of fluid retention and cutaneous reactions.

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8.7.12 References

Investigator's Brochure: Docetaxel. Rhone-Poulenc Rorer, June 14, 1995.

Pazdur R, *et al.* Phase I trial of Taxotere; Five-day schedule. *J Natl Cancer Inst* 84:1781-8, 1992.

Pazdur R, *et al.* Phase I trial of Taxotere (RP56976). *Proc Am Soc Clin Oncol* 11:111, 1992.

Burriss H, *et al.* A phase I clinical trial of Taxotere as a 6-hour infusion repeated every 21 days in patients with refractory solid tumors. *Proc Am Soc Clin Oncol* 11:137, 1992.

Bissett D, *et al.* Phase I study of Taxotere (RP56976) given as a 24-hour infusion. *Proc Am Assoc Cancer Res* 33:526, 1992.

Bruno R, *et al.* Clinical pharmacology of Taxotere (RP56976) given as a 1-2 hour infusion every 2-3 weeks. *Proc Am Assoc Cancer Res* 33:261, 1992.

DeValeriola D, *et al.* Phase I pharmacokinetic study of Taxotere (RP56976) administered as a weekly infusion. *Proc Am Assoc Cancer Res* 33:1563, 1992.

8.8 Tamoxifen

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.8.1 Other Names

Nolvadex, tamoxifen citrate, NSC# 180973

8.8.2 Classification

Hormone antagonist (antiestrogen).

8.8.3 Mode of Action

Tamoxifen and its metabolites possess antiestrogenic activity due to their ability to compete with estradiol for binding to receptors in the cells of tumors that contain high amounts of estrogen receptors (such as breast cancer). The tamoxifen-estrogen receptor complex is translocated from the cytoplasm of cancer cells to the nucleus where it reduces DNA synthesis and cellular responses to estrogen. Tamoxifen also displays mild estrogenic activity and induces secretion of transforming growth factor beta (TGF-beta), which has inhibitory effects on many types of epithelial cells.

8.8.4 Storage and Stability

Tamoxifen is stored at room temperature protected from light.

8.8.5 Dose Specifics

Please refer to Appendix III for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in Appendix III, please contact study chair.

8.8.6 Preparation

Not applicable, tablet is ready for administration.

8.8.7 Administration

Oral.

8.8.8 Incompatibilities

Tamoxifen is a potent inhibitor of hepatic cytochrome P450 mixed function oxidases (MFO). The effect of tamoxifen on the metabolism and excretion of other drugs requiring MFO for activation is unknown. Phenobarbital decreased tamoxifen serum level significantly in one patient. Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen levels. Tamoxifen may potentiate the anticoagulant effects of warfarin.

8.8.9 Availability

Tamoxifen is commercially available in 10 mg and 20 mg tablets.

8.8.10 Side Effects

1. Hematologic: Thrombocytopenia, usually mild and transient, leukopenia, anemia.
2. Dermatologic: Rash, erythema.
3. Gastrointestinal: Nausea, vomiting, anorexia (may lead to weight loss), diarrhea or constipation, distaste for food.
4. Genitourinary: Vaginal bleeding or discharge, menstrual changes (amenorrhea, menstrual irregularities), pruritus vulvae.
5. Hepatic: Increased liver enzymes, cholestasis, increased bilirubin, and fatty changes in the liver.
6. Neurologic: Depression, dizziness, lightheadedness, headache, confusion, lassitude, and syncope.
7. Cardiovascular: Hot flashes, thrombophlebitis, thromboembolism, pulmonary embolism, fluid retention and edema. Thrombotic events, DVT, clotting factor abnormalities.
8. Ocular: Retinopathy, corneal opacity, slight increased risk of cataracts; corneal scarring and retinal changes have been reported.
9. Metabolic: Hypercalcemia.
10. Other: Tumor "flare" may occur in the first month of therapy, manifested as an increase in tumor-related symptoms, such as bone pain, increase in tumor size, erythema. Weight gain, fluid retention, and edema.
11. Effects in pregnancy: classified as Category D; women should not become pregnant while taking tamoxifen.
12. Secondary cancers: Tamoxifen increases the risk for uterine cancer and the possibility of death from this disease. Patients receiving tamoxifen should have routine gynecologic exams and report any menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge and/or pelvic pain or pressure. Tamoxifen may possibly increase the risk for gastrointestinal cancers.

8.8.11 Nursing Implications

1. Monitor carefully for tumor flare reactions.
2. Teach patients and families to recognize signs and symptoms of hypercalcemia.
3. Advise patient of potential vaginal bleeding and menstrual changes, hot flashes.

8.8.12 References

Legha SS. Tamoxifen in the treatment of breast cancer. *Ann Intern Med* 1988; 109:219-228.

Love RR. Tamoxifen therapy in primary breast cancer: Biology, efficacy and side effects. *J Clin Oncol* 1989; 7:803-815.

Kaiser-Kupfer MI, Lippman ME. Tamoxifen retinopathy. *Cancer Treat Rep* 1978; 62:315-320.

Lipton A, Harvey HA, Hamilton RW. Venous thrombosis as a side effect of tamoxifen treatment. *Cancer Treat Rep* 1984; 68:887-889.

8.9 Exemestane

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.9.1 Other names

Aromasin®, NSC# 713563

8.9.2 Classification

Steroidal aromatase inhibitor.

8.9.3 Mode of Action

Exemestane irreversibly inhibits aromatase activity (approximately 98%) and reduces plasma estrone, estradiol and estrone sulphate levels by 85-95%. Exemestane is 150-times more potent than aminoglutethimide in inhibiting aromatase. Maximal aromatase suppression occurs at exemestane doses of 10-25 mg.

8.9.4 Storage and Stability

Exemestane is stored at room temperature protected from light.

8.9.5 Dose Specifics

Please refer to Appendix III for standard regimen dose and schedule. If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule if this drug is used.

8.9.6 Preparation

Not applicable

8.9.7 Administration

Exemestane is administered orally with food.

8.9.8 Incompatibilities

No clinically relevant changes in the results of clinical laboratory tests have been observed. There are no known drug-drug interactions reported.

8.9.9 Availability

Exemestane is commercially available as a 25 mg tablet..

8.9.10 Side Effects

1. Gastrointestinal: nausea, vomiting, abdominal pain, anorexia, diarrhea.
2. Hematologic: lymphocytopenia
3. Dermatologic: Hot flushes, rashes.
4. Hepatic: Increased GGT, SGOT (AST), SGPT (ALT).
5. Neurologic: Headache, dizziness, insomnia, depression, anxiety, fatigue.
6. Pulmonary: Cough
7. Cardiovascular: thrombophlebitis.
8. Musculoskeletal: bone pain, back pain, arthralgia, limb pain
9. Other: Hair thinning, sweating.

8.9.11 Nursing/Patient Implications

Inform patients of potential side effects (joint/bone pain, diarrhea, asthenia, headache, hot flushes, nausea).

8.9.12 References

<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=exemestane>

8.10 Anastrozole

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.10.1 Other names

Arimidex®, NSC# 719344

8.10.2 Classification and Chemical Information

Non-steroidal aromatase inhibitor.

8.10.3 Mode of Action

Anastrozole selectively inhibits aromatase and lowers serum estradiol concentrations without affecting adrenal corticosteroids or aldosterone. Many breast cancers have estrogen receptors, and growth of these tumors can be stimulated by estrogens. In postmenopausal women, the principal source of circulating estrogen is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissue, with further conversion of estrone to estradiol.

8.10.4 Storage and Stability

Stored at room temperature and protected from light.

8.10.5 Dose Specifics

Please refer to Appendix III for standard regimen dose and schedule. If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule if this drug is used.

8.10.6 Preparation

Not applicable.

8.10.7 Route of Administration

Oral.

8.10.8 Availability

Commercially available, Anastrozole is supplied as 1mg film-coated tablets.

8.10.9 Side Effects

1. Gastrointestinal: diarrhea, nausea, vomiting, abdominal pain, anorexia.
2. Hematologic: Anemia, leukopenia (2-5%).
3. Dermatologic: Hot flushes, rashes.
4. Hepatic: Increased GGT, SGOT (AST), SGPT (ALT).
5. Neurologic: Headache, pain, back pain, dizziness, insomnia, anxiety.
6. Pulmonary: Increased cough, dyspnea, sinusitis, bronchitis, rhinitis.
7. Cardiovascular: Hypertension, thrombophlebitis.
8. Musculoskeletal: bone pain, back pain, arthralgia, limb pain
9. Other: hair thinning, sweating.

8.10.10 Drug Interactions

Anastrozole does not appear to cause significant inhibition of cytochrome p450 mediated metabolism. Anastrozole did not alter the pharmacokinetics or activity of warfarin in a study of 16 male volunteers (Center For Drug Evaluation 2001).

8.10.11 Nursing/Patient Implications

Inform patients of potential side effects (joint/bone pain, diarrhea, asthenia, headache, hot flushes, nausea).

8.10.12 References

<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=anastrozole>

8.11 Letrozole

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.11.1 Other names

Femara®, NSC# 719345

8.11.2 Classification and Chemical Information

Non-steroidal aromatase inhibitor.

8.11.3 Mode of Action

Letrozole is an orally active highly selective, non-steroidal competitive inhibitor of the aromatase enzyme system. it binds to the P-450 portion of the aromatase enzyme to lower serum estradiol concentrations with no clinically relevant effect on progesterone or corticosteroidal synthesis. Aromatase inhibitors block the aromatase enzyme, consequently lowering estrogen levels and thereby deprive the tumor of its growth stimulus.

8.11.4 Storage and Stability

Stored at room temperature and protected from light.

8.11.5 Dose Specifics

Please refer to Appendix III for standard regimen dose and schedule. If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule if this drug is used.

8.11.6 Preparation

Not applicable.

8.11.7 Route of Administration

Oral.

8.11.8 Availability

Commercially available, Letrozole is supplied as 2.5 film-coated tablets.

8.11.9 Side Effects

1. Gastrointestinal: nausea, constipation, diarrhea, vomiting, anorexia, dyspepsia, and abdominal pain.
2. Hematologic: Anemia, leukopenia.
3. Dermatologic: Hot flushes, rashes.
4. Hepatic: Increased GGT, SGOT (AST), SGPT (ALT).
5. Neurologic: Headache, dizziness, insomnia, anxiety.
6. Pulmonary: Dyspnea, cough, chest wall pain.
7. Cardiovascular: Hypertension, thrombophlebitis.
8. Musculoskeletal: bone pain, back pain, arthralgia, limb pain
9. Other: Hair thinning, sweating.

8.11.10 Drug Interactions

Co-administration of tamoxifen and letrozole decreases serum letrozole concentration by 38%.

8.11.11 Nursing/Patient Implications

Inform patients of potential side effects (joint/bone pain, diarrhea, asthenia, headache, hot flushes, nausea).

8.11.12 References

<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=letrozole>

## 9. Statistical Considerations

The primary endpoint is disease-free survival (DFS), defined to be time from randomization to first event, where the first event is any of ipsilateral breast tumor recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers), or death without evidence of recurrence (as defined in reference 4). DFS is used for the primary endpoint rather than distant relapse-free interval (DRFI, as defined in Section 6), which was used as the primary endpoint in the development of the assay, because DFS is the standard endpoint for evaluating adjuvant treatments for breast cancer, and the important question here, as in other treatment studies, is whether chemotherapy results in an overall DFS benefit of sufficient magnitude to justify its use. Patients will be followed for distant failure following local recurrence. (Note: In various presentations, the primary endpoint of the analyses of the assay in the B-20 and B-14 studies was called DRFS, and it was called 'distant recurrence' in the NEJM paper, but the definition used is the same as DRFI here.) DRFI is a key secondary endpoint, and RFI and OS as defined in Section 6 will also be analyzed.

Patients being considered for this study will have their RS evaluated, most after pre-registration on this study, but RS evaluation prior to initial registration is also allowed. Patients with an RS of 11 – 25 will be randomized. The randomization will be stratified on tumor size ( $\leq 2$  cm vs.  $> 2$  cm), menopausal status (pre vs. post), planned chemotherapy (taxane containing or not), and planned radiation therapy [whole breast, no boost planned vs. whole breast, boost planned vs. partial breast irradiation planned vs. no planned radiation therapy (for patients who have had a mastectomy)], as described in Section 4.

The overall DFS hazard rate on the tamoxifen + CMF arm of B-20 was .025 / year, which under an exponential distribution, gives 5-year and 10-year DFS rates of approximately 88% and 78%. In the preliminary results, the 5-year and 10-year DRFIs in the RS 11 – 25 group on tamoxifen+chemo are 97% and 94%, and the 5-year and 10-year DFS rates are 91% and 76%. For purposes of the calculations here, we assume exponential failure distributions with 5-year and 10-year DFS rates of 90% and 81% and 5-year and 10 year DRFI rates of 97% and 94% with chemo+hormonal therapy for the RS 11 – 25 group.

This study uses a non-inferiority design to determine whether patients with Recurrence Score (RS) between 11 and 25 derive benefit from adjuvant chemotherapy. Studies have indicated that patients with a low RS receive little if any benefit from chemotherapy and patients with a high RS receive a substantial benefit. This is biologically plausible, since the RS is driven primarily by genes reflecting cell proliferation. The test of non-inferiority here uses a null hypothesis of no difference, as when testing for superiority, but with a larger type I error (one-sided 10%) and smaller type II error (5%) than usual. A decrease in the 5-year DFS rate from 90% with chemotherapy to 87.0% or lower on hormonal therapy alone would be considered unacceptable. This difference corresponds to a 32.2% increase in the DFS failure hazard rate from not giving chemotherapy (the hazard ratio for hormones alone / chemo + hormones is 1.322). DFS will be compared using a stratified log rank test, with the test stratified on the same factors used in the randomization. Patients not meeting the protocol eligibility criteria will be excluded from the primary comparison. The local lab's assessment of hormone receptor status and Her2 status will be used to determine eligibility.

It is possible that not all patients will comply with their assigned therapy. Since the primary analysis will compare the randomized treatment groups, non-compliance will dilute the treatment effect and reduce the power of this study. The design allows the sum of the non-compliance rates on the two arms to be up to 5%; that would occur, for example, if 2% of the patients assigned to hormonal therapy alone receive chemotherapy and if 3% of the patients assigned to chemo+hormonal therapy do not receive chemotherapy. To compensate for this level of non-compliance, the accrual and event numbers are inflated by 10.8% (based on the Lachin-Foulkes correction).

The design assumes randomization of 4,390 patients with RS of 11 – 25 over 3 years, of which it is assumed up to 5% may be ineligible for this study (so at least 4,172 eligible patients will be enrolled). Full information corresponds to 534 DFS events in the subset of eligible patients. This is expected to occur at a little over 7.1 years from activation (at a median follow-up of about 5.6 years) if the 5-year DFS rates are 90% and 87% in the two arms, and about 8 years after activation (at a median follow-up of about 6.5 years) if the 5-year DFS rates are 90% in both arms. Based on information provided by NSABP and GHI on the RS distribution in Her2 negative patients on NSABP B14, it is expected that 46% of the patients screened will have RS values of 11 – 25. It is assumed that at least 95% of these will agree to be randomized. Thus up to 10,046 patients may need to be screened to give the required number of randomizations. Patients with RS already evaluated, with RS values between 11 and 25, can enroll and proceed directly to randomization, so the total number of patients screened as part of this study should be lower than the estimated maximum value.

The sample size estimates for this trial are based upon distribution of RS data from the B14/B20 trials, which is likely to be representative of the distribution of RS observed in TAILORx. However, should the distribution of RS be more typical of that observed in the early post-marketing experience, it is anticipated that we will need to screen 6753 patients (if patients with Her2/neu positive disease are excluded), of whom 1080 patients will have a RS < 11, and 1283 will have a RS > 25.

This study will be monitored by the ECOG Data Monitoring Committee (DMC). The DMC meets twice each year. The first interim analysis will be performed at the first DMC meeting when at least 25% of the total planned number of DFS events (133 events in the primary analysis subset) has been reported. Interim analyses will be performed for each subsequent DMC meeting until either the criteria for early stopping are met or the total planned number of DFS events has been reported. At each interim analysis (and at the final analysis), the stratified log rank test statistic will be computed. The stopping boundary for rejecting non-inferiority will be based on a truncated version of the Lan-Demets error spending rate function corresponding to an O'Brien-Fleming shaped boundary with an overall one-sided type I error of 10%. At early analyses, the boundary will be truncated at a level corresponding to a one-sided nominal significance of 0.002. The boundary function will be computed to maintain the type I error rate adjusting for the effects of the truncation and the effects of the early stopping in favor of non-inferiority, discussed below. If the boundary is crossed at an interim analysis or at the final analysis, then the hypothesis of non-inferiority will be rejected. If the criteria for rejecting the hypothesis of non-inferiority are not met, then it will be concluded that hormonal therapy alone is not inferior to combined chemo+hormonal therapy.

To allow for early stopping in favor of non-inferiority, this study will also be monitored using repeated confidence interval (RCI) methodology. At each interim analysis, the two-sided 95% RCI on the log hazard ratio (for hormones alone / chemo + hormones) will be computed. This RCI uses the critical value from the O'Brien-Fleming error spending rate function with an overall one-sided 2.5% error rate. If the upper limit of this RCI lies below the minimum unacceptable log ratio of  $\log(1.322)$  then the study will be stopped in favor of non-inferiority. This monitoring rule has deliberately been chosen to be conservative, since the results must be convincing that the conclusion of non-inferiority is based on an adequate amount of information rather than on an underpowered comparison.

Accrual rates, the distribution of Recurrence Scores, and compliance rates with the assigned treatments will be closely monitored throughout the study. If there are significant deviations from the assumptions stated above, then design modifications to ensure that adequate power will be available will be considered by the Steering Committee. If the modifications needed are not feasible, then early termination of this study will be discussed with the Steering Committee, the Breast Intergroup and CTEP. These rates will also be reported to the DMC at every DMC meeting while this study is ongoing, and the DMC may also recommend changes to the design or early termination of this study.

At the time of the final analysis, DRFI will also be compared using a stratified log rank test with one-sided type I error of 10%. Under the accrual, follow-up and compliance assumptions given above, the DRFI test will have 95% power to detect a difference in DRFI corresponding to 5-year DRFI rates



of 97% on chemo+hormonal therapy vs. 95.2% on hormonal therapy alone. This analysis requires 182 DRFI failures in the subset of eligible patients. Note that in this analysis, patients who die without developing distant (breast cancer) metastases are censored at the time of death, and other intervening DFS events (eg local-regional recurrence) are ignored. While ideally this study would include an early stopping rule based on differences in DRFI, the expected number of events during the accrual period is too low to provide a meaningful stopping rule, and once accrual is completed, the release of results will be based on the primary endpoint.

Survival will also be compared. Overall survival rates are likely to be similar to the DRFI rates given above. Using a stratified log rank test with one-sided type I error of 10%, at a time when 284 deaths have been observed, there would be 95% power to detect a difference in survival corresponding to 5-year survival rates of 95% on chemo+hormonal therapy vs. 92.8% on hormonal therapy alone.

The interaction of the treatment effect with RS will also be examined for each of the endpoints. Smoothing spline methods (34) will be used to estimate the treatment hazard ratio as a function of RS and to test for treatment by RS interaction. One analysis will just analyze the patients in the randomized group (RS 11 – 25). A second analysis will be done estimating the failure rates as a function of RS separately in the chemo and no chemo groups. This analysis will use patients from Arms A and B to estimate the relationship without chemotherapy and patients from arms C and D to estimate the relationship with chemotherapy. This analysis should lead to more precise estimates of the relationships at the extremes of the intermediate group than the analysis limited to the RS 11 – 25 group. However, the question of whether there could be different patient selection in the three groups, potentially leading to biases in the second analysis, will also need to be considered.

Another secondary objective is to validate whether patients with Recurrence Scores <11 (Arm A) have failure rates that are low enough that adjuvant chemotherapy is unlikely to be of much absolute benefit. Depending on the distribution of RS values and on the total number of patients pre-registered for RS screening vs. entering with RS already evaluated, it is expected that 2400 – 2700 of the eligible patients enrolled on the pre-registration step will have  $RS \leq 10$  and will be followed for study endpoints. Based on data from NSABP B-20 and B-14, it is expected that the 10-year DRFI rate will be about 95% and the 10-year DFS rate will be between 80% and 85%. The null hypothesis of a 10-year DRFI rate of 95% will be tested by fitting an exponential model and using the Wald test statistic for the log hazard rate. With at least 2,515 eligible patients entered over 3 years and 5 years of additional follow-up, a one-sided test with type I error 2.5% will have power of at least 80% for the alternative that the 10-year DRFI rate is 93.5%. Full information for this test is 108 distant recurrence failures.

All patients with an elevated Recurrence Score > 25 (Arm D) who are assigned to receive chemotherapy will also be followed for relapse and survival. This will provide an extremely valuable resource for further correlative studies, and will be required for achieving the second primary objective (2.1.2) of evaluating emerging "Cancer Clinical Tests" as they develop. Identifying patients with a high Recurrence Score (>25) who relapse despite adjuvant chemotherapy will be just as informative as identifying patients with a low RS (<11) who relapse without chemotherapy. The ability to evaluate emerging future "Cancer Clinical Tests" will only be possible if outcome data is collected for all patients enrolled in all arms (A-D) of the trial.

For objective 2.2.4, the prognostic significance of the genomic variables (overall RS and the individual gene group scores for proliferation, HER2, ER, invasion, and other genes) will be evaluated by fitting proportional hazards regression models containing standard factors such as tumor size, hormone receptor status and tumor grade in addition to the genomic variables. The endpoint for the primary analyses will be DRFI, and models where the log hazard ratio is linear in the genomic variables will be used for the primary test of significance. For each genomic variable, the model will be fit using the standard factors and the genomic variable and the significance of the genomic variable will be determined. Additional analyses will be done to explore the functional form of the relationships using penalized spline methods and other exploratory modeling techniques. Joint models combining the gene group variables will also be fit to evaluate whether the different gene groups are of independent prognostic significance.

ER, PgR and Her2 will be centrally evaluated. Study eligibility (and hence whether cases are included in the primary analysis) will be determined by the results from the local labs. Secondary analyses excluding cases that are ER and PR negative on central review and excluding cases that are Her2 positive on central review will be performed to examine the sensitivity of the results to possible misclassification of these factors by the local labs.

Another objective of this study is to compare the prognostic and predictive power of Adjuvant! with the GHI RS and to determine if the classical information reflected in Adjuvant! adds significantly to RS. The Adjuvant! continues to undergo refinement and enhancement, but roughly it begins by estimated 10-year breast cancer specific mortality (BCSM) from SEER data based on tumor size, grade, nodal status and ER status. The benefit of treatment is estimated from the Oxford overview, and the effects of competing risks are factored in based on age and co-morbidities. Following the methodology in John Bryant's presentation at St. Gallen (2005), the Adjuvant! 10-year BCSM will be used to rank the risk level of the patients enrolled in this study. The Adjuvant! risk rankings (ARR) will then be analyzed in a similar way to the GHI RS. In the group of patients who do not receive chemotherapy (both the randomized group and the RS  $\leq$  10 cohort), models for DFS and DRFI will be fit containing RS and ARR separately and together to compare the prognostic power of these variables separately and in combination with other factors. Models with both RS and ARR will be used to determine whether either adds significant prognostic information to the other. A similar analysis will be done in the cohort of chemotherapy treated patients. Within the randomized group, analyses examining interaction of the ARR and the effect of chemotherapy, similar to those for RS, will also be performed.

Return of Research Results: The results of correlative science studies, including genomic studies, will require mature clinical results with at least five years of clinical followup, or longer. Since the research results are not anticipated to have clinical relevance to either the patient or their family members, these results will not be disclosed to the patient. If, unexpectedly, results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting is required. Research data will not be shared with individual patients when the data are generated. Sharing of research data with individual patients may occur when data have been validated by multiple studies, and testing done in CLIA-approved laboratories. The results of the research relative to objective 2.11 (the primary clinical objective) and 2.21 (a secondary clinical objective) will be released by the ECOG Data Monitoring Committee (DMC) in accordance with the ECOG DSMC Policies and Procedures and with the criteria stipulated in the statistical section of the protocol. Use of tissue and clinical information for objective 2.12 (specimen bank) will require review by the PACCT Correlative Science Committee (as described in Appendix VIII). Release of data regarding secondary objectives (2.21, 2.22, and 2.23) will require that a sufficient amount of time elapsed to achieve the primary objective, that the data analysis and review has been completed, and that the ECOG statistician has written a technical report describing the results. Standard procedures described in the ECOG DSMC Policies and Procedures will be followed in order to safeguard against the inadvertent release of data.

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Based on previous data from E2197, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	229	0	229
Not Hispanic or Latino	9817	0	9817
<b>Ethnic Category: Total of all subjects</b>	10046	0	10046
<b>Racial Category</b>			
American Indian or Alaskan Native	24	0	24
Asian	135	0	135
Black or African American	765	0	765
Native Hawaiian or other Pacific Islander	4	0	4
White	9118	0	9118
<b>Racial Category: Total of all subjects</b>	10046	0	10046

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Study Monitoring

This study will be monitored by the ECOG Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG DMC Policy can be obtained from the ECOG Coordinating Center.

## 10. Tissue and Blood Specimens

The submission of original diagnostic tumor tissue for *Oncotype* DX Assay to establish the *Oncotype* DX Recurrence Score (RS status) is MANDATORY for patients with unknown Recurrence Scores (see Section 10.1).

If the Recurrence Score was previously determined by Genomic Health (GH), diagnostic tumor tissue must be submitted within two weeks after randomization for central review and, with patient consent, banking. Blood samples (and frozen tumor tissue, if available) are requested for banking for future studies from all patients who consent to banking. These materials are to be submitted to the ECOG Pathology Coordinating Office-Reference Laboratory (PCO-RL) and are outlined in Section 10.2.

Processing and potential laboratory studies include assays to determine ER, PR, and Her2 status (tissue), proteomics (serum/plasma), TMA generation (tissue), RNA isolation (tissue), and DNA isolation (blood). Additional information is provided in Appendix VIII.

**NOTE:** If tissue was submitted at pre-registration for *Oncotype* DX RS assessment, additional materials are requested for correlative studies and banking.

**NOTE:** Summary of submissions is provided in Appendix IV. Guidelines for pathology submissions are outlined in Appendix V. Copies of the pathology report and a completed ECOG Pathology Material Submission Form (#638 v04.2) must be submitted to the ECOG PCO-RL for every pathology submission, including the tissue submission to Genomic Health.

**NOTE:** Submissions to establish *Oncotype* DX Recurrence Score are outlined in Section 10.1 and Appendix V. Samples for laboratory studies and banking for future research are defined in Section 10.2.

### 10.1 Submissions To Genomic Health

Contact Genomic Health Customer Service (866-662-6897) and request the “*Oncotype* Specimen Kit”.

If the kit is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration. The kit will be shipped overnight and will contain instructions, shipping kit (includes cryotubes and slide cassette), a mailer, and a requisition form containing barcode labels to place on the submitted materials. One *Oncotype* Specimen Kit and Requisition form should be completed per patient.

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

Summary submission guidelines, including a draft requisition form, are provided in Appendix V. *Oncotype* DX information packet provided in the packet is located in Appendix X.

[This section has been moved, via Addendum #1, and is now section 10.1.3]

10.1.1 The following must be submitted to Genomic Health:

- The *Oncotype* DX Requisition Form: DO NOT COMPLETE THE FORM IN APPENDIX V. Use the form, with the barcode labels, provided in the kit.

- ECOG Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Copy of the form is located in Appendix V. Place a barcode label from the Oncotype DX Requisition Form at the TOP of the form.
  - A copy of the surgical pathology report. The ECOG sequence number provided at registration should be written on the report. Include immunological studies, if available.
  - Primary Tumor Tissue Block
- NOTE:** If a block is not available, submit the following sections:
- six (6) 10µm sections, in two microcentrifuge tubes from the kit
  - H&E (4 or 5 µm) cut after the 10µm sections are cut.

*If alternative samples are submitted, additional materials MUST be forwarded to the ECOG PCO within two weeks following registration/randomization as outlined in Section 10.2.*

#### 10.1.2 Shipping Procedures

Ship the tumor tissue samples, completed forms, and the pathology report using the FedEx Airbill provided in the Oncotype Specimen Kit.

Ship to: Customer Service  
Genomic Health, Inc.  
301 Penobscot Drive  
Redwood Cit, CA 94063  
Telephone: 866-662-6897

Rev. 6/06 Submit a copy of the reports, completed requisition form, and completed ECOG Pathology Material Submission Form (#638 v04.2) to the ECOG Pathology Coordinating Office as indicated in Section 10.2.3. Note in the comment section on the Form #638 that the material was submitted to Genomic Health for analysis.

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**NOTE:** Residual block materials and RNA will be forwarded to the ECOG PCO-RL for laboratory studies and/or banking for possible use in future studies.

#### **NOTE: Forms Submission**

Rev. 6/06 The institutional pathology report, clinical reports, and the ECOG Pathology Material Submission Form (#638 v04.2) must be submitted to CTSU Data Operations, accompanied by a completed CTSU Data Transmittal Form and a completed TAILORx Source Document Coversheet (Form #2533). The original hard copy of the institutional pathology report, ECOG Pathology Material Submission Form (#638 v04.2), and completed requisition form must be shipped to the Genomic Health in the same package with the specimens. A copy of these documents should be retained for your files as well. **ECOG and non-ECOG sites alike must refer to the CTSU appendix (Appendix XI) for complete CTSU data submission instructions. If an RDC site, please take special note of the RDC instructions.**

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#### 10.1.3 NOTIFICATION OF RESULTS

Genomic Health will notify the institution of the recurrence score via the mechanism selected on the Oncotype Requisition Form within 14 days of receipt of the tissue by Genomic Health. Genomic Health will not distribute reports directly to the ECOG Coordinating Center.

Rev. 6/06 **NOTE:** After pre-registration and prior to registration/randomization, the institution must fax a copy of the report to the ECOG Coordinating Center (617-582-8578, ATTN: Pre-Registration/PACCT-1) as outlined in Section 4.1.5.3. Institution may register/randomize the patient (Section 4.2) 24 to 72 hours after submission of the report to ECOG.

10.2 Submissions to the ECOG Pathology Coordinating Office – Reference Laboratory (PCO-RL)

Primary tumor tissue is to be submitted within two weeks following registration/randomization for laboratory studies (defined in Section 10.3) and banking for future research.

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Pretreatment frozen tissue (if available) and blood samples, requested for banking for possible use in future studies, are to be submitted after registration/randomization. Shipping and collection kits for the submissions to the PCO are ordered by completing the *PACCT-1 Peripheral Blood Collection and Shipping Kit Order Form* (Appendix VI) and Faxing to Zemotak-International at 800-815-4675.

Questions pertaining to sample collection and shipment are to be directed to Dr. Michael Pins or Adekunle Raji at Tel: (312) 503-3384.

**NOTE:** Banking samples are to be submitted only from patients who have given written consent to allow submission and retention of samples for these purposes.

The submission of the following are required:

10.2.1 Pathology Reports and Forms

These forms must be submitted to the ECOG PCO-RL for all biological pathology materials submitted for this protocol, including tissue samples submitted to Genomic Health for Recurrence Score analysis.

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- ECOG Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- A copy of the *Oncotype* DX Requisition Form, if the material was submitted to Genomic Health after pre-registration for *Oncotype* DX testing.
- A copy of the surgical pathology report with identifiers removed. The ECOG sequence number provided at registration should be written on the report.
- Immunological studies, if available.

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10.2.2 Biological Materials

To order collection/shipping kits, FAX the kit order form (Appendix VI) to Zemotak-International at 800-815-4675. It is preferred that kits be requested after pre-registration, prior to registration/randomization.

A. One (1) paraffin block of the primary cancer.

Samples are to be shipped at ambient temperature within two weeks following registration/randomization. Pathology/surgical reports and completed ECOG Pathology Material Submission Form (#638v04.2) must accompany samples.

Requirements for block submissions to the ECOG PCO are:

- Pre-registration of patient with known RS score (no samples submitted to GH on protocol): MANDATORY
- Pre-registration of patient with unknown RS score:
  - If sections, rather than a block, were submitted to Genomic Health: Submission of tissue to PCO is MANDATORY
  - Blocks submitted to Genomic Health: additional materials are requested to be submitted to the ECOG PCO-RL. Be aware that if the material forwarded to the PCO-RL by Genomic Health is inadequate for the required diagnostic studies, submission of additional pathology materials will be required

**NOTE:** If an institution will not allow block release, the institution MUST contact the ECOG PCO-RL (312-503-3384, Fax 312-503-3385) to request alternative submission requirements.

B. Frozen Tissue

Frozen tissue, if available, from patients consenting to banking. Submit on dry ice with serum and plasma samples with completed ECOG Pathology Material Submission Form (#638 v04.2) and related pathology/surgical reports.

**NOTE:** Available frozen tissue may remain at local sites until requested by the ECOG PCO. If materials will be retained until requested, indicate frozen tissue availability on the TAILORx Material Submission Form (#2539) and submit a completed TAILORx Virtual Frozen Tissue Bank Form (#2675) to the ECOG PCO.

C. Blood samples: submit from patients consenting to banking

Samples are drawn after registration/randomization prior to start of therapy. Collect Sunday through Thursdays only. Do not collect on the day before a holiday.

Peripheral blood (CPT and PAXgene tubes) are to be shipped the day of collection. Serum and plasma require shipment on dry ice (preferred) or frozen kool packs. Samples from multiple patients may be batch shipped together.

Samples are to be submitted with a completed TAILORx Material Submission Form (#2539).

Draw tubes in the order listed.

1. Serum: **SST red/grey marble top** vacutainer

- a. Draw peripheral blood into vacutainer.
- b. Allow blood to coagulate 20 minutes, then centrifuge at 1500 rpm for 15 minutes.
- c. Pipette the serum into cryotubes provided in the kit.
- d. Stored frozen below  $-70^{\circ}\text{C}$  until shipped

2. Peripheral Blood: **citrate CPT** (blue/black top)

- a. Draw 8mL peripheral blood into vacutainer and gently invert 8-10 times.
- b. Within 20 minutes of collection, centrifuge at 1500xg for 20 minutes.
- c. Resuspend cells within the tube by gently inverting 1 time.
- d. Ship at ambient the day of collection.

3. Plasma: **EDTA purple top tube**

- a. Draw peripheral blood into vacutainer and gently invert 8-10 times.
- b. Within 20 minutes of collection, centrifuge at 1500 xg for 15 minutes.
- c. Pipette the plasma into cryotubes provided in the kit.
- d. Store frozen below  $-70^{\circ}\text{C}$  until shipped

4. Peripheral blood: one **PAXgene DNA tube**

- a. Draw peripheral blood into vacutainer then gently invert tube 8-10 times.
- b. Ship at ambient the day of collection.

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[This space remains blank due to an Addendum #1 change]

### 10.2.3 Shipping Procedures

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- A. Overnight shipments (blood and frozen tissue) are to be shipped on Sunday through Thursday only. Do not ship the day before a holiday. On the day of the shipment complete and fax the Shipping Notification Form (Appendix VII) to the ECOG PCO-RL at (312) 503-3385.

For overnight shipments, use the airbill provided in the kit.

- i. Fixed, paraffin embedded primary tumor tissue samples are to be submitted at ambient temperature within two weeks following registration/randomization. If possible, ship with peripheral blood samples.
- ii. Peripheral blood (CPT and DNA PAXgene tubes) are to be shipped overnight at ambient temperature on the day of collection. In hot weather, please include a kool pack but package so the samples cannot freeze.
- iii. Serum, plasma, and frozen tissue are to be shipped overnight on dry ice. Frozen tissue **MUST** be shipped on dry ice. If frozen tissue will not be submitted and dry ice is unavailable, the frozen plasma and serum samples may be shipped with a frozen kool pack. Multiple patient samples may be batched and shipped monthly.

- B. Submit materials to:

ECOG Pathology Coordinating Office  
Robert H. Lurie Comprehensive Cancer Center  
of Northwestern University Medical School  
Olson Pavilion - Room 8421  
710 North Fairbanks Court  
Chicago, IL 60611  
Tel: (312) 503-3384  
FAX: (312) 503-3385

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Pathology reports and ECOG Pathology Material Submission Form (#638 v04.2) must be submitted with all pathology shipments. The TAILORx Material Submission Form (#2539) is to be submitted with the peripheral blood samples.

#### **NOTE: Forms Submission**

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Copies of submitted institutional pathology reports, ECOG Pathology Material Submission Form (#638 v04.2), and the TAILORx Material Submission Form (#2539) must be submitted to CTSU Data Operations, accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533) and CTSU Data Transmittal Form. The original hard copy of the institutional pathology report, ECOG Pathology Material Submission Form (#638 v04.2), and/or the TAILORx Material submission Form (#2539) must be shipped to the ECOG PCO-RL in the same package with the specimens. A copy of these documents should be retained for your files as well. **ECOG and non-ECOG sites alike must refer to the CTSU appendix (Appendix XI) for complete**



**CTSU data submission instructions. If an RDC site, please take special note of the RDC instructions.**

10.3 Processing of Specimen in ECOG Pathology Coordinating Office

10.3.1 Blood and Frozen Tissue Samples

The frozen tissue and blood will be processed using standard mechanisms and will be stored frozen below  $-70^{\circ}\text{C}$ .

10.3.2 Tumor Tissue

10.3.2.1 **Processing of blocks, quality control, and Creation of Tissue Microarrays (TMAs):**

A 4 micron section will be cut for H&E staining for validation of diagnosis, histopathology evaluation, and mapping for tissue microarray construction. Three replica tissue microarrays with 0.6mm cores will be constructed before sections are cut from the blocks based on mapping of initial one 4 micron section stained with H&E. However, if upon initial evaluation, invasive tumor component is less than 1 cm in the block, only one 0.6 mm core will be sampled. The blocks are stored indefinitely at ECOG PCO-RL until the time of use for correlative science studies.

If the institution demands the return of the block, after sampling for the tissue microarray cores, ten 10 micron sections will be cut and stored in microfuge tubes at  $-70^{\circ}\text{C}$  (macrodissection will have to be performed at this time if required) and additional 20 five micron sections will be cut and mounted on charged slides for storage before returning the blocks. Whole sections will be stored at  $4^{\circ}\text{C}$  in oxidation free storage boxes.

10.3.2.2 **Central testing of ER, PR, Her2/neu:**

In order to validate the performance of the *Oncotype* Dx assay, ER, PR, and HER2 centrally assayed by ECOG PCO-RL using tissue microarray sections. ER and PR will be assayed with FDA approved Dako PharmDx kits and scored using Allred Scoring system. HER2 amplification will be evaluated using Vysis PathVysion FISH assay.

10.3.2.3 **Extraction of total RNA:**

Immediately upon receipt of blocks, three 10 micron sections (six 10 micron sections if macrodissected) will be processed to extract total RNA for correlative science studies and stored at  $-70^{\circ}\text{C}$ .

10.3.2.4 **Web based pathology review:**

H&E slides will be scanned with ScanScope (or other web enabled pathology image archiving system) to post the images on the web to the pathology community to develop consensus review of histologic grade and mitotic activity index that will eventually be incorporated for Adjuvant! Evaluation.

10.4 Banking

Samples submitted and derivatives of the submitted materials will be retained at the ECOG Central Repository for possible use in future ECOG approved studies. Residual materials from any laboratory studies, including the *Oncotype* DX Assay by Genomic Health, will also be returned to the ECOG Central Repository for possible use in future ECOG 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 ECOG PCO-RL.

10.5 Lab Data Transfer Guidelines

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

10.6 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used will be submitted to the ECOG Coordinating Center upon request. Inventories will be submitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be submitted via secure FTP transmission. All other correspondence should be addressed to the attention of the Translational Science Team.

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## 11. Records to be Kept

Please refer to the PACCT-1 Forms Packet for the forms submission schedule and copies of all forms. The PACCT-1 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (<http://www.ecog.org>).

Data management activities for the PACCT-1 (TAILORx) study will be performed by the Cancer Trials Support Unit (CTSU). For this reason, investigators and study support staff involved in the collection and reporting of study data must be registered members of the CTSU. Please see the CTSU website ([www.ctsu.org](http://www.ctsu.org)) for details on registering as a CTSU member.

### Data Completion and Submission Guidelines

All ECOG and non-ECOG sites are required to submit patient data via the CTSU (with the exception of Expedited Adverse Event Reporting; please follow instructions in section 5.3 for submission of AE data).

Sites that are pre-selected by ECOG to participate in the CTSU RDC system should take special note of the RDC instructions in the CTSU appendix of this protocol (Appendix XI). The CTSU help desk is available to answer questions about data submission at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

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 Coordinating Center to CTEP by electronic means.

#### 11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG Coordinating Center prior to destroying any source documents.

## 12. Patient Consent and Peer Judgment

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

### 13. References

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Version Date: June 13, 2006**

**Appendix I**

**Informed Consent Template**

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this trial because you have breast cancer that is estrogen receptor and/or progesterone receptor positive that has not spread to the axillary lymph nodes. Although you have received surgical treatment for your cancer, there is a chance that you may have a future recurrence of the cancer in the breast, chest wall, or other parts of your body. Based on our current knowledge about the treatment of breast cancer, your doctor believes that you are a candidate for chemotherapy in addition to hormonal therapy in order to reduce your risk of recurrence, a recommendation that is consistent with established guidelines for the treatment of your breast cancer. Chemotherapy is usually recommended if the risk of recurrence is at least 10% despite hormonal therapy. Approximately 80-85% of patients with your stage of disease are expected to be alive without evidence of recurrent breast cancer at 10 years with hormonal therapy alone. Because we are unable to precisely identify who benefits from chemotherapy, many patients receive chemotherapy unnecessarily.

This study involves the use of a new diagnostic test called the *Oncotype DX* (Genomic Health, Inc, Redwood, CA). This test involves analysis of cancer that has already been taken during your surgery and has been stored in the pathology laboratory affiliated with the facility where you had the surgery. Storage of the cancer in the pathology laboratory after surgery is a routine procedure. The analysis requires that several small slices of the tumor section be taken. The sections will be analyzed in a specialized laboratory that can measure the levels of a specific panel of genes in the tumor. The laboratory that performs this test (Genomic Health laboratory) has been certified by federal and state agencies in the United States to perform the test (*Oncotype DX*). The results of the test are computed into a score (called Recurrence Score). The results from initial studies indicate that tumors may be classified into the following groups:

- **Secondary Study Group-1 (Recurrence Score  $\leq$  10)**: This group has a 5% or less chance of having a relapse of breast cancer in other organs at 10 years if treated with hormonal therapy alone. In this group, chemotherapy has not been proven to reduce the risk of recurrence. Approximately 25% of patients have a tumor with a Recurrence Score of  $\leq$  10.
- **Secondary Study Group-2 (Recurrence Score  $\geq$  26)**: This group has about a 30% chance of having a relapse of breast cancer in other organs at 10 years if treated with hormonal therapy. In this group, chemotherapy reduced the risk of recurrence by about 75%. In other words, adding chemotherapy increases the chance of being without disease recurrence at 10 years from about 70% to about 90% in this group. About 35% of patients have a tumor with a Recurrence Score of  $\geq$  26.

- **Primary Study Group (Recurrence Score 11-25):** This group has about a 10% chance of having a relapse of breast cancer in other organs at 10 years if treated with hormonal therapy. In this group, although the risk of recurrence is high enough to recommend consideration of chemotherapy, it is unknown whether chemotherapy reduces the risk of recurrence and whether the overall health benefits favor the use of chemotherapy. About 40% of patients have a tumor with a Recurrence Score of 11-25.

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### Why is this study being done?

This study is being done because chemotherapy would normally be recommended for the treatment of your disease to lower the risk of your breast cancer recurring. The purpose of this study is to determine whether patients who have a tumor with an *Oncotype* DX Recurrence Score of 11-25 benefit from chemotherapy, and to confirm that patients who have *Oncotype* DX Recurrence Score of  $\leq 10$  have a very low risk of recurrence with hormonal therapy alone (and do not need chemotherapy to reduce their risk of recurrence). Another objective is to create a tissue and blood specimen bank that includes specimens from all women who participate in this study, and to collect follow-up information regarding the health status of all women who participate in the study. This will allow researchers to evaluate new diagnostic tests in the future as they develop that may predict benefit or side effects from certain treatments.

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### How many people will take part in the study?

Approximately 10,000 women with breast cancer will take part in this study.

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### What will happen if I take part in this research study?

If you agree to participate in this study, the sequence of events is outlined in the attached study plan, and described below.

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If you have not had the *Oncotype* DX test performed: In the "PREREGISTRATION PHASE", a tumor specimen will be sent to Genomic Health for the *Oncotype* DX test. It will take about 10 –14 days to obtain the results of the test back from Genomic Health. The results will be sent to your study doctor. Your study doctor will fax the report to the ECOG Coordinating Center. One to three days after the report has been sent to the ECOG Coordinating Center, you will proceed to the "REGISTRATION PHASE" and specific treatments will be recommended:

- **Secondary Study Group-1 (Recurrence Score  $\leq 10$ ):** You will receive hormonal therapy, but no chemotherapy (Arm A).
- **Secondary Study Group-2 (Recurrence Score  $\geq 26$ ):** You will receive chemotherapy plus hormonal therapy (Arm D).
- **Primary Study Group (Recurrence Score 11-25):** You will be randomly assigned by chance (like a coin flip) to treatment with either:
  - hormonal therapy alone (Arm B)
  - chemotherapy plus hormonal therapy (Arm C)



If you have already had the *Oncotype* DX test performed: You may be eligible for this trial if the Recurrence Score was 11-25. If this is the case, your study doctor will fax a copy of the Recurrence Score report to the ECOG Coordinating Center and then you will be enrolled on the "REGISTRATION PHASE". You will be randomly assigned by chance (like a coin flip) to receive either hormonal therapy, or chemotherapy followed by hormonal therapy. Also, a tumor specimen from a previous biopsy or surgery will be sent to central laboratories to be used for research studies.

Genomic Health will forward any left over tissue or other samples to the ECOG Pathology Coordinating Office to be used for research studies. Your study doctors may also forward tumor tissue to the ECOG Pathology Coordinating Office for research studies. The research studies performed using your tissue will be done to learn more about breast cancer. In addition, you will be asked to provide samples of blood and to allow left over tumor tissue to be stored in the ECOG Pathology Coordinating Office for possible use in future research. Your participation in this study will not be affected by your decision to donate or not donate the samples for future research.

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If you would like to know the results of the *Oncotype* DX test, speak to your study doctor.

### **Before you begin the study ...**

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

- History and physical examination
- Blood tests (including complete blood count and liver and kidney function tests)
- Mammogram

### **During the study ...**

A sample of your tumor will be sent to Genomic Health for the *Oncotype* DX test. You will be asked to donate a sample of your tumor and blood for banking and future research. Treatment will be assigned based upon the score of the *Oncotype* DX test, as described above under **What will happen if I take part in this research study?**

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## **During and after the treatment...**

When chemotherapy is given, it is usually administered over 3-6 months. Hormonal therapy is usually given for five years or longer, and begins after the completion of chemotherapy (if given). You will need the following tests and procedures during and after treatment in order to determine if there is a relapse of the breast cancer, or if another breast cancer develops. These procedures/tests are part of regular cancer care, and include the following:

- *History and physical exam every 3-6 months for the first five years, then yearly after year five*
- *Mammogram once yearly*

There are several different types of chemotherapy and hormonal therapy, which your study doctor will discuss with you. Chemotherapy usually consists of two or more drugs given intravenously for 4-8 treatments, and works by killing residual microscopic tumor cells. Hormonal therapy usually consists of an oral medication taken once daily, which may include either tamoxifen or drugs called aromatase inhibitors (e.g., anastrozole [Arimidex], letrozole [Femara], and exemestane [Aromasin]), all of which work by blocking the effects of the female hormone estrogen on residual microscopic breast cancer cells. These drugs are usually taken for at least five years, or longer. In addition to this trial, your study doctor may offer you participation in another clinical trial that is testing different types of chemotherapy and/or hormonal therapy and/or radiation therapy. Patients who have had a lumpectomy will also be treated with radiotherapy.

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If you have been randomized or assigned to hormonal therapy alone, it will begin within 14 days of registration. If you have been randomized or assigned to chemotherapy, it will also begin within 14 days after registration; after chemotherapy is completed, hormonal therapy will begin within 4 weeks after the last dose of chemotherapy. Treatment with hormonal therapy will be given at the same time as radiation therapy. However, treatment with radiation therapy will be given only after chemotherapy has been completed.

## **Laboratory Research Studies**

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Some of your tissue from the breast cancer will be sent to the ECOG Pathology Coordinating Office. This tissue will be used for research studies to learn more about breast cancer; the results of these tests will not be sent to your study doctor and will not be placed in your medical record. They are for research purposes only.

Genomic Health will also send to the ECOG Coordinating Center detailed results outlining how they determined your Recurrence Score and additional information describing the tissue samples sent to them. This information will NOT be sent to you or your study doctor or your insurance company. It will not be placed in your medical record. It will only be used for research to help better understand your disease and how to treat it.

Blood samples will also be requested before you begin treatment. These samples will only be collected if you agree to allow the samples to be kept by ECOG for future research. If you do not agree, it will not affect your medical treatment or your participation in this study.

### **How long will I be in the study?**

You will be followed by your study doctors for up to 20 years after you enroll on this study. Your study doctor will monitor you periodically as described above to monitor you for recurrence of the cancer, which is part of routine medical care.

### **Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the chemotherapy and/or hormonal therapy can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

### **What side effects or risks can I expect from being in the study?**

Commonly used chemotherapy regimens include doxorubicin (Adriamycin) and cyclophosphamide (called AC), AC followed by paclitaxel (called ACT), cyclophosphamide, methotrexate, and 5-fluorouracil (called CMF), cyclophosphamide, epirubicin, and 5-fluorouracil (FEC), and other regimens. The choice of the chemotherapy regimen used will be up to your study doctor and you. In addition to chemotherapy, treatment also always consists of at least 5 years of hormonal therapy, which usually begins within about 4 weeks after the completion of chemotherapy. Hormonal therapy consists of either tamoxifen or aromatase inhibitors. Several aromatase inhibitors are currently available and commonly used, including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). The choice of hormonal therapy will be left to your study doctor and you. If you have had a lumpectomy, radiation to the breast is also usually recommended after the completion of chemotherapy, or after you have adequately healed from the surgery if you don't receive chemotherapy. The decision regarding whether to administer radiation, and the type of radiation, will be left to your study doctor and you.

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

Risks and side effects related to the chemotherapy are summarized below. Other side effects may be expected depending upon with the specific regimen recommended your treating physician. You should discuss the side effect profile of your treatment regimen with your study doctor. **You should talk to your study doctor about any side effects that you have while taking part in the study.** Some of the most common side effects of chemotherapy include:

**Likely:**

- Nausea and/or vomiting
- Hair loss
- Fatigue
- Anemia
- Lowering of the white blood cell count
- If not yet menopausal, premature menopause and sterility

**Less Likely:**

- Infection
- Mouth sores
- Numbness/tingling in the hands/feet (for paclitaxel)
- Allergic reactions
- Irritation of the bladder

**Rare but serious** (occur only with some types of chemotherapy that include doxorubicin or epirubicin):

- Leukemia
- Heart failure

Risks and side effects related to the hormone therapy are listed below. Some side effects occur with tamoxifen, some with aromatase inhibitors, and some with both drugs.

**Likely:**

- Hot flashes
- Osteoporosis – bone loss (aromatase inhibitors)
- Vaginal discharge and/or dryness

**Less Likely:**

- Bone fractures from osteoporosis (aromatase inhibitors)
- Joint pains (aromatase inhibitors)
- Shortness of breath (aromatase inhibitors)
- Diarrhea (aromatase inhibitors)
- Painful intercourse

**Rare but serious:**

- Blood clots (tamoxifen)
- Uterine cancer (tamoxifen)

Reproductive risks: You should not become pregnant while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. For more information about risks and side effects, ask your study doctor.

### **Are there benefits to taking part in the study?**

Rev. 6/06 Taking part in this study may or may not make your health better. We expect that the information  
Rev. 6/06 from this study will help doctors learn more about how to better select patients for treatment with  
chemotherapy. This information could help future cancer patients.

### ***What other choices do I have if I do not take part in this study?***

Your other choices may include:

- Getting treatment for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Having the *Oncotype DX* test performed without participating in the study

Talk to your study doctor about your choices before you decide if you will take part in this study. If you take part in this study, you may also take part in other studies sponsored by the National Cancer Institute, as long as the treatment in those studies is consistent with the treatment assignment in this study (chemotherapy plus hormonal therapy vs. hormonal therapy alone).

### **Will my medical information be kept private?**

The Eastern Cooperative Oncology Group (ECOG) is conducting this study. ECOG is a cancer group that conducts studies for the National Cancer Institute. Your study doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. Note, however, that if an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

Finally, you should understand that your study doctor and ECOG are not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others and the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group (ECOG)
- North Central Cancer Treatment Group (NCCTG)
- Southwest Oncology Group (SWOG)
- Cancer and Leukemia Group B (CALGB)
- American College of Surgeons Oncology Group (ACOSOG)
- National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- The Breast Cancer Intergroup of North America (TBCI)

- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Central Laboratories
- Genomic Health, Inc.
- Cancer Trials Support Unit (CTSUS). The CTSUS is a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

### **How could the records be used in ways that might be harmful to me?**

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). Sometimes tissue or blood is used to better understand inherited genetic defects (genetic changes that are passed on in families) that predispose some people to develop cancer. This is often called 'genetic testing'. The results of genetic research may not apply only to you, but to your family members. For diseases caused by gene changes, the information in your health record could also be used against you or your family members. For example, insurance companies may also deny a patient insurance or employers may not hire someone if they have had a genetic test which indicates that they may be at greater risk for developing certain illness (such as cancer). If your tissue is used for genetic research, it will be done in such a way that the results cannot be related to you as an individual, and will not appear in your health records.

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### **How am I protected?**

The Eastern Cooperative Oncology Group and other federally funded research groups participating in this study will make sure that information about you is kept private. These groups will take careful steps to prevent misuse of records. Your name, address, phone number and other identifying information will be taken off anything associated with your tissue before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person, which will help to protect your privacy.

### **What are the costs of taking part in this study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The *Oncotype* DX test that is being used in this trial is commercially available and the Genomic Health laboratory is certified by federal and state agencies (CLIA) in the United States to perform this test. Your insurance company will be billed for the cost of the test. Representatives from Genomic Health are available to answer any questions that you or your insurance company may have about the cost of the test or reimbursement for the test (1-866-662-6897).

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Rev. 6/06 If your insurance company denies payment of the test, Genomic Health will appeal this denial. It is likely that you will be receiving statements, or Explanation of Benefits forms (EOB), from your insurer. These are not bills.

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

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

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

**For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage> . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.**

**Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.**

### **What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### **What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

### **Who can answer my questions about the study?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ *[name(s)]* at \_\_\_\_\_ *[telephone number]*.

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

\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[\*Only applies to sites using the CIRB.]*



## ***Consent Form for Use of Tissue and/or Blood for Research***

### ***About Using Tissue and/or Blood for Research***

You have had a biopsy (or surgery) to diagnose your breast cancer. A sample of left over cancer tissue and/or blood is routinely stored in the pathology laboratory of the hospital where you had your biopsy, which is part of standard medical practice. If you participate in this study, a sample of your breast cancer tissue will be sent to laboratories for research studies.

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We would like to keep any tissue that is left over, and if available, extra tissue from the pathology laboratory of the hospital to be sent and stored for possible use in future research. You will also be asked to donate 4 tubes of blood (about 2-3 tablespoons) before you start any treatment. The tissue and/or blood samples will be stored in the Eastern Cooperative Oncology Group (“ECOG”) Pathology Coordinating Office.

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If you agree, this tissue and/or blood will be kept and may be used in research to learn more about cancer and other diseases.

Your tissue and/or blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue and/or blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and/or blood will not be given to you or your study doctor. These reports will not be put in your health record. The research will not have an effect on your care.

### ***Things to Think About***

The choice to let us keep the left over tissue and/or blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and/or blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and/or blood. Then any tissue and/or blood that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Eastern Cooperative Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and/or blood is used for genetic research (about diseases that are passed on in families). Even if your tissue and/or blood is used for this kind of research, the results will not be put in your health records.

Your tissue and/or blood will be used only for research and will not be sold. The research done with your tissue and/or blood may help to develop new products in the future.

### ***Benefits***

The benefits of research using tissue and/or blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

### ***Risks***

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

### ***Making Your Choice***

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your study doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in future research to learn about, prevent, or treat cancer.

Yes                  No

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2. I give permission for samples of my blood to be drawn and sent to ECOG to be kept for use in future research to learn about, prevent, or treat cancer.

Yes                  No

Rev. 6/06

3. I give permission for samples of my tissue and blood (if submitted) to be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes                  No

Rev. 6/06

4. Someone may contact me in the future to ask me to take part in more research.

Yes                  No

Rev. 6/06

### **Where can I get more information?**

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

**Signature**

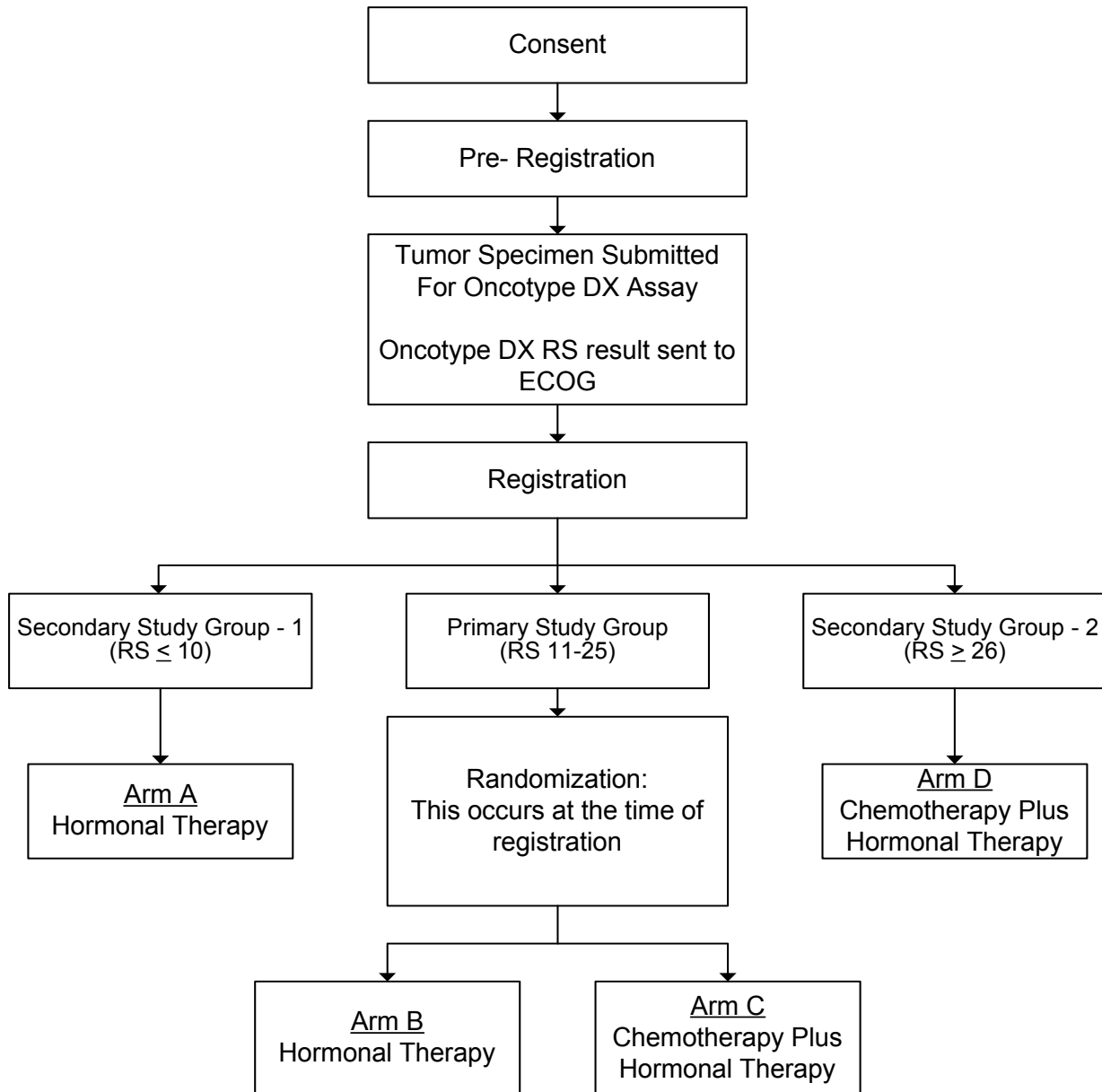
I have been given a copy of all 13 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_

### Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



Patients who have had breast conservation surgery will also be treated with radiotherapy

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Appendix II**

**Chemotherapy Regimens**

Regimen Code	Regimen Name	Regimen Dose/Schedule	Regimen Schedule	No. of Cycles
1	Oral CMF	C 100 mg/m <sup>2</sup> /day PO x 14 days M 40 mg/m <sup>2</sup> IV days 1, 8 F 600 mg/m <sup>2</sup> IV days 1, 8	Every 4 weeks	6
2	IV CMF	C 600 mg/m <sup>2</sup> IV M 40 mg/m <sup>2</sup> IV F 600 mg/m <sup>2</sup> IV	Every 3 weeks	6-8
3	Standard AC	A 60 mg/m <sup>2</sup> IV C 600 mg/m <sup>2</sup> IV	Every 3 weeks	4
4	Dose dense AC	A 60 mg/m <sup>2</sup> IV C 600 mg/m <sup>2</sup> IV Plus G-CSF	Every 2 weeks	4
5	Standard AC - T	A 60 mg/m <sup>2</sup> and C 600 mg/m <sup>2</sup> IV every 3 weeks x 4 cycles ⇒ T 175 mg/m <sup>2</sup> every 3 weeks x 4 cycles	Every 3 weeks	8
6	Dose dense AC - T	A 60 mg/m <sup>2</sup> and C 600 mg/m <sup>2</sup> IV plus G-CSF every 2 weeks x 4 cycles ⇒ T 175 mg/m <sup>2</sup> plus G-CSF every 2 weeks x 4 cycles	Every 2 weeks	8
7	FEC	F – 500 mg/m <sup>2</sup> IV E – 50 mg/m <sup>2</sup> IV C – 500 mg/m <sup>2</sup> IV	Every 3 weeks	6
8	TAC	T - 75 mg/m <sup>2</sup> A - 50 mg/m <sup>2</sup> C - 500 mg/m <sup>2</sup> <b>NOTE:</b> TAC should be used only in women <= 70 years of age	Every 3 weeks	3
9	TC	T - 75 mg/m <sup>2</sup> C - 600 mg/m <sup>2</sup>	Every 3 weeks	4
10	Other protocol-specified regimens	Participating in other CTSU trials including chemotherapy	As specified in protocol	As specified in protocol
11	Other regimens not protocol-specified	<b>Contact study chair:</b> Not participating in other CTSU trials; treating physician elects to use regimen other than regimens 1-9; contact study chair, Joseph Sparano, M.D.		
Abbreviations: C – cyclophosphamide; T - paclitaxel (Taxol) in AC-T regimens (regimen codes 5 or 6), or docetaxel (Taxotere) in TC and TAC regimens (regimen codes 8 and 9) A – doxorubicin (Adriamycin); E - epirubicin; G-CSF – granulocyte colony stimulating factor (or pegfilgrastim); M – methotrexate; IV - intravenous F – 5-fluorouracil;				

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix III**

**Hormonal Therapy Regimens**

**Years 1- 5**

<b>Regimen Code</b>	<b>Menopausal Status</b>	<b>Regimen</b>
A	Pre, Peri, or Post	Tamoxifen 20 mg PO daily
B	Post	Anastrozole (Arimidex) 1 mg PO daily
C	Post	Letrozole (Femara) 2.5 mg PO daily
D	Post	Exemestane (Aromasin) 25 mg PO daily
E	Pre or Peri	Participating in another CTSU study; as specified in treatment protocol
F	Post	Participating in another CTSU study; as specified in treatment protocol

Note: Patients who are intolerant of one hormonal regimen may switch to another regimen.

**Years 6-10**

<b>Regimen Code</b>	<b>Menopausal Status at year 6</b>	<b>Treatment during years 1-5</b>	<b>Treatment years 6-10</b>
1	Pre or Peri	Tamoxifen 20 mg PO daily	No further treatment
2	Post	Tamoxifen 20 mg/ PO daily	Any aromatase inhibitor
3	Post	Any aromatase inhibitor	No further treatment
4	Post	Any aromatase inhibitor	May continue aromatase inhibitor
5	Pre or Peri	Any treatment	Participating in CTSU study; as specified in protocol
6	Post	Any treatment	Participating in CTSU study; as specified in protocol

**Definition of Menopausal Status:**

Menopausal will be defined according to the following criteria:

Post-menopausal:

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4 IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

Pre- or peri-menopausal:

Not meeting definition for postmenopausal outlined above

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix IV  
Submission of Biological Materials and Related Documents**

Biological Materials	Report/Forms <sup>5</sup>	Requirement	Patient Status	Ship to:
Rev. 6/06	Onco <sup>1</sup> type DX Patient Report (redacted) <sup>2</sup>	MANDATORY	All Patients: Pre-registration	ECOG Coordinating Center, ATTN: Pre-Registration/PACCT-1 FAX: 617-582-8578
Rev. 6/06	Onco <sup>1</sup> type DX Requisition Form Pathology/Surgical Report ECOG Pathology Material Submission Form (#638 v04.2)	MANDATORY	Onco <sup>1</sup> type DX RS score not previously performed	Genomic Health (Section 10.1)
Rev. 6/06	Onco <sup>1</sup> type DX Requisition Form(copy) Pathology/Surgical Report ECOG Pathology Material Submission Form (#638 v04.2)	MANDATORY	Onco <sup>1</sup> type DX RS score NOT previously performed	
Rev. 6/06	Pathology/Surgical Report ECOG Pathology Material Submission Form (#638 v04.2)	MANDATORY	Onco <sup>1</sup> type DX RS score previously performed	ECOG PCO-RL (Section 10.2)
Rev. 6/06	Pathology/Surgical Report ECOG Pathology Material Submission Form (#638 v04.2)	MANDATORY	Onco <sup>1</sup> type DX RS score previously performed (RS score 11-25)	
Rev. 6/06	Frozen Tumor Tissue (if available) <sup>4, 6</sup>	Patient consented to banking		
Rev. 6/06	Plasma, purple top <sup>4</sup>			
Rev. 6/06	Serum, SST <sup>4</sup>			
Rev. 6/06	Peripheral blood, citrate CPT <sup>4</sup>			
Rev. 6/06	Peripheral blood PAXgene DNA <sup>4</sup>			

1. **MANDATORY:** One tumor tissue block must be submitted to Genomic Health (see Section 10.1 and Appendix IV). Requisition forms for tissue submission and Onco<sup>1</sup>type DX Recurrence Score assessments must be ordered within one day after pre-registration (call Genomic Health, 866-662-6897). Samples are to be submitted within 3 days of pre-registration. ECOG Pathology Material Submission Form (#638 v04.2) must be completed and copies distributed to both Genomic Health (with the samples and requisition form) and the ECOG PCO-RL (with the pathology report).

**NOTE:** If additional material is available, at least one tumor block is to be forwarded to the ECOG PCO-RL for correlative studies and banking.

2. Indicate on the report, the protocol number (PACCT-1) and ECOG patient **pre-registration** sequence number. Submit after pre-registration (617) 582-8578, ATTN: Pre-Registration/PACCT-1. Institution may register/randomize patient (Section 4.2) 24 to 72 hours after submission of the report to ECOG.

3. Submit within two weeks following registration/randomization. Required if Onco<sup>1</sup>type DX Recurrence Score previously determined, or additional material from patients with materials submitted to Genomic Health.

4. From patients who have given written consent to allow banking of samples for possible future use. Collection and shipping kits ordered by Faxing *PACCT-1 Collection and Shipping Kit Order Form* (Appendix VI) to ZymoGen International at 800-815-4675.

5. Refer to Appendix XI for descriptions of reports or forms to be submitted to CTSU.

6. Indicate frozen tissue availability on the TAILORx Material Submission Form (#2539). If frozen tissue will be retained at the local site, submit a completed TAILORx Virtual Frozen Tissue Bank Form (#2675) to the ECOG PCO.



**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
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**Appendix V**

**Pathology Submission Guidelines**

The following items are included in Appendix V:

1. Checklist for submissions.
2. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
3. List of Required Materials for PACCT-1
4. Instructional memo to submitting pathologists
5. ECOG Pathology Submission Form (#638 v04.2)
6. Copy of Genomic Health *Oncotype* DX Requisition Form

Checklist for Submissions:

A. *Oncotype* DX Recurrence Score NOT previously performed

Submit to GENOMIC HEALTH:

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

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

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

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

OR

Six (6) 10µm sections, in two microcentrifuge tubes from the kit (three sections each) and H&E (4 or 5 µm) cut after the 10µm sections are cut. Label each with barcode.

\_\_\_\_\_ Pathology Report

\_\_\_\_\_ Completed ECOG Pathology Material Submission Form (#638 v04.2)

\_\_\_\_\_ Completed *Oncotype* DX Requisition Form

(DO NOT USE THE REQUISITION FORM IN THIS APPENDIX, use the form provided in the kit)

Instructions for completing the form are on the back of the form. The form is to be completed as instructed except for the following fields:

- For the “PROCESSING CODE” **enter the protocol number and the ECOG patient case number** assigned at pre-registration (e.g. PACCT-1-10001).
- Method of payment (section III): Complete with patient’s insurance information.
- ADDITIONAL PHYSICIAN (section V): Enter the contact information of the Institutional CRA coordinating the PACCT-1 study.
- COMMENT, section VII (REQUIRED): Again, enter the protocol number “PACCT-1” and the patient’s ECOG pre-registration case number.

“**BLOCK RETURN**” information (section VI). After testing, all residual block material will be forwarded by Genomic Health to the ECOG Central Tissue Repository at ECOG PCO-RL.

- BLOCK RETURN CONTACT = ECOG Pathology Coordinating Office
- BLOCK RETURN ADDRESS = Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Olson Pavilion- Room 8421, 710 North Fairbanks Court
- CITY = Chicago, STATE = IL, ZIP = 60611
- BLOCK RETURN PHONE NUMBER = (312) 503-3384

Submit to the ECOG PCO-RL:

Rev. 6/06 **NOTE:** Frozen tumor tissue and baseline whole blood, serum, and plasma samples are requested on all registered/randomized patients consenting to banking. See Section 10.2 for kit requests, sample preparation, and shipping guidelines.

\_\_\_\_ Additional Primary Tissue Block, if available

\_\_\_\_ Pathology report, including immunological studies if performed.

\_\_\_\_ Copy of completed ECOG Pathology Material Submission Form (#638 v04.2)

\_\_\_\_ Copy of *Oncotype* DX Requisition Form

Submit to ECOG Coordinating Center:

Rev. 6/06 \_\_\_\_\_ *Oncotype* DX Patient Report (redacted), ATTN: Pre-registration/PACCT-1 (FAX: 617-582-8578)

**NOTE:** Institution may register/randomize patient 24 hours (72 hours if weekend or holiday) after submission of the report to ECOG).

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B. *Oncotype* DX Recurrence Score (score 11-25) performed prior to pre-registration.

Rev. 6/06 **NOTE:** Frozen tumor tissue and baseline whole blood, serum, and plasma samples are requested on all registered/randomized patients consenting to banking. See Section 10.2 for kit requests, sample preparation, and shipping guidelines.

Submit to the ECOG PCO-RL within two weeks following randomization:

\_\_\_\_ Primary Tissue Block

\_\_\_\_ Pathology report, including immunological studies if performed.

\_\_\_\_ Completed ECOG Pathology Material Submission Form (#638 v04.2)

Rev. 6/06 Submit to ECOG Coordinating Center, ATTN: Pre-registration/PACCT-1 (FAX: 617-582-8578) following pre-registration:

\_\_\_\_\_ *Oncotype* DX Patient Report (redacted).

NOTE: Registration/randomization may proceed 24 hours and up to 72 hours (if weekend or holiday) after submission of the report to ECOG.

### Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG Pathology Material Submission Form (# 638 v04.2)

These are also requested for samples submitted to Genomic Health on PACCT-1

#### Instructions:

1. Place the Patient ID label provided by the ECOG Coordinating Center in Part A of the ECOG Pathology Material Submission Form.

If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

- Patient's name (last, first)
- Protocol number
- Protocol case number (the patient's ECOG sequence number)
- Patient's hospital number
- Institution
- Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material and the ECOG Pathology Material Submission Form, to the appropriate pathologist.

3. The pathologist should return to you the required pathologic samples and surgical pathology reports, along with the completed ECOG Pathology Material Submission Form (# 638) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.

4. Keep a copy of the ECOG Pathology Material Submission Form (# 638) for your records (the original should be sent to the PCO-RL).

5. Double check that ALL required forms, reports, and pathology samples are included in the package to send to the Pathology Coordinating Office (see appropriate List of Required Material).

**Pathology specimens submitted for a patient WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.**

6. Tissue to be submitted for the determination of Oncotype Recurrence Score is to be shipped as outlined in section 10.1 and Appendix IV.

Customer Service  
Genomic Health, Inc.  
301 Penobscot Drive  
Redwood Cit, CA 94063

To order specimen kits and requisition forms, contact Genomic Health Customer Service (866-662-6897).

7. Mail all pathology reports, and pathology materials for additional laboratory studies and banking to:

ECOG Pathology Coordinating Office  
Robert H. Lurie Comprehensive Cancer Center, Northwestern University  
Olson Pavilion - Room 8421  
710 North Fairbanks Court  
Chicago, IL 60611

If you have any questions concerning the above instructions, or if you anticipate any problems in meeting the pathology material submission deadline of 72 hours for the Recurrence Score assessment, or within two weeks following registration/randomization for banking samples, contact the Pathology Coordinator at the ECOG Pathology Coordinating Office at Tel: (312) 503-3384 or Fax: (312) 503-3385.

8. Copies of all submitted forms and reports must be submitted to CTSU as indicated in Appendix XI.

## LIST OF REQUESTED MATERIAL

Program for the Assessment of Clinical Cancer Tests (PACCT-1): *Trial Assigning Individualized Options for Treatment: The TAILORx Trial*

### **Pre-Treatment**

MANDATORY: For the determination Oncotype DX Recurrence Score and laboratory studies defined in Section 10.3

To Genomic Health: (All items must be labeled with barcode from Oncotype DX Specimen Kit).

1. Oncotype DX Requisition Form from the (see Appendix IV for instructions)
2. ECOG Pathology Material Submission Form (# 638) – Parts A & B completed
3. Pathology Report
4. Required path materials

- Primary tumor tissue block:

**NOTE:** If block is not available, submit the following sections:

- Six (6) 10 µm sections, in two microcentrifuge tubes from the kit (three sections each)
- H&E (4 or 5 µm) cut after the 10µm sections are cut

To ECOG Pathology Coordinating Office:

1. ECOG Pathology Material Submission Form (# 638) – Parts A & B completed
2. Institutional pathology report (**must be included with EVERY pathology submission, including submissions to Genomic Health**).
3. Copy of Oncotype DX Requisition Form (if material sent to Genomic Health).
4. Required pathology material (from all eligible patients with previously determined RS scores and, if available, from patients with samples submitted to Genomic Health for analysis)

- Primary tumor tissue block

**NOTE:** If an institution will not allow block release, the institution MUST contact the ECOG PCO-RL (312-503-3384, Fax 312-503-3385) to request alternative submission requirements.

- Frozen tumor tissue, if available, from consenting patients

**NOTE:** Tissue may be retained at the local site until requested by the ECOG PCO. If retained by site, indicate frozen tissue availability on the TAILORx Material Submission Form (#2539) and submit a completed TAILORx Virtual Frozen Tissue Bank Form (#2675) to the ECOG PCO.

**NOTE:** Blocks from patients consenting to banking will be available for purposes of individual patient management on specific written request directed to the ECOG PCO-RL. Be aware that blocks may be depleted by use for laboratory studies and therefore, may be unavailable for return.



# Eastern Cooperative Oncology Group

## Coordinating Center

Frontier Science  
900 Commonwealth Avenue • Boston, MA 02215  
(617) 632-3610 • Fax: (617) 632-2990  
Randomization: (617) 632-2022

Jean MacDonald, Director of Research Operations  
Mary Steele, Director of Group Administration

Group Chair: Robert L. Comis, M.D.  
Group Statistician: Robert Gray, Ph.D.

Revised 6/06, Addendum #1

## MEMORANDUM

**TO:**

(Submitting Pathologist)

**FROM:**

Stanley Hamilton, M.D.  
Chair  
ECOG Laboratory Science and Pathology Committee

**DATE:**

**SUBJECT:**

Submission of Pathology Materials for Program for the Assessment of Clinical Cancer Tests (PACCT-1): *Trial Assigning Individualized Options for Treatment: The TAILORx Trial*

Rev. 6/06

The patient named on the attached ECOG Pathology Material Submission Form (# 638) has been entered onto an ECOG protocol by \_\_\_\_\_ (ECOG Investigator). This protocol requires the submission of pathology materials for determination of Oncotype DX Recurrence Score (RS), pathology review, laboratory studies, and banking.

Rev. 6/06

For submission of tissue to Genomic Health for RS assessment, complete PART B of the ECOG Pathology Material Submission Form provided in this appendix, and the Oncotype DX Requisition Form provided in the Oncotype DX Specimen Kit. On the requisition form, the PROCESSING CODE must be completed with the protocol number PACCT-1, and the patient's ECOG case number. Complete the BLOCK RETURN section with the ECOG PCO information as indicated on page 2 of Appendix V. All residual material will be forwarded to the ECOG Pathology Coordinating Office –Research Laboratory (PCO-RL) after testing.

Copies of the completed forms and pathology report are to be forwarded to the ECOG PCO-RL.

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.

Rev. 6/06

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

Questions may be directed to Genomic Health Customer Service (650-556-9300) or the ECOG PCO-RL (Tel: 312-503-3384 or FAX: 312-503-3385).

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

Thank you.

Instructions: **This form is a required part of pathology submission.** Please complete and submit along with all pathology material and corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

**ECOG PCO-RL IS FULLY-COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS**

Tel. 312-503-3384 Fax 312-503-3385

**PART A: To Be Completed By Data Manager/CRA**

Date sample sent to ECOG \_\_\_\_/\_\_\_\_/\_\_\_\_ (M,D,Y)  
 Data Manager \_\_\_\_\_  
 Address \_\_\_\_\_  
 \_\_\_\_\_  
 Telephone No. ( ) \_\_\_\_\_  
 Fax No. ( ) \_\_\_\_\_  
 Email address \_\_\_\_\_

**DO NOT USE INITIALS – Submit Patient’s FULL Name**  
 (The Patient has authorized the use of PHI.)

Patient’s Name:  
 Last \_\_\_\_\_ First \_\_\_\_\_  
 ECOG Prot. No. \_\_\_\_\_ ECOG Patient Seq. No. \_\_\_\_\_  
 Participating Group \_\_\_\_\_ Participating Group  
 Prot. No. \_\_\_\_\_ Patient ID No. \_\_\_\_\_  
 Group \_\_\_\_\_ Institution \_\_\_\_\_ PI \_\_\_\_\_  
 Step No. \_\_\_\_\_ Affiliate \_\_\_\_\_  
 ECOG Parent Prot. No. \_\_\_\_\_ Seq. No. \_\_\_\_\_

**PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST**

							PCO-RL Use Only
Complete for Slides/Vials	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Slides/Vials	Specimen ID Numbers	Type of Stain	PCO ID Numbers
			/ /				
		/ /					
Complete for Blocks/Punch	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Blocks/Punch	Specimen ID Numbers	Fixative	PCO ID Numbers
		/ /					
		/ /					

**\*Status:** Please identify the clinical status of the sample. List **all** that apply:

- Original diagnostic material
- AML/MDS diagnosis
- Pre-protocol treatment biopsy/tissue
- Post-protocol treatment biopsy/tissue
- Post-surgery biopsy/tissue
- Relapse/recurrence
- Remission/response
- Other, specify: \_\_\_\_\_

Submitting Pathologist \_\_\_\_\_  
 Telephone No. ( ) \_\_\_\_\_  
 Address \_\_\_\_\_  
 \_\_\_\_\_

**Did the patient consent to participate in the storage of samples for future research?** Yes No

**MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)**

Does the submitting institution’s policy require the return of any submitted material (blocks, H&E slides, etc.)? ..... Yes No

If so, please indicate which materials must be returned \_\_\_\_\_

All materials will be returned to the **submitting pathologist** unless an alternate address is indicated here \_\_\_\_\_

**If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission. Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.**

Federal/State Regulations \_\_\_\_\_ Hospital/Institutional Policy \_\_\_\_\_ Insufficient Tissue \_\_\_\_\_ Other \_\_\_\_\_ (Specify) \_\_\_\_\_

Pathologist of Investigator’s Signature \_\_\_\_\_

(PCO-RL Use Only)  
 PV \_\_\_\_\_

**PART C: ECOG PATHOLOGY COORDINATING OFFICE USE ONLY**

Date Sample Received at PCO \_\_\_\_/\_\_\_\_/\_\_\_\_ Date Sent to Reviewer \_\_\_\_/\_\_\_\_/\_\_\_\_ Date Sent to PI/Central Lab \_\_\_\_/\_\_\_\_/\_\_\_\_

Site Compliance % \_\_\_\_\_ Name of Reviewer \_\_\_\_\_ PI/Central Lab \_\_\_\_\_

PCO Comments: \_\_\_\_\_ Staff Init. \_\_\_\_\_

Investigator: *Keep a copy for your files and submit original form to the destination specified in protocol.* 2/05



Genomic Health, Inc.  
301 Penobscot Drive  
Redwood City, CA 94063  
Tel (866) ONCOTYPE  
www.oncotypedx.com

DO NOT MIX LABELS BETWEEN PATIENTS.

BARCODE	BARCODE
BARCODE	BARCODE

BARCODE

XXXXX

REQUISITION FORM

First submission  Resubmission - Associated Requisition \_\_\_\_\_ Processing Code (if applicable) **PACCT1/#####**

I. ACCOUNT INFORMATION II. PATIENT INFORMATION

**ENTER PROTOCOL# AND CASE:  
PACCT1/#####**

NAME OF PATIENT: Last name First name MI  
DOB Sex:  Female  Male  
ADDRESS  
CITY STATE ZIP  
PHONE #  
MEDICAL RECORD/PATIENT # SSN

III. BILLING INFORMATION

SUBMITTING DIAGNOSIS  
ICD-9 CODE  
METHOD OF PAYMENT  
 BILL PRIVATE INSURANCE  
 BILL MEDICARE  
 BILL MEDICAID  
 BILL ACCOUNT *No further billing information required.*  
 PATIENT SELF-PAY: *Check (US only), certified funds, money order, or credit card information required for processing. No further billing information required.*  
Name on Credit Card  
CC#  
Expiration Date \_\_\_\_/\_\_\_\_/\_\_\_\_

**MEDICARE ONLY:**  
 Hospital Inpatient  Hospital Outpatient  Non-Hospital Patient  
 SIGNED ABN ATTACHED IF REQUIRED  
 COPY OF FRONT AND BACK OF PATIENT INSURANCE CARD ATTACHED *if not, fill out all information below and to right.*  
MEMBER ID # GROUP #  
RELATIONSHIP TO INSURED:  
 Self  Spouse  Dependent  Other \_\_\_\_\_  
NAME OF INSURED: Last name First name MI  
DOB Sex:  Female  Male

PRIMARY INSURANCE NAME  
PRIMARY INSURANCE ADDRESS  
CITY  
STATE ZIP  
PRIMARY INSURANCE PHONE #  
REFERRAL/AUTHORIZATION #  
SECONDARY INSURANCE:  YES  NO  
*If you would like us to bill secondary insurance, you must copy of the front and back of the secondary insurance card.*

IV. REQUIRED SIGNATURE V. ORDER INFORMATION

SIGNATURE OF ORDERING PHYSICIAN  
**X**  
DATE  
PRINT NAME

TREATING PHYSICIAN UPIN  
PHONE # FAX #  
SPECIALTY:  Surgery  Oncology  Other \_\_\_\_\_  
OVERNIGHT MAIL ADDRESS:  Same as account  
CITY STATE ZIP  
REPORT DELIVERY PREFERENCES:  
 Overnight Mail  Fax  Online Secure Access  
E-MAIL ADDRESS (for report notification)

ADDITIONAL PHYSICIAN (optional)  
**CRA NAME**  
**CRA PHONE#, FAX#**  
**PACCT1 CRA**  by  Other \_\_\_\_\_  
OVERNIGHT MAIL ADDRESS:  Same as account  
**SHIPPING ADDRESS**  
**SHIPPING ADDRESS**  
REPORT DELIVERY PREFERENCES:  
 Overnight Mail  Fax  Online  
E-MAIL ADDRESS (for report notification)  
**CRA e-mail**

VI. PATHOLOGY INFORMATION

SUBMITTING PATHOLOGIST UPIN  
PHONE # FAX #  
OVERNIGHT MAIL ADDRESS:  Same as account  
CITY STATE ZIP  
REPORT DELIVERY PREFERENCES:  
 Overnight Mail  Fax  Online Secure Access  
E-MAIL ADDRESS (for report notification)

DATE OF SURGERY  
DATE BLOCK PULLED FROM ARCHIVE (Required for Medicare)  
SPECIMEN/BLOCK ID SPECIMEN TYPE:  BLOCK  SECTIONS  
**ECOG Pathology Coordinating Office**  
**Northwestern Univ., Olson Pavilion, Rm 8421, 710 N Fairbanks Crt**  
**Chicago IL 60611**  
BLOCK RETURN PHONE NUMBER: **312-503-3384**

VII. COMMENTS VIII. SHIPPING INVENTORY

Comments:  
**PACCT1/#####**

SHIPPING INVENTORY — DIAGNOSTIC SPECIMEN, NOT RESTRICTED, PACKED IN COMPLIANCE WITH IATA 650 PACKAGING INSTRUCTION.  
• Fixed Paraffin-Embedded Tumor Tissue (human, non-infectious).

Customer Support: (866) ONCOTYPE (662-6897) XXXXX SPECIMEN REQUIREMENTS AND INSTRUCTIONS FOR COMPLETING THIS FORM ARE INCLUDED ON BACK

301 Penobscot Drive Redwood City, CA 94063 (650) 556-9300 www.genomichealth.com and www.oncotypedx.com

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**REQUISITION FORM INSTRUCTIONS**

A. Check the box indicating whether this is a new submission or resubmission.

**Section I: Account Information**

A. Ensure that the Account Information is correct. If blank, fill out institution name, address and phone number.

**Section II: Patient Information**

A. Complete all lines. Some lines require more than one piece of information.

**NOTE:** For Non-US patients, leave SSN blank.

**Section III: Billing Information**

- A. Enter the ICD-9 Code. The ICD-9 must be to the highest level of specificity available (at least 4 digits).
- B. Indicate the party responsible for payment of OncoType DX™ Breast Cancer Assay.
  - 1. If Medicaid/Medicare/Private Insurance, please include a copy of the front and back of the patient insurance card. If this is included, no further billing information is required (except for Medicare patients). If not, please complete all other fields in this section.
  - 2. If Bill Account, no further billing information is required. The account specified in Section I will be billed for the assay.
  - 3. If Patient self-pays, payment is required for processing. Payment forms include credit card (name on card, card number, expiration date), money order, certified funds, or check (US only). No further billing information is required.
- C. For Medicare patients only, check the box to indicate whether the patient is a Hospital Inpatient, Hospital Outpatient, or Non-Hospital Patient.
- D. For Medicare patients only: If necessary, obtain a signed ABN.
- E. Check the box indicating whether the patient has secondary insurance. If "yes," please attach a photocopy of the front and back of the secondary insurance card.

**Section IV: Signature of Ordering Physician — REQUIRED**

- A. Sign and date the Requisition Form and print your name. The signature must be of an ordering physician (treating physician or pathologist) or their authorized representative.
- B. To be medically necessary, diagnostic laboratory tests must be ordered by a treating physician (or their authorized representative) who provides a consultation or treats a patient for a specific medical problem and who uses the findings in the management of the patient. If the ordering physician is not the treating physician, the ordering physician confirms by signing this form that the treating physician has ordered the OncoType DX Breast Cancer Assay. This order may have been conditioned on findings from the initial pathological examination.

**Section V: Order Information**

- A. Enter the Treating Physician's name, UPIN, Phone Number, Fax Number, specialty and all other applicable information.
- B. If there is another physician who has requested a copy of the report and who is responsible for the care of this patient, enter the applicable information in the spaces provided.

**NOTES:** • Reports can't be sent to PO boxes or e-mailed. The e-mail address is only used for notification that the report has been generated.  
• For Non-US physicians, leave UPIN blank.

**Section VI: Pathology Information**

- A. Complete all fields. Some lines require more than one piece of information.
- B. Enter the Submitting Pathologist's name, UPIN, Phone Number, Fax Number and all other applicable information.
- C. For block submissions, enter the Block Return Contact, Address and Phone Number.

**NOTE:** Before shipping, remove the copy (second sheet) of the Requisition Form and retain it for your records. Then place the Requisition Form (top sheet) and relevant patient insurance materials in the OncoType® Specimen Kit.

**SPECIMEN REQUIREMENTS**

• For specimen criteria, visit [www.genomichealth.com/oncotype/logistics](http://www.genomichealth.com/oncotype/logistics) or call (866) ONCOTYPE (866-662-6897).

• Please send either:

- Two microcentrifuge tubes each containing three 10-micron sections of fixed paraffin-embedded breast cancer tissue and one H&E slide from the same block

OR

- One fixed paraffin-embedded tumor block

• All specimens must be labeled with barcode labels from the Requisition Form for this patient.

• Please call (866) ONCOTYPE (866-662-6897) with questions.

**NOTE:** The OncoType DX report is based upon Genomic Health's analysis of the submitted specimen and information provided on the Requisition Form (including the Comments Section). Additional materials or information that may have been submitted with the specimen are not considered in analyzing the specimen or preparing the report. If you have any questions, please contact Customer Service at (866) ONCOTYPE (866-662-6897).

**DOMESTIC SHIPPING INSTRUCTIONS**

**I. Materials and Equipment**

- A. OncoType Specimen Kit containing the patient specimen
- B. FedEx® USA Airbill pre-printed with Genomic Health, Inc. shipping information
- C. FedEx® Clinical Pak, Large — a plastic overwrap used to ship the specimen to Genomic Health, Inc.
- D. FedEx® adhesive outer sleeve for the FedEx® Airbill

**NOTE:** All materials listed are included in the OncoType Specimen Kit. To order additional kits call (866) ONCOTYPE (866-662-6897).

**II. Place the OncoType Specimen Kit into the FedEx® Clinical Pak.**

**III. Check the box on the Clinical Pak indicating that the packaging is in compliance with IATA 650 packaging regulations. Genomic Health, Inc. has designed the OncoType Specimen Kit to comply with these packaging regulations. A summary of the regulations can be found at [www.oncotypeDX.com](http://www.oncotypeDX.com).**

**IV. Complete the FedEx® USA Airbill noting the following areas:**

- A. Sec 6. Special Handling: Under the question, "Does this shipment contain dangerous goods?" please check "No." The fixed paraffin-embedded (FPE) specimen is non-infectious, thus it is not classified as a dangerous good.
- B. Release Signature: Do not sign here.

**V. Place the package in the designated FedEx® pickup location at your site.**

**VI. If your site does not have standard FedEx® pickup, please call (800) GO FEDEX (800-463-3339) to arrange for pickup or call (866) ONCOTYPE.**

**NOTE:** For International Specimens, please call (866) ONCOTYPE.

**QUESTIONS? CALL (866) ONCOTYPE**



**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Appendix VI**

**PACCT-1 Peripheral Blood Collection and Shipping Kit Order Form**

Rev. 6/06 **NOTE:** It is preferred that kits be requested after pre-registration, prior to registration/randomization.

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

To obtain the proper kit, provide the following information:

Rev. 6/06 PACCT-1 ECOG patient case number: \_\_\_\_\_  
Rev. 6/06 (This is the ECOG sequence number assigned to the patient at pre-registration).

Kit is to be shipped to:

Institution Contact: \_\_\_\_\_

Phone number for contact: \_\_\_\_\_

Rev. 6/06 Fax number for contact: \_\_\_\_\_

Rev. 6/06 E-mail for contact: \_\_\_\_\_

Institution Address:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Rev. 6/06 FAX Completed form to Zemotak-International at 800 815-4675

**NOTE:** Questions are to be directed to the ECOG PCO-RL, Attn: Adekunle Raji,  
Tel: (312) 908-9595                      Pager: (312) 695-5802

Comments:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Appendix VII**

**PACCT-1 Shipment Notification Form**

**DATE :** \_\_\_\_\_ **Fax To: (312) 503-2792** \_\_\_\_\_

Ship To: Pathology Coordinating Office  
Robert H. Lurie Comprehensive Cancer Center  
Attn: Adekunle Raji  
710 N. Fairbanks - Olson 8421  
Chicago, IL 60611  
Tel: (312) 908-9595                      Pager: (312) 695-5802

Fedex Tracking Number: \_\_\_\_\_

Shipped by: \_\_\_\_\_ Phone #: \_\_\_\_\_

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

Use overnight Fedex Account. Contact the ECOG PCO-RL to obtain account number.

Rev. 6/06 **This account is for PACCT-1 Shipments to the ECOG PCO-RL Only.**

- Please mark "For Immediate Delivery. Fragile".
- Friday shipments are ill advised, similarly shipping before a long holiday is often problematic. The Laboratory is closed on Saturday, Sunday and holidays.
- Please make sure the shipments have appropriate regulatory labels provided.

Comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Appendix VIII**

**Correlative Science for the PACCT-1 Trial**

**Background:** The clinical trial design of the PACCT-1 trial is based the Genomic Health analysis of NSABP B20 described in the preliminary data section. To summarize, the low risk group receiving tamoxifen alone experienced an event rate of five relapses out of 135 cases (4%). In the intermediate group there were eight relapses out of 45 cases (18%). In the high risk group there were 18 relapses out of 47 cases (38%). These estimates were validated with samples from the tamoxifen arm of the B14 trial. On the chemotherapy plus tamoxifen arm of NSABP B20, the event rates were, 5%, 10% and 11% respectively. The advantage for chemotherapy was only statistically significant in the high risk group RR 0.258 (0.126-0.528). The design of the PACCT-1 trial is essentially a prospective trial to confirm these findings in the context of contemporary practice.

Even if the risk estimates provided by the B14 and B20 analysis are replicated, there remain areas for assay improvement, for example:

1. The registry design will allow study of patients in the low risk group who relapse (5%) since they were misclassified as low risk. Identifying the molecular signatures of the tumors that do unexpectedly poorly would allow additional biomarkers to be added to the model to ensure that as few patients as possible are under-treated.
2. The registry design will also allow the study of patients in the intermediate and high risk groups who relapse despite tamoxifen and chemotherapy. If patients with treatment resistant tumors can be prospectively identified they could be singled out for more effective treatment.
3. There are too few cases in the intermediate group to be certain what the chemotherapy benefit is seen within this group. The randomization of patients with intermediate risk scores to chemotherapy versus observation in the PACCT-1 study is designed to answer this question. If chemotherapy is shown to provide benefit, the over treatment problem will remain substantial for the intermediate group because overall the risk status is still favorable. Alternative risk models or a modification of the assay will be a critical focus for further investigation.

**Procedures for accessing samples:** A large number of samples will be accrued during the conduct of the PACCT-1 trial. These samples will be used for independent analyses using alternative approaches and statistical models proposed by academic or industry investigators. An important consideration is that the PACCT-1 research must be conducted in an “open source” environment as the best models may, in the end, involve a synthesis of a number of different biomarker approaches. The following research outlines are not intended to be specific or inclusive, but are designed to inform institutional review boards, patients and investigators of the scope of the research that is likely to be undertaken. The samples will be banked at ECOG (FFPE, plasma, DNA, RNA not consumed by the Oncotype DX assay, and frozen tumor from the virtual tumor bank) and access will depend on further approval. The only correlative science aims that are considered “embedded” are tests for ER, PgR by IHC and HER2 FISH using whole sections, the construction of a TMA and a centralized histopathology grading exercise. Activating an new analysis requires the development of a concept sheet (using the standard TBCI form) with the active collaboration of the PACCT-1 correlative science committee (CSC) to ensure all the relevant components of an application have been provided and the proposal has high scientific merit (this is mandatory). The concept will then be submitted to the TBCI correlative science committee for approval (see <http://ctep.cancer.gov/resources/tbci/>). An approved concept will lead to a PACCT-1 sub-protocol that will be approved by the CIRB and CTEP. Institutional IRB approval of sub-protocols involving sample analysis will only have to be sought from institutions that will receive samples for

analysis. All samples will be stripped of identifiers and the marriage of clinical and research data will use an honest broker approach to prevent the identity of a patient being divulged to laboratory investigators or individual laboratory results inappropriately communicated to physicians or patients.

**Banking procedures:** The FFPE blocks will be accessed on an ongoing basis at the ECOG PCO. A cutting schema will be in place for 5 sections for ER IHC, PgR IHC, HER2 FISH, Standard H+E and one spare for assay failure problems. The H+E will be reviewed for “block mapping” and central grade assignment and 2 cores will be removed for TMA construction. The remaining specimen will then be banked until they are ready to be accessed for further analysis through approved sub-protocols.

**Summary of approved banking procedures for PACCT-1.** The following banking procedures are intrinsic to this protocol and are embedded aspects of the study.

1. The procurement of five 4 micron sections for H+E, ER IHC, PgR IHC, HER2 FISH and one spare for assay failures.
2. TMA construction with three cores.
3. Baseline plasma banking
4. Genomic DNA banking from peripheral blood
5. RNA “left over” from the Genomic Health Assay.
6. Consent for the acquisition of samples from the “virtual frozen tumor bank”.

A sub-protocol that will focus on frozen tumor accrual will be developed by ACOSOG and will be approved separately.

The following considerations provide the rationale for these banking procedures:

**Tissue Microarray (TMA) Construction:** The goal of the TMA construction will be a resource that can be used to study additional biomarkers in a format that preserves resources to the greatest possible extent.

**Tumor RNA banking:** We anticipate that there will be RNA remaining from a significant proportion of the specimens after the *Oncotype* assay has been performed. This RNA will be sent in a timely manner in batches to ECOG for storage. Sub-protocols will be encouraged that test alternative risk models based on mRNA profiling have been developed and present alternative solutions to the problem of outcome prediction in early stage breast cancer. These assays, like *Oncotype DX*, will typically also be based on q RT PCR, although other RNA analysis techniques such as microarray analysis could also be entertained.

**Tumor and adjacent normal tissue DNA.** RNA expression profiling reflects the effect of somatic mutation, most obviously through gene over-expression as a result of gene amplification. However other somatic mutations such as deletions and single nucleotide mutations probably play an important role in determining the eventual clinical outcome. The ability to identify these abnormalities is amenable to high-throughput techniques such as DNA sequencing and array-based comparative genomic hybridization.

**Baseline plasma banking:** Considerable advances in proteomic techniques have taken place in the last several years. These techniques may ultimately prove valuable in defining patients with low volume residual disease though the presence of circulating tumor products or though certain immune responses to the presence of malignant cells. These techniques could prove very valuable in the area of prognosis, which is essentially an exercise in the identification of patients with metastatic spread of tumor. These samples could also be used to study steroid hormone level and other risk factors for the development of breast cancer.

**Baseline Genomic DNA banking:** When clinical data become available from the PACCT-1 study, studies of genetic variation can be focused on the impact of genetic variation in the efficacy and safety of adjuvant endocrine and chemotherapy treatment. For example an Aromatase SNP has already been linked to the outcome of AI therapy for advanced disease. Colomer et al recently reported that advanced disease patients with the aromatase polymorphism rs4646 had markedly better time to progression upon treatment with letrozole in comparison with those with a “normal” gene.

**Virtual frozen tumor bank.** Frozen samples from tumors are reasonably often banked under institutional banking protocols. The consent form of the PACCT-1 trial includes language that requests permission to access these samples to address specific questions that have been approved through the process outlined above. If patients provide consent to future research, frozen tumor tissue that has been collected at the local institution will be submitted after registration/randomization or, if retained at the local site until requested, will be considered part of the “Virtual Tumor Bank”. In the MA27 clinical trial a virtual tumor bank was piloted. In the initial cohort of over 1000 patients, approximately 10% of cases were recorded to have frozen tumor banked at the institution and that the patient had given permission for the tissue to be sent to another institution for analysis. Thus in a large trial, such as PACCT-1, a relatively large number of frozen tumors will be accrued. ACOSOG will conduct a targeted effort to increase the number of tumors banked and available for analysis through this mechanism.

Rev. 6/06

Rev. 6/06

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
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**Appendix IX**

**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 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 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]  
[PATIENT ADDRESS]

[DATE]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important clinical program. Programs like this offer a chance to get the best care while helping us make better care available for all patients. Many questions remain unanswered in cancer. With the help of people like you who participate in these programs, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe this program will provide you with high quality, thorough care. Your physician and research staff will maintain very close contact with you. This is important to allow your physician 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 Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Appendix X**

**Oncotype DX Assay Information**

Rev. 6/06 This appendix contains **examples** of the “Oncotype DX Patient Report” and information sheets (provided in the Oncotype DX Specimen Kit) distributed by Genomic Health.

For patients without determined Recurrence Scores:

To order the “Oncotype Specimen Kit” contact Genomic Health Customer Service (866-662-6897). Kit should be ordered prior to pre-registration. 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.

As outlined in Appendix V, materials are submitted AFTER pre-registration to Genomic Health. An example of the “Oncotype DX Requisition Form” and instructions on how the requisition form MUST be completed are in Appendix V.

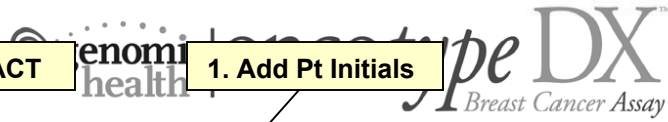
Only one Oncotype Specimen Kit and Requisition form should be completed per patient.

Recurrence Scores determined prior to or during pre-registration:

After pre-registration, **fax** a redacted copy of the “Oncotype DX Patient Report” (labeled with protocol number (PACCT1), patient initials and case number) to the ECOG Operations Office (FAX: 617-582-8578, Attn: Pre-registration/PACCT-1).

Registration/randomization may proceed 24 to 72 hours after submission of the report the ECOG Operations Office.

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Genomic Health, Inc.  
301 Penobscot Drive  
Redwood City, CA 94063  
Tel (866) ONCOTYPE (866-662-6897)  
www.oncotypedx.com



3. REDACT

1. Add Pt Initials

PATIENT REPORT	
Patient: Doe, Jane <b>D,J</b>	Requisition: R00003G
Sex: Female	Date Received: 12/01/2004
DOB: 01/01/1950	Date Reported: 12/01/2004
Medical Record/Patient #: 556677771	Client: Community Medical Center
Date of Surgery: 11/23/2004	Treating Physician: Dr. Harry D Smith
Specimen ID: SURG-0001	Submitting Pathologist: Dr. John P Williams
	Additional Physician: Dr. Sally M Jones

DO NOT REDACT

ASSAY DESCRIPTION

2. ADD PROTOCOL# AND CASE:  
PACCT1/#####

CR to determine the expression of a panel of 21 genes in tumor tissue. A clinically validated test to determine the individual Recurrence Score™. The Recurrence Score range is from 0-100.

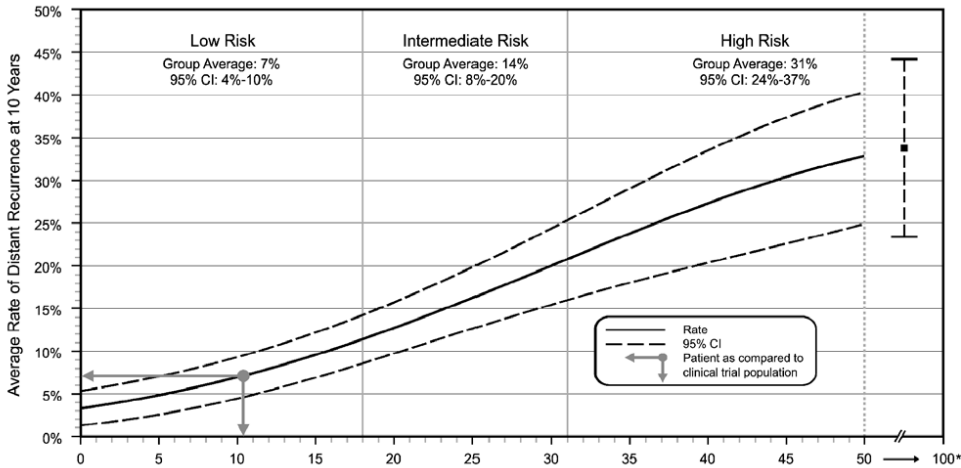
Recurrence Score = **10**

Test results should only be used in populations consistent with the clinical trial experience outlined below.

Patients with a Recurrence Score of 10 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **7% (95% CI: 5%-9%)**

CLINICAL EXPERIENCE

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



4. FAX REDACTED COPY OF REPORT (labeled as above) TO 617-585-8578, ATTN: PACCT1/Pre-registration

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been approved or cleared by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These results are adjunctive to the ordering physician's workup.

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypedx.com  
© 2005 Genomic Health, Inc. Oncotype DX and Recurrence Score are trademarks of Genomic Health, Inc.

GH1004 Rev006 01/10/2005

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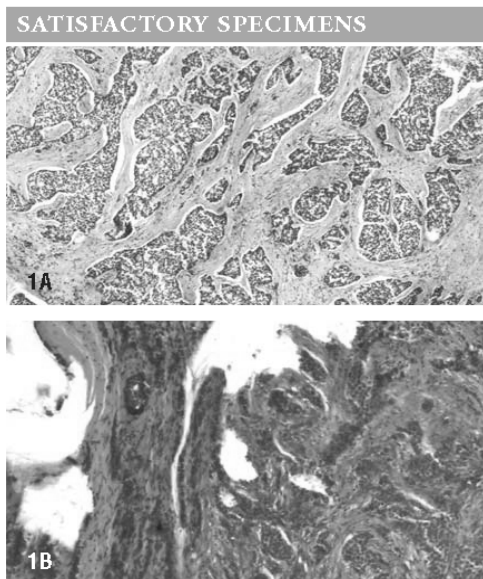




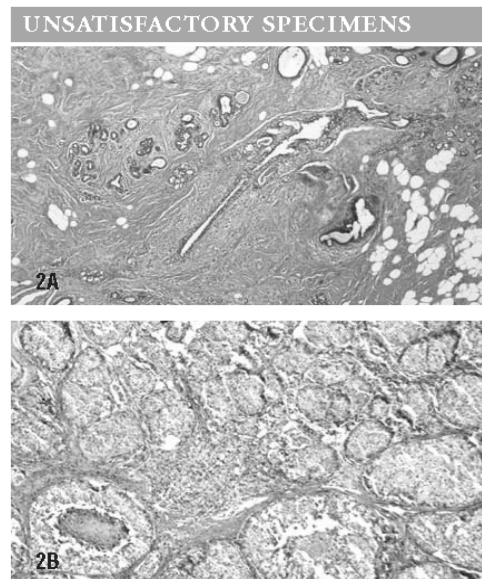
PATHOLOGY GUIDELINES FOR BLOCKS

## RECOMMENDATIONS FOR SELECTING THE MOST REPRESENTATIVE BLOCK

1. **Select the paraffin-embedded tumor block containing the greatest amount of invasive breast carcinoma that is morphologically consistent with the submitting diagnosis.**
  - A. Choose the block with the greatest amount/area of invasive breast carcinoma/associated stroma and the least amount of non-invasive mammary epithelium (*in situ* carcinoma, hyperplastic epithelium, normal epithelium). Focal or microinvasive breast cancer alone is not sufficient.
  - B. These criteria may be similar to those used when selecting a block for immunohistochemistry (i.e., ER, PR, HER2).
  - 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. A pathologist at Genomic Health will review the submitted specimen for consistency with clinical trial experience.



**Figure 1A.** Invasive carcinoma comprises the majority of the tissue section. **Figure 1B.** The invasive carcinoma infiltrates around small foci of ductal carcinoma in situ. Both of these slides show invasive cells comprising most of the overall epithelial component. (H&E A  $\times 40$  and B  $\times 40$ )



**Figure 2A.** Rare infiltrating, single-file cells characteristic of lobular carcinoma in the lower half of the figure constitute a very small percentage of the overall epithelial component. **Figure 2B.** The section is predominantly ductal carcinoma in situ with a single focus, in the middle of the figure, of invasive ductal carcinoma. (H&E A  $\times 20$  and B  $\times 40$ )

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

PREPARATION INSTRUCTIONS FOR BLOCKS

## SPECIMEN PREPARATION INSTRUCTIONS FOR BLOCKS

### 1. Materials and equipment

- A. Fixed paraffin-embedded (FPE) breast cancer tissue block
- B. *Oncotype*<sup>™</sup> Specimen Kit
- C. *Oncotype* DX<sup>™</sup> Breast Cancer Assay Requisition Form
- D. Frozen 3 oz. ice pack (provided with *Oncotype* Specimen Kit, chilled in freezer overnight)

**NOTES:**

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

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

### 2. To submit a tumor block:

- A. Place a barcode label from the patient's *Oncotype* DX Requisition Form on the back of the tumor block cassette. (See Figure 3)
- B. Place the tumor block in the small plastic bag and seal the bag. Place a barcode label on the small plastic bag.
- C. Please do not send an H&E slide when you are submitting tumor block. Genomic Health will perform the H&E on site.



Figure 3

### 3. Complete the *Oncotype* DX Requisition Form.

- A. Instructions for filling out the form can be found on the back of the form.
- B. One *Oncotype* Specimen Kit and Requisition Form should be completed for each patient. Extra barcode labels should be left on the form and should NOT be used for another patient.
- C. Before shipping, remove the copy (second sheet) of the Requisition Form and retain it for your records.

### 4. Place the Requisition Form (top sheet) and relevant patient insurance materials in the *Oncotype* Specimen Kit, between the box and the large secondary containment bag.

- 5. Please consider adding a frozen ice pack on top of the foam, inside the large secondary containment bag (before it is sealed).
- 6. Seal the large secondary containment bag and close the box using the tab.

## DOMESTIC SHIPPING INSTRUCTIONS

### 1. Materials and equipment

- A. *Oncotype* Specimen Kit containing the patient specimen
- B. FedEx<sup>®</sup> USA Airbill pre-printed with Genomic Health, Inc. shipping information
- C. FedEx<sup>®</sup> Clinical Pak, Large — a plastic overwrap used to ship the specimen to Genomic Health, Inc.
- D. FedEx<sup>®</sup> adhesive pouch for the FedEx<sup>®</sup> Airbill

### 2. Place the *Oncotype* Specimen Kit into the FedEx<sup>®</sup> Clinical Pak and seal the Clinical Pak.

### 3. Check the box on the Clinical Pak indicating that the packaging is in compliance with IATA 650 packaging regulations. Genomic Health, Inc. has designed the *Oncotype* Specimen Kit to comply with these packaging regulations. A summary of the regulations can be found at [www.oncotypedx.com](http://www.oncotypedx.com).

### 4. Complete the FedEx<sup>®</sup> USA Airbill noting the following areas:

- A. Sec 6. Special Handling: Under the question, "Does this shipment contain dangerous goods?" please check "No." The fixed paraffin-embedded (FPE) specimen is noninfectious and is not classified as a dangerous good.
- B. Release Signature: Do not sign here.

### 5. Place the package in the designated FedEx<sup>®</sup> pickup location at your site.

### 6. If your site does not have standard FedEx<sup>®</sup> pickup, please call (800) GO FEDEX (800-463-3339) to arrange for pickup.

**NOTE:** For international specimens, please call (866) ONCOTYPE (866-662-6897) or visit [www.oncotypedx.com](http://www.oncotypedx.com).

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



PATHOLOGY GUIDELINES FOR SECTIONS

RECOMMENDATIONS FOR SELECTING THE MOST REPRESENTATIVE BLOCK

1. Select the paraffin-embedded tumor block containing the greatest amount of invasive breast carcinoma that is morphologically consistent with the submitting diagnosis.
  - A. Choose the block with the greatest amount/area of invasive breast carcinoma/associated stroma and the least amount of non-invasive mammary epithelium (*in situ* carcinoma, hyperplastic epithelium, normal epithelium). Focal or microinvasive breast cancer alone is not sufficient.
  - B. These criteria may be similar to those used when selecting a block for immunohistochemistry (i.e., ER, PR, HER2).
  - 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. A pathologist at Genomic Health will review the submitted H&E slide for consistency with clinical trial experience.

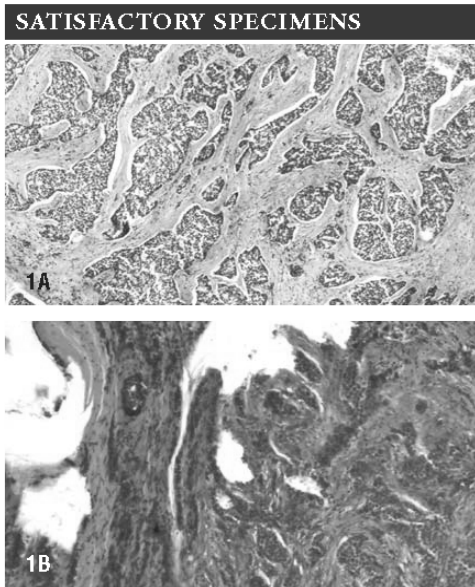


Figure 1A. Invasive carcinoma comprises the majority of the tissue section. Figure 1B. The invasive carcinoma infiltrates around small foci of ductal carcinoma in situ. Both of these slides show invasive cells comprising most of the overall epithelial component. (H&E A x40 and B x40)

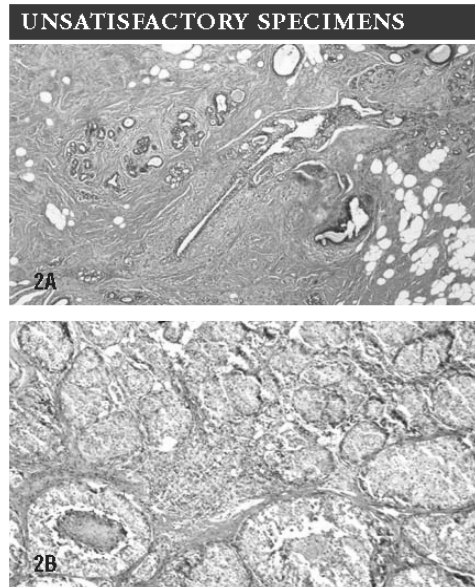


Figure 2A. Rare infiltrating, single-file cells characteristic of lobular carcinoma in the lower half of the figure constitute a very small percentage of the overall epithelial component. Figure 2B. The section is predominantly ductal carcinoma in situ with a single focus, in the middle of the figure, of invasive ductal carcinoma. (H&E A x20 and B x40)

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

PREPARATION INSTRUCTIONS FOR SECTIONS

SPECIMEN PREPARATION  
INSTRUCTIONS FOR SECTIONS

1. **Materials and equipment**
  - A. Fixed paraffin-embedded (FPE) breast cancer tissue block
  - B. *Oncotype*™ Specimen Kit
  - C. *Oncotype DX*™ Breast Cancer Assay Requisition Form

**NOTES:**

Use only the microcentrifuge tubes provided in the *Oncotype Specimen Kit*.

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

2. Place **3** sections of tissue into each microcentrifuge tube (two tubes total) using a microtome depth setting of **10 µm**.
  - A. To minimize cross-contamination between specimens (blocks) when sectioning, be sure to use a new area of the blade.
  - B. Apply the barcode label lengthwise on each microcentrifuge tube. (See Figure 3)
  - C. When finished, place both tubes in the small plastic bag and seal the bag.
3. Prepare an **H&E** slide using a microtome depth setting of **4 or 5 µm**.
  - A. We recommend that the H&E section is cut after the sections are cut for the microcentrifuge tubes (i.e., the final section cut from the block).
  - B. Write the Specimen ID on the "frosted" end of the slide using your standard procedure; leave room to place the Genomic Health barcode on the slide after it is stained. (See Figure 3)
  - C. **After H&E staining is complete**, place the barcode label on the slide.
  - D. Allow the mounting media to dry before placing it in the provided slide carrier.

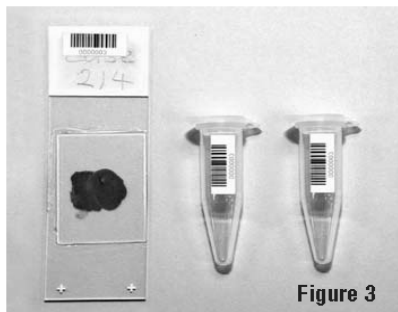


Figure 3

4. Complete the *Oncotype DX* Requisition Form.
  - A. Instructions for filling out the form can be found on the back of the form.
  - B. One *Oncotype Specimen Kit* and Requisition Form should be completed for each patient. Extra barcode labels should be left on the form and should **NOT** be used for another patient.
  - C. Before shipping, remove the copy (second sheet) of the Requisition Form and retain it for your records.
5. Place the Requisition Form (top sheet) and relevant patient insurance materials in the *Oncotype Specimen Kit*, between the box and the large secondary containment bag.
6. Seal the large secondary containment bag and close the box using the tab.

DOMESTIC SHIPPING  
INSTRUCTIONS

1. **Materials and equipment**
  - A. *Oncotype Specimen Kit* containing the patient specimen
  - B. FedEx® USA Airbill pre-printed with Genomic Health, Inc. shipping information
  - C. FedEx® Clinical Pak, Large — a plastic overwrap used to ship the specimen to Genomic Health, Inc.
  - D. FedEx® adhesive pouch for the FedEx® Airbill
2. Place the *Oncotype Specimen Kit* into the FedEx® Clinical Pak and seal the Clinical Pak.
3. Check the box on the Clinical Pak indicating that the packaging is in compliance with IATA 650 packaging regulations. Genomic Health, Inc. has designed the *Oncotype Specimen Kit* to comply with these packaging regulations. A summary of the regulations can be found at [www.oncotypedx.com](http://www.oncotypedx.com).

**NOTE:** The *Oncotype Specimen Kit* is shipped at ambient (room) temperature.

4. Complete the FedEx® USA Airbill noting the following areas:
  - A. Sec 6. Special Handling: Under the question, "Does this shipment contain dangerous goods?" please check "No." The fixed paraffin-embedded (FPE) specimen is noninfectious and is not classified as a dangerous good.
  - B. Release Signature: Do not sign here.
5. Place the package in the designated FedEx® pickup location at your site.
6. If your site does not have standard FedEx® pickup, please call (800) GO FEDEX (800-463-3339) to arrange for pickup.

**NOTE:** For international specimens, please call (866) ONCOTYPE (866-662-6897) or visit [www.oncotypedx.com](http://www.oncotypedx.com).

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

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):**  
*Trial Assigning Individualized Options for Treatment:*  
The **TAILORx** Trial

**Appendix XI**

**Cancer Trials Support Unit (CTSU) Participation Procedures**

**REGISTRATION/RANDOMIZATION**

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. 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 registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU 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. All forms and documents associated with this study can be downloaded from the PACCT-1 Web page on the CTSU registered member Web site (<http://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

**Requirements for PACCT-1 site registration:**

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet

**Pre-study requirements for patient enrollment on PACCT-1:**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed (including tumor, blood, and plasma samples).
- Contact Genomic Health Customer Service (866-662-6897) and request the “Oncotype Specimen Kit” for mandatory submission of one tumor block for the determination of the Oncotype DX Recurrence Score. If the kit is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration. Materials must be submitted no later than 3 days after pre-registration as outlined in Section 10.1.

[If patient previously had an Oncotype DX Recurrence Score performed by Genomic Health, and the RS is 11-25, blocks should be submitted for central review following registration as outlined in Section 10.2.]

**CTSU Procedures for Patient Enrollment**

**PLEASE NOTE:** These instructions for patient enrollment apply ONLY to non-ECOG sites. All ECOG member sites should refer to Section 4 of the protocol for ECOG patient registration procedures.

**Pre-Registration**

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that a pre-registration forthcoming. For immediate registration needs, i.e. within one hour, call the registrar cell phone at 1-301-704-2376. Complete the following forms:
  - CTSU Patient Enrollment Transmittal Form
  - PACCT-1 Pre-registration Step 1 Eligibility Checklist
2. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies.
3. Once investigator eligibility is confirmed and pre-registration documents deemed complete, the CTSU registrar will contact the ECOG, to obtain assignment of an ECOG pre-registration sequence number. The CTSU registrar will relay this information to the enrolling site and follow up with a confirmation of pre-registration via e-mail or fax.

*Reminder: If the "Oncotype Specimen Kit" is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration.*

**Oncotype DX Assay and Recurrence Scoring**

- If patient previously had an *Oncotype* DX Recurrence Score performed by Genomic Health, and the RS is 11-25, a redacted copy of the *Oncotype* DX Patient Report should be FAXed to the ECOG Coordinating Center (617-582-8578, ATTN: Pre-registration/PACCT-1) within 24 to 72 hours (if weekend or holiday) of pre-registration. Indicate on the report the protocol number (PACCT-1), and patient's ECOG pre-registration sequence number.
- If patient is having an *Oncotype* DX Assay performed by Genomic Health, Genomic Health will notify the submitting site of the assay results within 14 working days of receipt of the sample. Once received, FAX a redacted copy of the "*Oncotype* DX Patient Report" to the ECOG Coordinating Center prior to registration/randomization (617-582-8578, ATTN: Pre-registration /PACCT-1). Indicate on the report the protocol number (PACCT-1), and patient's ECOG pre-registration sequence number.

Important notes:

- In all cases, the "*Oncotype* DX Patient Report" and completed TAILORx Source Document Tracking Worksheet (Form #2533) must be faxed to the ECOG Coordinating Center prior to proceeding to registration/randomization.
- It will take 24 hours and up to 72 hours (if weekend or holiday) for ECOG to enter the *Oncotype* DX Patient Report results in their system, therefore CTSU CANNOT register/randomize a patient until this time has lapsed.

### Registration/Randomization

Important: It will take 24 hours and up to 72 hours (if weekend or holiday) for ECOG to enter the Oncotype DX Patient Report results in their system, therefore CTSU CANNOT register/randomize a patient until this time has lapsed.

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that a patient registration is forthcoming. For immediate registration needs, i.e. within one hour, call the registrar cell phone at 1-301-704-2376. Complete the following forms:
  - CTSU Patient Enrollment Transmittal Form
  - PACCT-1 Registration Step 2 Eligibility Checklist
2. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the ECOG, to obtain assignment of a treatment arm. The CTSU registrar will relay this information to the enrolling site and follow up with a confirmation via e-mail or fax.

*Patients must not start protocol treatment prior to registration/randomization.*

*Treatments should begin within 14 working days after registration/randomization.*

### DATA SUBMISSION

All documentation associated with this study may be downloaded from the PACCT-1 Web page located on the CTSU registered member Web site (<http://members.ctsu.org>). CTSU investigators must use the current version of all documents and forms and adhere to the PACCT-1 schedule for data submission.

### Submission via Hard Copy

Rev. 6/06

Original and amended post-enrollment CRFs (including Specimen Submission forms), clinical reports and responses to query and delinquency letters must be mailed directly to the CTSU Data Operations Center accompanied by a properly completed CTSU Data Transmittal Form. Copies of clinical reports submitted to the CTSU must include the Patient ID and protocol number on all pages of the report. The patient's name must be redacted.

A CTSU Data Transmittal Form must accompany all data submissions. Data submitted with an improperly completed CTSU Data Transmittal Form or without a CTSU Data Transmittal Form will be returned to the site for corrective action without being processed.

Rev. 6/06

Mail original and amended post-enrollment CRFs, clinical reports [accompanied by completed TAILORx Source Document Tracking Coversheet (Form #2533)], and responses to query and delinquency letters to:

Westat  
CTSU Data Operations Center  
5615 Kirby Dr. Suite 710  
Houston, TX 77005

### **Submission via Remote Data Capture**

**(These instructions are ONLY for pre-selected RDC sites. These sites were selected by ECOG and will submit patient data via CTSU's RDC system.)**

All participating sites are required to submit patient data via the CTSU's Remote Data Capture (RDC) system. The CTSU Remote Data Capture system allows sites to enter patient data into an Oracle Clinical® (OC) database over a secure Internet connection. The RDC system also allows for data correction at the point of entry, and is used to communicate and resolve issues relating to discrepant data. Sites can connect to the OC-RDC application via the Remote Data Capture link on the CTSU member website.

Institutional pathology reports and other clinical reports cannot be entered in the OC-RDC application; therefore, a copy accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533) should be submitted to the CTSU Data Operations for tracking purposes. Please include the Patient ID and protocol number on all pages of the report and redact the patient's name. Submit along with a completed CTSU Data Transmittal Form.

Sites experiencing technical problems (e.g., firewall issues) with RDC must contact the CTSU help desk (1-888-823-5923) to obtain permission for a waiver to submit hard-copy CRFs in lieu of using RDC.

### **SPECIAL MATERIALS OR SUBSTUDIES**

#### **Submission of Mandatory Tumor Block:**

Mandatory submission of one tumor block for the determination of the *Oncotype* DX Recurrence Score is to be submitted to Genomic Health (see Section 7.2, 10 and Appendix IV). Kits for tissue submission and *Oncotype* DX Recurrence Score assessments must be ordered within 24 hours following pre-registration. Samples are to be submitted within 3 days of pre-registration. Pathology report and the ECOG Pathology Material Submission Form (#638 v04.2) must be completed and copies distributed to both Genomic Health (with the samples and requisition form) and the ECOG PCO-RL. If the Recurrence Score was previously determined by Genomic Health, tissue block **MUST** be submitted to the ECOG PCO-RL within 2 weeks following randomization.

All materials and reports must be labeled with the Patient ID and protocol number; patient names should be redacted from the pathology report. Specimens should not be submitted to the CTSU, although CTSU should be copied on **all** transmittal forms and (ECOG Pathology Material Submission Form #638, *Oncotype* DX Requisition Form) pathology reports. See protocol Section 10 and Appendix V for further details on shipping details, sample collection and preparation.

*Special Notes for pre-selected Remote Data Capture (RDC) sites:*

All Specimen bank submission CRFs must be entered in the RDC system.

Institutional pathology reports and other clinical reports cannot be entered in the OC-RDC application; therefore hard copy should be submitted as described in the section above under the header "Submission of Mandatory Tumor Block" and accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533).

Sites experiencing technical problems (e.g., firewall issues) with RDC must contact the CTSU help desk (1-888-823-5923) to obtain permission for a waiver to submit hard-copy CRFs in lieu of using RDC.

#### **Additional Studies/Banking:**

Provided patient consent is obtained, primary tumor tissue is to be submitted within two weeks following registration/randomization for laboratory studies (defined in Section 10.3) and banking for future research. Peripheral blood and plasma samples, requested for banking for possible use in future studies, are to be collected after registration/randomization, prior to start of treatment.



Rev. 6/06 Shipping and collection kits for the frozen tissue and blood samples are ordered by completing the *PACCT-1*  
Rev. 6/06 *Peripheral Blood Collection and Shipping Kit Order Form* (Appendix VI) and Faxing to Zemotak-International  
Rev. 6/06 at 800-815-4675. See Section 10 and Appendix V for further details on sample collection, preparation, and  
shipping. Specimens (and all associated forms and reports) are to be submitted to the address provided in  
Section 10 and Appendix VI of the protocol. All materials and reports must be labeled with the Patient ID  
and protocol number; patient names should be redacted from the pathology report. Specimens should not  
be submitted to the CTSU, although CTSU should be copied on all transmittal forms (ECOG Pathology  
Material Submission Form #638, TAILORx Material Submission Form (#2539) and the pathology reports.

*Special Notes for pre-selected Remote Data Capture (RDC) sites:*

Rev. 6/06 All Specimen bank submission CRFs must also be entered in the CTSU RDC system. Institutional pathology  
reports and other clinical reports cannot be entered in the OC-RDC application; therefore, hard copy should  
be submitted as described in the section above under the header “Additional Studies/Banking” and  
accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533).

Sites experiencing technical problems (e.g., firewall issues) with RDC must contact the CTSU help desk (1-  
888-823-5923) to obtain permission for a waiver to submit hard-copy CRFs in lieu of using RDC.

## ADVERSE EVENT (AE) REPORTING

### Assessing and submitting expedited reports

This study will utilize the CTCAE version 3.0 for toxicity and Adverse Event (AE) reporting. A link to the  
CTCAE guidelines is available on the CTSU registered member Web site  
<http://ctep.cancer.gov/reporting/ctcnew.html>. CTSU investigators should assess adverse events according to  
the instructions and tables in Section 5.3 of the protocol. All reporting should be conducted within the time  
frames specified in Section 5.3 of the protocol.

CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding  
submission of documentation of adverse events. Local IRBs must be informed of all reportable serious  
adverse events.

Expedited reports should be transmitted electronically using the CTEP AdEERS application. A link to the  
AdEERS application can be found on the CTSU member homepage.

Some adverse events require AdEERS 24-hour notification to NCI and ECOG (refer to table 5.3.3). Select  
the 24 Hour Notification reporting track in the AdEERS system. A full AdEERS report is due within 5  
calendar days.

Rev. 6/06 **NOTE:** Although most study data, from ECOG and non-ECOG institutions alike, is submitted to CTSU  
Data Operations, this does not include Expedited Adverse Event Reporting; data regarding  
expedited AEs must be submitted to ECOG and the NCI (not CTSU). Please follow instructions in  
protocol section 5.3 for submission of AE data.

### Secondary AML/MDS/ALL reporting:

Rev. 6/06 Upon diagnosis of AML/MDS/ALL, please submit copies of the following to the CTSU:

- NCI Secondary AML/MDS/ALL Report Form,
- Pathology report confirming the AML/MDS/ALL
- Cytogenetics report (if available)

Once received, the CTSU will send this information to ECOG where it will be forwarded on to the NCI.

### **Reporting other secondary malignancies:**

Upon diagnosis of a secondary cancer, please submit copies of the following to the CTSU within 30 days of diagnosis:

- \* ECOG Second Primary Form (#1677)
- \* A copy of the pathology report (if available)
- \* Any additional supporting documentation

Once received, the CTSU will forward this information to ECOG. Do not send original pathology reports to the CTSU.

### **DRUG PROCUREMENT:**

CTSU investigators should refer to Section 8 for detailed instructions on drug procurement, formulation, storage, administration, and potential toxicities.

Commercial agents: Cyclophosphamide, Methotrexate, Fluorouracil (Infusional), Doxorubicin, Paclitaxel, Epirubicin, Docetaxel, Tamoxifen, Exemestane, Anastrozole, Letrozole

### **REGULATORY AND MONITORING**

#### Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

#### Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the informed consent section of this protocol document; however, authorization for the release of Protected Health Information is considered separate and distinct from the Informed Consent process for participation in this clinical trial.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

#### Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

ECOG-ACRIN Cancer Research Group  
and  
The Breast Cancer Intergroup

Program for the Assessment of Clinical Cancer Tests  
(PACCT-1): Trial Assigning Individualized Options for  
Treatment: The TAILORx Trial

Rev. 6/14

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**Version Date:** April 25, 2014

**NCI Update Date:** December 16, 2014

**STUDY PARTICIPANTS**

**ACTIVATION DATE**

Rev. 9/06	<b>ALLIANCE</b> / Alliance for Clinical Trials in Oncology	April 7, 2006
Rev. 6/14	<b>SWOG</b> / SWOG	Update #1 – Incorporated Prior to Activation
Rev. 9/06	<b>NCIC-CTG</b> / NCIC Clinical Trials Group	Addendum #1 – 9/06
Rev. 9/06	<b>NRG</b> / NRG Oncology Foundation, Inc	Update #2 – 9/06
Rev. 9/06	Institutions aligned with ECOG-ACRIN will enroll	Addendum #2 – 9/07
Rev. 9/06	patients via ECOG-ACRIN. Institutions <u>not</u> aligned with	Update #3 – 11/07
Rev. 9/06	ECOG-ACRIN will enroll patients via the NCI Cancer	Addendum #3 – 8/08
Rev. 9/06	Trials Support Unit (CTSU).	Addendum #4 – 3/09
Rev. 9/06	Data management activities will be performed by the	Update #4 – 3/09
Rev. 9/06, 8/08	Cancer Trials Support Unit (CTSU). All non-RDC sites	Addendum #5 – 1/10
	will fax hard-copy case report forms and query	Update #5 – 7/10
	responses to 301-545-0406.	Update #6 – 9/11
	<b>NOTE:</b> This does not include Expedited Adverse	Addendum #6 – 2/12
	Event Reporting; please follow instructions	Addendum #7 – 2/13
	in Section <a href="#">5.3</a> for submission of AE data.	Update #7 – 3/13
Rev. 9/06	The CTSU will use the PACCT-1 number as required for	Update #8 – 10/13
	reporting to ECOG-ACRIN and the NCI and when	Update #9 – 11/13
	registering patients through ECOG-ACRIN.	Addendum #8 – 6/14
	CTSU participants and institutions will be instructed to	Update #10 – 12/14
	use the PACCT-1 study number on all data forms,	
	reports, and communications.	

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## Cancer Trials Support Unit (CTSUS) Address and Contact Information

Data management activities for the study will be performed by CTSUS with the exception of the Quality of Life component.

All sites, ECOG-ACRIN and non-ECOG-ACRIN alike, will submit data via the CTSUS. For this reason, investigators and study support staff involved in the collection and reporting of study data must be registered members of the CTSUS. QOL data, for ECOG-ACRIN and non-ECOG-ACRIN sites, will be submitted to the ECOG-ACRIN Operations Office – Boston.

### To submit site registration documents:

CTSUS Regulatory Office  
1818 Market Street, Suite 1100  
Philadelphia, PA 19103  
Phone - 1-888-823-5923  
Fax – 215-569-0206  
Email: [CTSUSRegulatory@ctsus.cocccg.org](mailto:CTSUSRegulatory@ctsus.cocccg.org) (for submitting regulatory documents only)

### For patient enrollments:

Please refer to patient enrollment section for instructions on using the OPEN system, which can be accessed at [https://www.ctsus.org/OPEN\\_SYSTEM/](https://www.ctsus.org/OPEN_SYSTEM/) or <https://OPEN.ctsus.org>.

Contact the CTSUS Help Desk with any OPEN-related questions at [ctsuscontact@westat.com](mailto:ctsuscontact@westat.com).

**NOTE:** No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.

### For data submission:

Data management activities for PACCT-1 (TAILORx) will be performed by the CTSUS for ECOG-ACRIN and non-ECOG-ACRIN sites alike. Sites pre-selected by ECOG-ACRIN will submit case report forms and manage discrepancies via CTSUS's Remote Data Capture (RDC) system. All non-RDC sites will fax CRFs, clinical reports and responses to query and delinquency letters to 301-545-0406.

Data management activities for the QOL study will be performed by the ECOG-ACRIN Operations Office – Boston for both ECOG-ACRIN and non-ECOG-ACRIN sites.

**NOTE:** This does not include Expedited Adverse Event Reporting; please follow instructions in Section 5.3 for submission of AE data.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSUS Member Web site located at <https://www.ctsus.org>. Access to the CTSUS members' websites is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

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**For patient eligibility or treatment-related questions:**

Questions regarding eligibility or treatment should be directed to the ECOG-ACRIN Study Chair (Joseph Sparano, M.D.) and/or Study Chair Liaison (Una Hopkins, R.N.) or the CTSU Help Desk at 1-888-823-5923. An email to the following email address is PREFERRED, and will be reviewed by the Study Chair and Study Chair Liaison (and other study team members); a response will be provided within 24 hours ([ecog.tailorx@jimmy.harvard.edu](mailto:ecog.tailorx@jimmy.harvard.edu)). For questions regarding patients who have been pre-registered or registered, please provide the sequence number in the subject heading and/or content of the email.

**For QOL questions:**

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For questions regarding the quality of life portion of the study, please contact Dr. Lynne Wagner at: (312) 695-6946 or [lwagner@northeastern.edu](mailto:lwagner@northeastern.edu).

**All other questions (including forms-specific questions) should be communicated by phone or e-mail to the CTSU Help Desk at:**

CTSU General Information Line – 1-888-823-5923, or [ctscontact@westat.com](mailto:ctscontact@westat.com). All calls and correspondence will be triaged to the appropriate CTSU representative.

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**For detailed information on the regulatory and monitoring procedures for CTSU sites:**

Please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website <https://www.ctsu.org> > education and resources tab > CTSU Operations Information > CTSU Regulatory and Monitoring Policy

**The CTSU Public Web site is located at: [www.ctsu.org](http://www.ctsu.org)**

**The CTSU Registered Member Web site is located at <http://members.ctsu.org>**

### Schema



Rev. 3/09 Accrual Goal = 11,248 patients

Patients who have had breast conservation surgery will also be treated with radiotherapy.  
Refer to Section 5.2 for RT guidelines

1. A tumor specimen MUST be sent to Genomic Health for the Oncotype DX assay (see Section 10 and Appendix V for details). Residual tumor tissue and RNA will be forwarded to the ECOG PCO-RL by Genomic Health, and will be retained by the ECOG PCO-RL for individuals who have consented to use of tissue for future research (or returned to the site if consent was not granted). Patients who have had the Oncotype DX assay performed prior to pre-registration may also enroll if the RS was 11-25, the patient has signed consent, and all eligibility criteria are met. In this case, tumor specimen must be sent directly to the ECOG PCO-RL.

2. Patients will receive hormonal therapy of the treating physician's choice (see Appendix III for details).

3. Patients will receive chemotherapy plus hormonal therapy of the treating physician's choice (see Appendices II & III for details).

4. See Appendix III for status definitions

Rev. 9/06, 9/07 5. See Section 10.2 for submission of samples to the ECOG PCO-RL.

6. For patients with a RS ≥ 26 who do not register on another CTSU study, the enrolling site is asked to provide baseline and follow-up information on a voluntary basis. Requested information will include the following: (1) a baseline case report form, (2) a report of disease relapse event (as defined in Section 6), and/or second primary cancer, and/or death (if any of these events occur), (3) and a report of disease and survival status 5 years after registration.

Rev. 1/10 7. QOL assessments should be completed for all patients registered/randomized to the TAILORx trial at baseline, 3 months, 6 months, 12 months, 24 months, and 36 months. See Section 7.3 for additional scheduling information.

Rev. 2/13 8. Patients become potentially eligible for EL112LAB if disease free and were registered to step 1 (Arm A, B, C or D) at least 4.5 years (54 months) and no more than 7.5 years (90 months) prior to registration to step 3. To assist sites, ECOG will provide a list of patients with date ranges of their potential eligibility.

Rev. 2/13 9. Following registration to EL112LAB: blood samples are submitted at registration and upon recurrence; recurrence tumor tissue upon recurrence; and health information at registration and yearly for 5 years.

## 1. Introduction

### 1.1 Background

In 2004, it is projected that there will be 215,900 new cases of female breast cancer and 40,110 deaths due to the disease in the United States (1). Cancer is the leading cause of death in women between the ages of 40-79, with breast cancer being the most common cancer in this group, and the second leading cause of cancer death. Breast cancer mortality has declined over the past 10 years due largely to the earlier detection of cancer by mammographic screening, but also in part due to the increasing use of adjuvant hormonal therapy and chemotherapy (2,3). The selection of adjuvant hormonal therapy based upon expression of the estrogen receptor (ER) and/or progesterone receptor (PR) has remained consistent (about two-thirds of all cancers) over the past 30 years. However, indications for adjuvant chemotherapy have expanded considerably to now include even women at very low risk of systemic recurrence. For example, the addition of adjuvant chemotherapy to tamoxifen reduces the risk of relapse in patients with axillary node negative, estrogen receptor (ER)-positive disease by approximately 30% (4-7). Indeed, attention has now begun to focus on who should not rather than who should receive chemotherapy (8). Models have been developed that can assist physicians in estimating the absolute benefit for an individual patient, although such models are based purely on clinical data and have inherent limitations (9,10). An International Expert Consensus Panel (11) defined “minimal risk” and “average-risk” groups for “endocrine-responsive” disease, and suggested that adjuvant chemotherapy be considered for women in the “average risk” group (Table 1) who are less than 70 years of age; by definition, “average risk” does not include patients with pure tubular or colloid histology, histologic patterns associated with a very favorable prognosis. A limitation of these guidelines is their reliance on histologic and/or nuclear grade for risk classification, which some have reported to have great interobserver variability, even amongst expert pathologists (12). Another limitation is that a relatively small proportion of patients with axillary node-negative, ER-positive disease are classified as “minimal risk”. Evidence-based practice guidelines issued by the National Comprehensive Cancer Center Network ([www.nccn.org](http://www.nccn.org)) use a lower threshold for recommending adjuvant chemotherapy in addition to hormonal therapy (Table 1). Although the NCCN guidelines do not use the terms “minimal risk” or “average risk”, these terms have been used in Table 1 to draw comparisons between the two guidelines for groups who are advised to receive or not to receive adjuvant chemotherapy. Finally, the United States National Institute of Health Consensus Development Panel concluded, “On the basis of available data, it is accepted practice to offer cytotoxic chemotherapy to most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both lymph node-negative and lymph node-positive). For women with lymph node-negative cancers smaller than 1 cm in diameter, the decision to consider chemotherapy should be individualized. Similarly, in patients with small lymph node-negative breast cancers with favorable histologic subtypes, such as tubular and mucinous cancers, retrospective data support long-term survival following primary therapy without the need for adjuvant chemotherapy.” With regard to age, the panel concluded, “There are limited data to define the optimal use of adjuvant chemotherapy for women more than 70 years of age....”

Increased participation of women over the age of 70 years in randomized clinical trials and studies specifically addressing the value and tolerance of adjuvant chemotherapy in these women are urgently needed” (13).

**Table 1 - Recommendations for Adjuvant Therapy of Axillary Lymph Node-Negative, Endocrine Responsive Disease**

	Definition	Premenopausal	Postmenopausal
<b>International Consensus Guidelines (Goldhirsch, 2003)</b>	<b>Minimal Risk (*):</b> Tubular or colloid histology OR All of the following features (*): pT<2 cm, and Grade 1, and Age ≥ 35 years	Hormonal Therapy OR None	Hormonal Therapy OR None
<b>NCCN Guidelines (<a href="http://www.nccn.org">www.nccn.org</a>)</b>	Tubular or colloid histology OR pT < 1 cm and no unfavorable features	Hormonal Therapy OR None	Hormonal Therapy OR None
<b>International Consensus Guidelines (Goldhirsch, 2003)</b>	<b>Average Risk:</b> ER and/or PR expressed, and at least one of the following features: pT > 2 cm, or Grade 2 or 3, or Age < 35 years	Chemotherapy ⇒ Hormonal Therapy OR Hormonal Therapy	Hormonal Therapy OR Chemotherapy ⇒ Hormonal Therapy
<b>NCCN Guidelines (<a href="http://www.nccn.org">www.nccn.org</a>)</b>	pT > 1cm, AND Histology ductal (NOS), lobular, mixed, or metaplastic OR Tumor 0.6-1.0 cm with unfavorable features+	Chemotherapy ⇒ Hormonal Therapy	Chemotherapy ⇒ Hormonal Therapy OR Hormonal Therapy (if > 60 years of age)

Abbreviations and/or definitions: pT – pathologic tumor size, defined as size of invasive component of tumor; Grade – histologic and/or nuclear grade; ER – estrogen receptor; PR – progesterone receptor; unfavorable features (+) – for NCCN guidelines, defined as angiolymphatic invasion, poor nuclear grade, poor histologic grade, or Her2 overexpression

Minimal Risk (\*) – some panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal risk

## 1.2 Axillary Lymph Node Negative Breast Cancer and Indications for Chemotherapy

According to Surveillance and Epidemiology and End Results (SEER) data, approximately 25% of women present with “average risk” node-negative disease in the United States, accounting for about 54,000 women diagnosed with breast cancer each year (14). Although adjuvant chemotherapy is of clear benefit even in “average risk” populations, the majority of women are treated unnecessarily to benefit a few. Assuming a relative risk reduction of 30% from the addition of

adjuvant chemotherapy to hormonal therapy, the absolute benefit derived from the addition of chemotherapy is low, even in individuals at higher risk for relapse. For example, using the ADJUVANT! decision analysis model, approximately 100 women must be treated in order to benefit only 3 or 4 patients (Table 2). A recent report indicated that this decision tool performed remarkably well when validated using an independent population based dataset including 4083 women with pT1-2, pN0-1 breast cancer, including patients with lymph node negative disease (15). The decision aid did overestimate prognosis, however, for ER-positive disease (10 year breast cancer specific survival projected 84.9% with ADJUVANT! vs. 83.0% in validation dataset) and for the benefit for adjuvant chemotherapy (projected 75.2% vs. actual 70.6%). Although such decision aids may be useful in estimating the benefit of chemotherapy, they are not sufficiently reliable to distinguish individuals who will not derive benefit from adjuvant chemotherapy.

**Table 2 - Absolute Improvement in 10-Year Disease Free Survival in Node-Negative Breast Cancer Treated by Addition of Chemotherapy to Tamoxifen (tam)**

St. Gallen Risk Group	Grade	Tumor size (cm)	Tam x 5 years	Tam x 5 years plus chemo	Absolute risk reduction by addition of chemo to tam
Minimal Risk	1	1.1-2.0	93%	94%	1%
Average Risk	2	1.1-2.0	81%	83%	2%
Average Risk	3	1.1-2.0	78%	81%	3%
Average Risk	1	2.1-3.0	75%	78%	3%
Average Risk	2	2.1-3.0	73%	76%	3%
Average Risk	3	2.1-3.0	68%	72%	4%

Calculations based upon Adjuvant Online model ([www.adjuvantonline.com](http://www.adjuvantonline.com)) (10).

Calculation based upon women age 55 in perfect health, ER-positive tumor, negative axillary lymph nodes; chemotherapy regimen is AC (doxorubicin 60 mg/m<sup>2</sup>, cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks x 4 cycles)

### 1.3 Genomic Profiling in Breast Cancer

Gene expression profiling of human breast cancer has been shown to be potentially useful in identifying breast tumor subtypes associated with distinct phenotypic characteristics that may have clinical implications. A series of studies have been reported over the past few years that have utilized expression profiling for the following purposes: (1) identifying distinct molecular subtypes of breast cancer, (2) identifying molecular signatures associated with a good vs. poor prognosis (i.e., prognostic factor), and (3) identifying molecular signatures that predict benefit from specific therapies (ie, predictive factor).

#### 1.3.1 Identifying Molecular Subtypes of Breast Cancer

Perou initially reported variations in gene expression patterns in 40 breast tumors analyzed by cDNA microarrays and hierarchical clustering that classified tumors into a basal epithelial-like group, a luminal group, an ERBB2-overexpressing group, and a normal breast-like group (16). A subsequent report by the same group that included

78 cancers, 3 fibroadenomas, and 4 normal breast tissues indicated that the previously characterized luminal epithelial/ER-positive group could be divided into at least two subgroups with distinctive expression profiles, and that these subtypes were associated with differing prognoses when analyzed in a uniformly treated group of patients (17). Another report by the same group provided additional evidence supporting their original findings in two different data sets that included 115 patients with breast cancer treated with neoadjuvant chemotherapy; a favorable prognosis noted for the luminal A subgroup, unfavorable prognosis for the basal and Her2 group, and an intermediate prognosis was noted for the luminal B group (18). It is noteworthy that routine immunohistochemical markers for hormone receptor expression and Her2/neu expression may be used to approximate these genomic subtypes, with the basal type characterized by absence of ER/PR and Her2/neu expression, luminal types characterized by ER and/or PR expression without Her2/neu expression, and Her2 type characterized by presence of Her2/neu expression irrespective of ER/PR expression status

### 1.3.2 Identifying Molecular Signatures Associated with Prognosis (ie, Prognostic Factor)

Other groups have evaluated gene expression profiles by performing supervised clustering analyses on the basis of clinical outcome (relapsers vs. non-relapsers) in order to identify specific gene expression profiles associated with prognosis. Some of these studies are summarized in Table 3, and discussed in further detail below. For the purposes of this discussion, the techniques may be broadly categorized as those that utilize routinely processed tissue (e.g., formalin-fixed, paraffin embedded tissue) and those that require specialized processing not routinely performed in clinical pathology laboratories (e.g., snap frozen fresh tissue).

**Table 3 – Characteristics and Performance of Selected Molecular Profiling Techniques**

	<u>Van de Vijver, 2002</u>	<u>Piccart, 2004</u>	<u>Wang V, Klijn JG, Zhang Y, et al., 2005</u>	<u>Paik, 2003</u>	<u>Esteva, 2003</u>
Tissue	Fresh frozen	Fresh frozen	Fresh frozen	Paraffin-embedded	Paraffin-embedded
Molecular technique	Rosetta Inpharmatics RNA expression	Rosetta Inpharmatics RNA expression	Affymetrix human U133a GeneChip RNA expression	Genomic Health RT-PCR RNA expression	Genomic Health RT-PCR RNA expression
Tissue processing	Thirty 30 micron sections	Thirty 30 micron sections	Thirty 30 micron sections	Three 10 micron sections	Three 10 micron sections
No. genes in panel	70 genes	70 genes	76 genes	16 genes (plus 5 reference genes)	16 genes (plus 5 reference genes)
Training/Validation	Validation	Validation	Training & validation	Training & validation	Validation
No. selected/evaluable	295/295	301/291	286/286	2167/675	220/149
ER Expression	77%	67%	70%	100%	70%
Axillary Nodes Positive	51%	0%	0%	0%	0%
Axillary Nodes Negative	49%	100%	100%	100%	100%
Adjuvant therapy Tamoxifen	7%	0%	0%	100%	0%
Adjuvant therapy Chemotherapy	31%	0%	0%	0%	0%
Adjuvant therapy Both	7%	0%	0%	0%	0%
Median followup	6.7 years	10 years	8.4 years	10.9 years	Minimum of 5 years
Genetic signature Good	61%	63%	34%	51%	32%
Genetic signature Intermediate	Not applicable	Not applicable	Not applicable	22%	14%
Genetic signature Poor	39%	37%	64%	27%	54%

### 1.3.2.1 Frozen Tissue Specimens

A group from the Netherlands Cancer Institute in Amsterdam identified a 70 gene panel that was evaluated in a training set of 78 breast cancers measuring less than 5 cm in size associated with negative axillary nodes in patients less than 55 years of age, by characterizing the molecular signature of patients who did and did not have systemic relapse within five years (19). The “good” and “poor” signature profiles outperformed established clinical criteria. The technology involved use of an RNA expression profile in fresh frozen tissue (Rosetta Inpharmatics; 25,000 transcripts). This methodology was subsequently evaluated in a validation set of 295 consecutive patients with stage I or II breast cancer younger than 53 years old, of whom 151 had lymph-node–negative disease and 144 had lymph–positive disease



(Table 3) (20). Adjuvant therapy was given to 44% of all patients, including 6% of the lymph node negative group and 83% of the lymph node positive group; adjuvant therapy included chemotherapy in 31%, hormonal therapy in 7%, and both in 7%. Among the 295 patients, 180 had a good-prognosis signature (61%) and 115 had a poor-prognosis signature (39%). At 10 years, the probability of remaining free of distant metastases was 51% ( $\pm 5\%$ ) in the group with a poor-prognosis signature and 85% ( $\pm 4\%$ ) in the group with a good-prognosis signature. Multivariate Cox regression analysis showed that prognosis profile was a strong independent factor predicting disease outcome. For the lymph node negative group, the estimated 5-year distant disease free survival was 95% ( $\pm 3\%$ ) for the good signature group and 66% ( $\pm 5\%$ ) for the poor signature group. When comparing the expression profiling with established clinical criteria in lymph node negative disease, the expression profile assigned many more to the low-risk group (good-prognosis signature) than did the clinical criteria (40% vs. 15% for St. Gallen criteria and 7% for NIH criteria). In addition, low-risk patients identified by gene-expression profiling had a higher likelihood of metastasis-free survival than those classified according to the St. Gallen or NIH criteria, and high-risk patients identified by gene-expression profiling tended to have a higher rate of distant metastases than did the high-risk patients identified by the St. Gallen or NIH criteria. This result indicates that both sets of the currently used clinical criteria misclassify a substantial number of patients. Indeed, the high-risk group defined according to the NIH criteria included many patients who had a good-prognosis signature and a good outcome. Conversely, the low-risk group identified by the NIH criteria included patients with a poor-prognosis signature and poor outcome. Similar subgroups were identified within the high-risk and low-risk groups identified according to the St. Gallen criteria. Since both the St. Gallen and the NIH subgroups contain misclassified patients (who can be better identified through the prognosis signature), these patients would be either overtreated or undertreated in current clinical practice. An external validation study of the 70 gene profile was subsequently performed by the TRANSBIG Network, and a preliminary analysis of this study has been presented (21). This study included frozen tumor specimens from 301 patients with node-negative breast cancer who had primary treatment rendered at six non-Dutch centers in the United States and Europe, and who received no systemic adjuvant therapy. Sixty-three percent had high-risk profile (consistent with the 60% incidence for the original Dutch report), and this signature was associated with a 1.8-fold increased risk of systemic recurrence and 2.5-fold

increased risk of death. However, there was significant heterogeneity between original Amsterdam and external validation samples, and the overall performance of the prognostic signature was inferior in the external validation set. Another group from the Erasmus Medical Center in Rotterdam reported their experience with RNA expression profiling using a different platform (Affymetrix Human U133a GeneChip; 23,000 transcripts), which included 286 node-negative breast cancer patients who received no adjuvant systemic therapy (including 115 patients in the training set and 171 in the validation set) (22). In the training group of 115 patients (80 ER-positive), a 76-gene signature (60 for ER-positive and 16 for ER-negative) was identified that was predictive of distant metastases within 5 years. A high-risk gene signature was associated with a significantly increased risk of distant metastases within 5 years when adjusted for known prognostic variables (hazard ratio [HR] 5.78;  $p < 0.00003$ ), including in subgroups of patients with tumors between 1-2 cm in size (N=79; HR 14.1,  $p < 0.00003$ ), premenopausal women (n=84; HR 9.6;  $p < 0.0002$ ), and postmenopausal women (N=87; HR 4.04,  $p = 0.0017$ ). In the subgroup of 42 ER-negative patients in the validation set, a 16 gene profile had strong predictive value (HR 8.74,  $p = 0.012$ ).

#### 1.3.2.2 Formalin-Fixed Paraffin Embedded Specimens

Another technique that utilizes a 21-gene panel RT-PCR assay that can be performed on formalin-fixed paraffin embedded tissue (FPET). The 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. It uses three specific reagents for each gene results in high specificity. The assay (Oncotype DX™ Breast Cancer Assay, Genomic Health, Redwood, CA; <http://www.genomichealth.com/oncotype>) is performed within 10-14 days, and has received CLIA approval in the United States. The training set that was used to develop this assay consisted of three studies involving 449 patients from three groups, including 224 patients treated with node-negative, ER-positive disease treated with tamoxifen (23), 79 patients with 10 or more positive axillary nodes (24), and 146 additional patients with operable breast cancer (25). Two hundred fifty candidate genes were selected from the literature for study in this training set. Univariate analysis of 185 cancer related genes indicated that 41 genes were associated with relapse free survival ( $p < 0.05$ ), including 22 with  $p < 0.01$ , 10 with  $p < 0.001$ . Expression of many genes were tightly correlated. A

“Recurrence Score” (RS) was calculated using a weighted algorithm based upon gene expression profiles of groups of genes (e.g., proliferation, ER, Her2, and invasion-associated genes) and some individual genes that emerged as predictive in the training set (e.g., CD69, BAG-1, GSTM-1) (Table 4). Each group of genes receives a RS of up to 15, with each unit of RS equivalent to a two-fold increase in RNA expression level. The score for each gene group is weighted toward the proliferation, Her2, and ER-associated genes using the adjustment outlined in Table 4. In the training set, groups were identified that had a high (RS  $\geq$  31), low (RS  $<$ 18), or intermediate (RS 18-30) risk of systemic recurrence.

**Table 4: Genomic Health Recurrence Score (RS) Algorithm (Oncotype DX)**

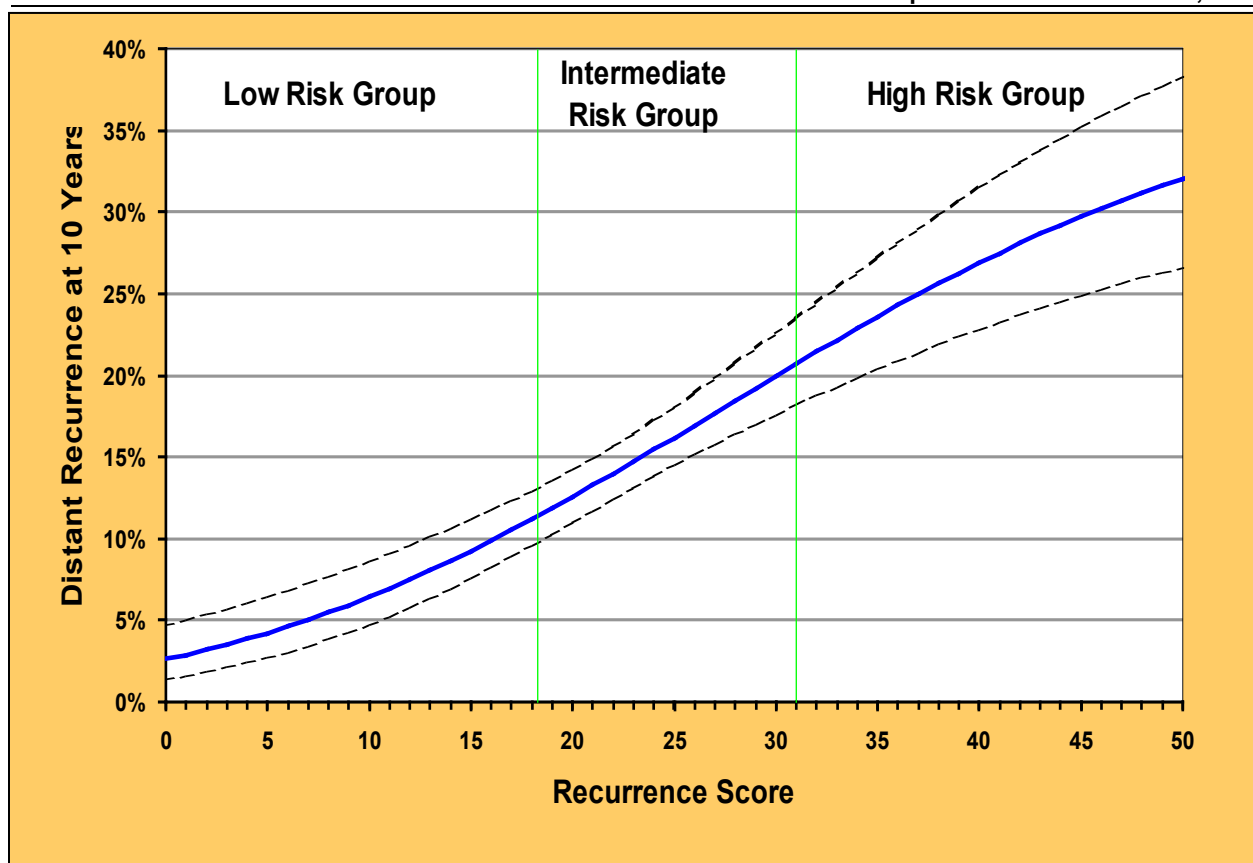
<b>Group</b>	<b>Genes</b>	<b>Adjustment</b>
Proliferation	Ki67, STK15, survivin, cyclin B1, MYB2	+1.04
<b>Her2</b>	Her2, Grb7	+0.47
<b>ER</b>	ER, PR, BCL-2, SCUBE2	-0.34
<b>Invasion</b>	Stromelysin-3, CAT	+0.10
<b>CD68</b>	CD68	+0.05
<b>BAG-</b>	BAG-1	-0.07
<b>GSTM-1</b>	GSTM-1	-0.08

The Genomic Health RS was subsequently evaluated in a validation set that consisted of a subset of patients with ER-positive, node negative breast cancer enrolled on NSABP trial B-14 (23, 26). Of the 2167 patients enrolled on this trial who were either randomized or registered to receive tamoxifen, tumor blocks were available for 675 cases with at least 5% invasive cancer; there was no difference in patient characteristics or outcome for those who did or did not have blocks available for study. The mean age of the study population was 52.4 years, mean tumor size was 2 cm, and median follow up was 10.9 years. The results of the analysis are contrasted with other studies in Table 3, and outlined in greater detail in Table 5. The primary study endpoint was distant recurrence free survival (DRFS) at 10 years; for the primary endpoint, patients were censored at the time of development of contralateral breast cancer, second non-breast cancer, or death without breast cancer recurrence.

**Table 5. Genomic Health Recurrence Score in B-14 Trial (N=668)**

Recurrence Score (1–100)	Risk group	No. (%)	10-year distant recurrence rate (95% C.I.)	5-year distant recurrence rate (95% C.I.)
< 18	Low	338 (51%)	6.8 % (4–9.6%)	2.1% (0.6-3.7%)
18 –30	Intermediate	149 (22%)	14.3% (8.3–20.3%)	9.2% (4.4-14%)
>= 31	High	181 (27%)	30.5% (23.6–37.4%)	22.1% (15.9-28.2%)

Approximately 50% of patients were classified as having a low risk RS (<18), a group that experienced only a 6.8% distant recurrence rate at 10 years. There was a significantly inferior 10-year DRFS rate for those with a high RS compared to those with a low RS ( $p < 0.00001$ ). Cox proportional hazard model indicated that the only factor that emerged as significant variable at 10 years was the RS (hazard ratio [H.R.] 3.21, 95% confidence intervals [C.I.] 2.23, 4.61;  $p < 0.00001$ ). A continuous model was also developed that plots RS (X-axis) vs. 10-yr DRFS (Y-axis), and allows estimation of 10-year distant recurrence rate for specific RS. Information regarding 5-year distant recurrence rate is also provided in Table 5. These data illustrate that about one-third of distant relapses occurred between year 5 and 10 for patients with an intermediate or high RS tumor; in contrast, about two-thirds of relapses in the low RS group occurred between years 5 and 10.



**Figure 1. Genomic Health Recurrence Score as a Continuous Variable.**

Although the arbitrarily defined cut points as defined in Table 5 identified groups with disparate and substantially different risks of relapse that are clinically relevant, other analysis indicates that the RS also predicts relapse as a continuous variable (Figure 1). This point has relevance for the risk groups defined in this trial as described in Section [1.4](#).

The Genomic Health RS was also evaluated in 149 evaluable patients with node-negative breast cancer who were referred to MD Anderson Cancer Center over a 20-year period and who did not receive adjuvant chemotherapy (27). Tumor blocks were available for only 149 of the 220 patients who met these criteria during this time period. The characteristics of the study population are contrasted with the B-14 validation set in Table 3. In this study, RS was not predictive of distant relapse. An unusual feature of this study was that patients with good nuclear grade had a worse outcome compared with patients with intermediate or high nuclear grade. This study points out that the distinct assays may need to be developed for ER-positive and ER-negative cancers. The *Oncotype DX* assay is CLIA-approved only for patients with ER-positive, node negative breast cancer.

Finally, the reliability of the Genomic Health RS was also validated in a population-based case-control study (28). The study included patients with node-negative breast cancer treated at 19 Kaiser Permanent hospitals between 1985 and 1995 who were less than 75 years of age and received no adjuvant chemotherapy. Of the 4964 patients identified, there were 227 eligible cases who died of breast cancer and 446 eligible controls who did not die of breast cancer and were matched for clinical characteristics. The results indicated that RS score was the strongest predictor of breast cancer death in multivariate analysis (odds ratio for death 6.5,  $p=0.002$ ), that RS significantly predicted breast cancer death in patients treated with or without tamoxifen, and that the risk of breast cancer death at 10 years was similar in this population as in the B-14 population.

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### 1.3.3 Identifying Molecular Signatures Associated with Response to Treatment (ie, Predictive Factor)

A follow up report by the NSABP and Genomic Health provided further information regarding the predictive value the 21 gene *Oncotype DX* panel. The study included 357 of 373 patients with ER-positive node negative breast cancer in the placebo arm of the B-14 trial, and 424 of 430 patients treated with tamoxifen plus CMF (or MF in trial B-20) (29). In the B-20 trial, the addition of CMF chemotherapy to tamoxifen significantly improved 5-year disease free survival (DFS; 89% vs. 85%;  $p=0.001$ ) and distant recurrence-free survival (DRFS; 91% vs. 87%;  $p=0.006$ ). Similar results were evident for MF chemotherapy. Overall, the addition of CMF to tamoxifen reduced the event rate by 35% for DFS, and 33% for DRFS (4). When the data were analyzed by RS risk group, there was a significant interaction between RS and benefit from chemotherapy (interaction  $p=0.0368$ ); chemotherapy significantly reduced the risk of distant recurrence in the high RS group (hazard ratio 0.258), but not in the intermediate or low risk groups. In addition, when evaluating the effect of tamoxifen by RS group in patients treated with tamoxifen only or a placebo, there was a significant interaction between tamoxifen benefit and RS ( $p<0.001$ ); RS was found to be an independent prognostic factor in the placebo arm, and tamoxifen reduced the risk of recurrence only in patients with a low or intermediate recurrence score.

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The predictive accuracy of the RS in the tamoxifen alone arm of this analysis does not provide an independent validation set and must be interpreted with caution, as the tamoxifen arm of the B20 trial was used as the training set for development of the RS. Nevertheless, the analysis suggests that RS may be used to identify individuals who are more likely to derive benefit from chemotherapy.

**Table 6. Genomic Health Recurrence Score and Response to Chemotherapy in B-20 Trial (N=651)**

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Risk group (RS ranges)	No. Patients	10-year DRFS Tam	10-year DRFS Tam + Chemotherapy	Hazard Rate (and 95% C.I.) for Distant Recurrence in Patients Treated with Chemotherapy	P-Value
Low (< 18)	353 (54%)	97%	96%	1.312 (0.456, 3.777)	0.76
Intermediate (18-30)	134 (21%)	91%	89%	0.613 (0.236, 1.59)	0.71
High (> 30)	164 (25%)	61%	88%	0.258 (0.126, 0.528)	0.001

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1.4 Rationale for the Proposed Study

Clinical breast cancer research over the past 30 years has focused on expanding indications for adjuvant chemotherapy, and has been successful in establishing that even patients expected to have a very good prognosis with hormonal therapy alone derive some small absolute benefit from adjuvant chemotherapy (13). Previous attempts to refine prognostic and predictive factors using standard histopathologic criteria (e.g., tumor grade), indices of proliferation (S-phase fraction, Ki-67) or genomic instability (e.g., DNA ploidy), or single gene/protein expression profiles (e.g., Her2/neu, p53 expression) have not been sufficiently reliable to merit routine clinical use in patients with low to moderate-risk disease (12, 30).

Although several distinct molecular signatures identified by differing methodologies have been developed that may serve as useful prognostic markers, we have chosen to utilize Oncotype DX Breast Cancer Assay in this trial for the following reasons: (1) It is a standardized, multi-gene RT-PCR-based molecular technique performed in a single laboratory, (2) It may be applied to tissue specimens routinely processed in clinical pathology laboratories, (3) It has received CLIA approval in the United States to "...assess the likelihood that a women's breast cancer will...recur..." ([www.genomichealth.com](http://www.genomichealth.com)), (4) It more reliably predicts prognosis than standard clinical criteria in patients with ER-positive, node-negative disease than standard clinical criteria, including tumor size, histologic grade, and age, (5) Its performance has been validated in a large population-based study, (6) Preliminary data indicates that it predicts benefit from adjuvant chemotherapy. Patients with ER-positive, axillary node negative breast cancer account for nearly one-half of all breast cancer diagnosed in the United States, and is the group in which more patients unnecessarily receive adjuvant chemotherapy.

Patients with ER and/or PR-positive, axillary lymph node negative breast cancer who meet standard clinical criteria for adjuvant chemotherapy, who are medically suitable candidates for chemotherapy, will be eligible to participate in this trial. Although these patients meet established clinical criteria for chemotherapy, the typical patient may be expected on average to derive a 3% improvement in 10-year DFS from such treatment. In this trial, the Oncotype DX Breast Cancer Assay will be utilized to prospectively guide treatment decisions for low risk and high risk tumors. In addition, the trial will attempt to refine the precision of the test

in individuals who have intermediate risk tumors where the assay result is indeterminate in its ability to identify whether chemotherapy is beneficial. Patients will be assigned to treatment according to the schema indicated below. The definitions of low, intermediate, and high risk utilized in this trial are slightly different than those previously defined.

- **“Secondary Study Group-1”** (RS  $\leq$  10): Patients will be assigned to receive hormonal therapy alone. A RS of  $\leq$  10 was selected as the threshold for low risk because it is associated with a 10 year distant recurrence rate on average of  $\leq$  5% if treated with tamoxifen alone, and because no benefit from chemotherapy has been demonstrated in this group.
- **“Primary Study Group”** (RS 11-25) Patients will be randomly assigned to receive chemohormonal therapy vs. hormonal therapy alone. The risk of distant recurrence if treated with tamoxifen alone is sufficiently high to recommend chemotherapy (approximately 10% for the entire group), but chemotherapy has not been established to be clearly beneficial in this specific group.
- **“Secondary Study Group-2”** (RS  $\geq$  26): Patients will be assigned to receive chemotherapy plus hormonal therapy. A RS of  $\geq$  26 was selected as the threshold for high risk because it is associated with a 10 year distant recurrence rate of on average of 20% or more, and because chemotherapy has been shown to be beneficial in this group.

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The primary clinical endpoint will be disease-free survival in patients in the “Primary Study Group.” Co-primary endpoints will include distant relapse-free interval, relapse free interval, and overall survival (as defined in Section 6). The trial will be adequately powered to determine whether hormonal therapy is not inferior to chemotherapy plus hormonal therapy in patients in the “Primary Study Group.” Should hormonal therapy be shown not to be inferior to chemohormonal therapy, it will spare the need for chemotherapy in up to 40% of women with ER-positive, axillary node negative breast cancer. In addition, all patients identified to have a non-elevated RS in this trial will be spared the need for adjuvant chemotherapy.

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This study will include only patients with Her2/neu negative disease. Only 8% of patients enrolled in the B14 validation study had Her2/neu positive disease, and < 1% with a RS of < 26 demonstrated Her2/neu amplification. The outcomes for the recurrence score categories used in the PACCT trial for distant recurrence-free survival (DRFS) and disease free survival (DFS) are shown in Table 7 (10-year outcomes) and Table 8 (5 year outcomes) (29). For the analyses described in Tables 6-8, the following definitions are used: (1) disease-free survival (DFS) - time to first local, regional, or distant recurrence, second primary cancer, or death due to any cause, and (2) distant recurrence free survival (DRFS) - time to first distant recurrence or death from cancer (contralateral breast cancers, other second primary cancers, and deaths due to other cancers were censored; local and regional recurrences were ignored).



Table 7:

Genomic Health Recurrence Score and Response to Chemotherapy in B20 Trial (N=651) by RS Distribution in PACCT Trial (10 year outcomes)

RS	No. Patients	Tam 10-year DRFS	Tam + Chemo 10-year DRFS	H.R. (& 95% CI) For DRFS Event by Addition of Chemo	P-Value	Tam 10-year DFS	Tam + Chemo 10-year DFS	H.R. (& 95% CI) For DFS Event by Addition of Chemo	P-Value
< 11	177 (27%)	98%	95%	1.788 (0.360, 8.868)	0.471	77%	85%	0.605 (0.317, 1.153)	0.124
11-25	279 (43%)	95%	94%	0.755 (0.313, 1.824)	0.531	81%	76%	1.106 (0.671, 1.823)	0.691
> 25	195 (30%)	63%	88%	0.285 (0.148, 0.551)	<0.0001	53%	75%	0.446 (0.270, 0.738)	0.0012

Rev. 9/07 Abbreviations: H.R. - hazard ratio; CI - confidence intervals; DRFS - distant recurrence-free survival; DFS - disease free survival; Tam - tamoxifen; chemo - chemotherapy (which included cyclophosphamide, methotrexate, 5-fluorouracil or methotrexate/5-fluorouracil.

Table 8:

Genomic Health Recurrence Score and Response to Chemotherapy in B20 Trial (N=651) by RS Distribution in PACCT Trial (5-year outcomes)

RS	No. Patients	Tam 5-year DRFS	Tam + Chemo 5-year DRFS	H.R. (& 95% CI) For DRFS Event by Addition of Chemo	P-Value	Tam 5-year DFS	Tam + Chemo 5-year DFS	H.R. (& 95% CI) For DFS Event by Addition of Chemo	P-Value
< 11	177 (27%)	98%	99%	1.788 (0.360, 8.868)	0.471	92%	95%	0.605 (0.317, 1.153)	0.124
11-25	279 (43%)	97%	97%	0.755 (0.313, 1.824)	0.531	94%	91%	1.106 (0.671, 1.823)	0.691
> 25	195 (30%)	69%	94%	0.285 (0.148, 0.551)	<0.0001	63%	85%	0.446 (0.270, 0.738)	0.0012

Rev. 9/07 NSABP data indicates the following incidence of Her2/neu amplification in 668 patients evaluated in the B14 validation study: positive 55 (8%), missing 8 (1%), negative 605 (91%). The proportion of patients with Her2/neu amplification by RS as categorized in the B14 validation study is as follows: RS < 18 - 0/334; RS 18-31 – 5/147 (3%); RS > 31 – 50/179 (28%). The distribution for the RS groups as defined in the PACCT trial for the B14 validation study is as follows: RS < 11 – 0/159, RS 11-25 – 2/283 (<1%); RS > 25 – 53/218 (24%). For this reason, we have altered eligibility to include only patients with Her2/neu negative disease, which will serve to reduce the number of patients screened in order to identify patients with a RS of 11-25 from 11,553 to10,046.

### 1.5 Correlative Science

Although the purpose of PACCT-1 is to validate the utility of the Genomic Health Recurrence Score, tumor RNA will be banked in addition to FPET tissue microarrays, plasma, and germ-line DNA. By virtue of the chemotherapy vs. no chemotherapy comparison in patients in the primary study group, we will be able to assess the utility of other “Clinical Cancer Tests” as they evolve (e.g., other genomic and/or epigenomic technologies, tumor and/or serum proteomic patterns, single nucleotide polymorphisms in drug and/or estrogen metabolizing enzymes, etc). Toward this end, all patients participating in this trial will be asked to donate specimens of tumor, lymphocytes, and serum for banking. As previous experience indicates that about 90% of patients who donate biological specimens consent to unspecified future research, it is anticipated that a number of additional studies will be planned in the future as technology evolves and as the trial matures. The background and rationale for selecting these biological specimens for long-term storage is provided in [Appendix- VIII](#), as well as the process required for utilizing these specimens for future research.

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### 1.6 Quality of Life Component

The quality of life component for PACCT-1 proposes to evaluate differences between women with breast cancer receiving hormonal treatment alone (Arm B) versus women receiving chemotherapy followed by hormonal treatment (Arm C) on the following domains: (1) cognitive impairments, (2) fatigue, (3) fear of recurrence, (4) endocrine symptoms and (5) overall health-related quality of life (HRQL). Our primary question of interest is the extent to which chemotherapy plays a causal role in the development of cognitive impairments. PACCT-1 offers a unique and previously unavailable opportunity to assess breast cancer patients from the study group who are randomized to receive hormonal therapy alone versus chemotherapy + hormonal therapy. Prior to the availability of genetic testing to determine risk of recurrence as is used in TAILORx, randomization to chemotherapy versus no chemotherapy would not be ethical. Given the randomized design, the assessment of women enrolled on this trial will allow us to more definitively evaluate the extent to which chemotherapy contributes to the development of perceived cognitive dysfunction. A significant weakness of research on chemotherapy-related cognitive function to date has been the lack of an adequate control group, leading to results that are confounded by systematic differences in disease status (95). Women participating on TAILORx who are randomized to hormonal treatment alone will provide a comparison group that is comparable with regard to disease, sociodemographic characteristics, educational level, symptoms of mood disorders and other characteristics that may affect cognitive function. Previous studies in this area have been confounded by systematic differences in disease status, and so the TAILORx design will allow us to draw definitive conclusions regarding the impact of chemotherapy on cognitive impairment.

As secondary endpoints, we are interested in the contribution chemotherapy makes to the severity of fatigue and endocrine symptoms. We seek to evaluate the extent to which chemotherapy exacerbates or attenuates fear of recurrence. We are also interested in the long-term trajectory of these symptoms throughout and following treatment. Last, we seek to evaluate the trajectory of HRQL as

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women transition from treatment to survivorship status and to assess the overall effect of these symptoms on HRQL post-treatment.

The TAILORx trial includes a correlative science component that holds the potential to advance our understanding of genetic markers for susceptibility to disease- and treatment-related symptom burden. TAILORx participants bank tumor RNA, FPET tissue microarrays, plasma, and germline DNA. Banked biological specimens can be evaluated in future studies as “Clinical Cancer Tests” evolve (e.g. other genomic and/or epigenomic technologies, tumor and/or serum proteomic patterns, single nucleotide polymorphisms in drug and/or estrogen metabolizing enzymes, etc.) to identify genetic predictors of cognitive impairments associated with cancer and cancer treatments. At the ASCO 2004 Annual Meeting Plenary session, Sloan presented compelling data from a Gastrointestinal Cancer Intergroup phase III trial for metastatic colorectal cancer that demonstrated differences in quality of life among patient groups that differed based on the presence of genetic variants. Specifically, Sloan and colleagues (90) demonstrated a link between genetic structure and fatigue. Ahles (2007) has postulated that genes associated with brain function, neural or vascular repair in the central nervous system, drug metabolism, or blood-brain transporter systems might be important for predicting which patients will be more vulnerable to chemotherapy-related cognitive impairments. The prospective collection of cognitive function among TAILORx participants simultaneously with the collection of baseline plasma and genomic material offers the exciting opportunity for future research projects to identify genetic predictors for cognitive impairment among individuals with cancer. The identification of genetic predictors for cognitive impairment would significantly advance the science in this area and could lead to more targeted interventions for individuals at greatest risk for long-term cognitive deficits following anti-cancer treatment.

#### 1.6.1 Evidence for the Clinical Significance of Chemotherapy-Related Cognitive Impairment

Many cross-sectional studies have demonstrated impairments in cognitive function among adults who have received chemotherapy in comparison to adults with cancer who did not undergo chemotherapy. Schagen et al. (84) found that women with breast cancer who received adjuvant chemotherapy were more likely to report difficulties with concentration and memory compared to breast cancer patients who did not. When patients’ underwent neuropsychological assessment, those receiving chemotherapy were significantly more likely to demonstrate cognitive impairment compared to those who did not receive chemotherapy. Neuropsychological impairment was not affected by mood, fatigue, or time since diagnosis (84). Brezden and colleagues (42) found that breast cancer patients receiving adjuvant chemotherapy had worse memory and language functioning compared to healthy controls, even after statistically controlling for age, education, and menopausal status. Between-groups differences were not found on a measure of mood, suggesting that the cognitive differences were not related to a mood disturbance. In the same study, a group of patients who had completed chemotherapy at least one year earlier had cognitive tests scores that were between scores from the current chemotherapy and healthy control groups suggesting

that these impairments may last for months following treatment completion (42). Ahles et al. (37) examined breast cancer and lymphoma survivors who were a minimum of 5 years post-treatment and disease free and found that survivors treated with systemic chemotherapy scored significantly lower on neuropsychological testing than survivors who received local therapy only ( $p < 0.04$ ). Ahles and colleagues' findings indicated that a subgroup of survivors experience long-term cognitive deficits, which tend to be subtle in nature. Despite this growing body of evidence, findings from cross-sectional studies are difficult to interpret because patients receiving chemotherapy vary systematically from those receiving local therapy alone in terms of disease-related factors. Thus, the role of chemotherapy in the development of cognitive dysfunction cannot be teased apart from confounding factors.

As more research has been conducted in this area, meta-analyses have aggregated research findings to obtain a better understanding of chemotherapy-related cognitive impairment. Anderson-Hanley and colleagues (38) conducted a meta-analysis of the neuropsychological effects of systemic therapies for cancer and found significant negative effect sizes for patients compared to normative data and control patient data on several cognitive domains, including executive function, verbal memory, and motor function. Even when samples were limited to those with "less severe" diagnoses and treatments, the effect sizes remained significant. However, when they calculated effect sizes for the limited number of studies that included a pre-treatment assessment of cognitive function they did not find evidence of changes in cognitive function. Falletti and colleagues (52) conducted a meta-analysis based on 6 studies that examined cognitive function among breast cancer patients receiving adjuvant chemotherapy. Results from cross-sectional studies indicated a negative effect size in each cognitive domain examined with a significant relationship between effect size and time since completing chemotherapy. However, findings from prospective studies indicated a positive effect size, or improvement in cognitive function, from pre-chemotherapy to 3 weeks and one year post-chemotherapy. These findings support the need for prospectively designed studies to fully understand the trajectory of cognitive function throughout treatment for cancer.

Wefel and colleagues (110) conducted the first prospective study among 18 breast cancer patients who were planning to undergo chemotherapy. In their sample, 33% of participants demonstrated cognitive impairments prior to starting treatment, 61% demonstrated a decline in their cognitive function relative to their baseline performance 3 weeks post-chemotherapy, and at 1 year post-chemotherapy 50% of patients who declined demonstrated improvement. This finding that one-third of participants had evidence of cognitive impairment prior to chemotherapy was surprising to clinicians, researchers, and patient advocates who had operated on the assumption that cognitive impairments during cancer treatment were attributable to chemotherapy – hence the term "chemo-brain"

which has evolved from patient advocacy groups. Upon the presentation of Wefel and colleagues' results, we examined data collected from our own larger prospective trial of breast cancer patients receiving adjuvant chemotherapy and found similar results. We administered a 90-minute neuropsychological assessment and patient-reported outcomes assessment prior to chemotherapy, at Cycle 4 Day 1, and at a 6 month follow-up (107). Among our sample of 57 breast cancer patients, prior to chemotherapy 17-29% demonstrated cognitive impairments depending on the criteria used to classify participants as impaired (51). These findings underscore the importance of utilizing a prospective, longitudinal design to understand the extent of impairment due to chemotherapy versus disease burden and other contributing factors, particularly since the pathophysiology is unknown (37,81,85). While prospectively designed studies offer a more solid evidence base for an association between chemotherapy and cognitive impairment, methodological challenges such as the lack of a comparable control group with the same disease characteristics and, therefore the same disease-related symptom trajectory, limit assumptions about causality. The proposed trial complies with recommendations for advancing our scientific knowledge base in the area of chemotherapy-related cognitive impairments by employing a prospective design that includes a pre-treatment assessment and utilizing a comparison group (98).

The primary hypothesis for this study is that women randomly assigned to receive chemotherapy + hormonal therapy will have a higher level of self-reported cognitive impairments than women randomized assigned to receive hormonal therapy alone. Chemotherapy-induced menopause has been suggested as a possible etiology for cognitive decline, however, to date the extent of impairment between pre- and post-menopausal breast cancer patients has been found to be similar (97). The inclusion of pre- and post-menopausal women in our sample will allow us to examine differences in the extent of decline based on menopausal status among women assigned to receive chemotherapy.

The relationship between estrogen and cognitive function is complex and has warranted numerous studies, as discussed in a literature review published by Shilling et al. (88). Few studies have examined the effect of hormone therapy for breast cancer on cognition. Schagen and colleagues (84) did not find differences between breast cancer patients who received tamoxifen and those who did not. Jenkins and colleagues (61) examined 94 women from the Anastrozole, Tamoxifen or Combined (ATAC) trial in comparison to 35 women without breast cancer. ATAC participants demonstrated mild impairments on a processing speed task and a measure of immediate verbal memory. The proposed trial will allow us to prospectively evaluate the trajectory of perceived cognitive function among women randomized to receive hormonal therapy alone. We acknowledge that women assigned to receive hormonal therapy may experience changes in cognitive function associated with hormonal treatment, which will be taken into

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consideration in interpreting any differences observed between participants treated on Arm B versus Arm C.

1.6.2 Evidence for the Clinical Significance of Cancer-Related Fatigue

Cancer-related fatigue is perhaps one of the most common symptoms associated with cancer and has been associated with significant decrements in quality of life (76). Fatigue among individuals with cancer can be related to the disease itself and metabolic changes associated with cancer, as well as from the effects of treatment (94). Some investigators have conceptualized cognitive impairments as a component of fatigue, labeling this symptom “attentional fatigue” (46). Vogelzang and colleagues (101) found that among patients treated with chemotherapy or radiotherapy, more than one-third reported that fatigue interfered with their ability to work, relationships with others, and physical and emotional well-being. Many cancer survivors may experience fatigue for months or even years post-treatment, even those who remain disease-free (87).

The collection of genetic material as part of the TAILORx trial design will allow future research to potentially identify genetic predictors of treatment-related fatigue. Because fatigue is commonly a symptom of cancer and a side effect of cancer treatment, it is virtually impossible to tease apart the extent to which fatigue is a disease-related versus treatment-related (for review see Wagner, Cella & Peterman, 2003). This is an important distinction when weighing the risks versus benefits of undergoing chemotherapy, particularly when chemotherapy may only provide marginal survival benefit. Given the randomized assignment to treatment, this trial offers a unique opportunity to quantify the extent to which chemotherapy contributes to fatigue among individuals with breast cancer.

Research on cognitive impairments among individuals with cancer has consistently demonstrated an association between fatigue severity and cognitive function (37,60). Among our own sample of breast cancer patients undergoing chemotherapy, we found modest correlations between perceived cognitive function and fatigue (.51 - .62; unpublished data). Based on this association, it is important to include fatigue as a secondary endpoint in the proposed trial. We hypothesize that women assigned to receive chemotherapy plus hormonal therapy will report a greater level of fatigue than those assigned to only receive hormonal treatment.

1.6.3 Evidence for the Clinical Significance of Fear of Recurrence

Approximately 60-99% of women with breast cancer report ongoing fears regarding the possibility of a breast cancer recurrence, even among samples up to 5 years post-treatment (71,78,92,100,103). Previous studies have indicated that more physically and psychologically aversive treatment protocols, such as chemotherapy or mastectomy, may be associated with a higher fear of recurrence (62,86), however other studies have not replicated this finding (48,71). It seems plausible that the measured increase in fear of recurrence among women undergoing intensive treatments could have been due

to a more generalized increase in overall distress associated with more aggressive disease in comparison to those receiving less aversive treatment. Evidence for increased distress at the completion of chemotherapy in the “re-entry” literature suggests that women with breast cancer perceive a protective benefit from chemotherapy, which reduces fear of recurrence (75). Distress at treatment termination has been so well-documented that the end of chemotherapy has become a common entry point for introducing coping and stress management interventions.

The ECOG protocol E2Z04 (Study Chair: V. Champion) is a currently active study which is examining psychosocial characteristics of women with breast cancer who were previously treated on a cooperative group protocol. Preliminary results from this protocol have demonstrated that women who were younger at diagnosis ( $\geq 45$  years of age) have a higher fear of recurrence than women who were 55-70 years of age at diagnosis (112).

The proposed trial offers a unique opportunity to evaluate whether chemotherapy exacerbates or attenuates fear of recurrence, without confounding disease characteristics and other factors which may directly influence fear of recurrence. Based on existing literature and what we have learned thus far from E2Z04, we hypothesize that premenopausal women randomly assigned to hormone therapy will experience a higher fear of recurrence than premenopausal women assigned to chemotherapy + hormonal treatment. We also hypothesize that younger age will be associated with a higher fear of recurrence. In addition, women with cancer may perceive that their cognitive function is compromised by a preoccupation with health-related concerns. The inclusion of this secondary endpoint will allow us to explore whether an association exists between perceived cognitive impairments and fear of recurrence. If an association is demonstrated, future clinical research could evaluate whether interventions for fear of recurrence lead to an improvement in perceived cognitive function.

#### 1.6.4 Evidence for the Clinical Significance of Endocrine Symptoms and Health-Related Quality of Life

Few randomized trials have evaluated the long-term impact of hormonal treatment on quality of life and the extent to which adjuvant chemotherapy exacerbates symptom burden from subsequent hormonal therapy. Fallowfield and colleagues (53) examined the quality of life of postmenopausal women on the ATAC trial. The investigators found an increase in patient-reported endocrine symptoms from baseline to the 3 month assessment, after which endocrine symptoms stabilized at follow-up assessments. The sample of participants examined by Fallowfield and colleagues did not receive adjuvant chemotherapy prior to hormonal treatment. Previous trials of adjuvant chemotherapy have failed to measure the impact of treatment on endocrine-related symptoms. In the recent Adjuvant Breast Cancer (ABC) chemotherapy trial, women who received adjuvant tamoxifen were randomized to standardized chemotherapy

(87% received CMF) versus none. Of the 199 women who participated in the quality of life sub-study, women who received chemotherapy reported more problems with chronic effects in particular those relating to vasomotor symptoms (e.g. night sweats that continued for up to 30 months; Adjuvant Breast Cancer Trials Collaborative Group, 2007). These results suggest that an assessment of endocrine-related symptoms among our study sample may provide important data pertaining to differences in symptom burden among women assigned to hormonal therapy alone or chemotherapy + hormonal therapy.

While it is recognized that the majority of the acute effects of chemotherapy (e.g., nausea, vomiting, diarrhea, stomatitis, alopecia, and neutropenia) will resolve, there is increasing concern that the sub-acute effects and long-term sequelae of chemotherapy may have a lasting impact on the quality of life of the breast cancer survivors. Modern day adjuvant chemotherapy is associated with premature menopause, weight gain, arthritic complaints, mood disorders, fatigue, and cognitive effects that may potentially impair the quality of life of women. Some women who are < 40 years of age (estimates between 13-38%) and the vast majority of women over the age of 40 (estimates between 57-96%) will experience premature menopause following adjuvant chemotherapy (53,77). Premature menopause is associated with increased menopausal symptoms, such as hot flashes, genitourinary problems, and sexual dysfunction. Additionally, women following premature menopause will have accelerated bone mineral density loss (43,59). Weight gain has been reported in more than 50% of women receiving adjuvant chemotherapy with mean gains of 2.5-5 kilos (50,57). Weight gain appears to be more common in pre-menopausal women who experience menopause secondary to chemotherapy. This type of weight gain is likely to have an influence on a women's physical health. With increasing use of dose-intensive and taxane-based regimens, previously unobserved sequelae such as neuropathy and myalgias are increasingly common. Many of these symptoms are very slow to resolve and may have long-term consequences for women. Additionally, moderate to long-term effects of fatigue are also increasingly recognized (41,68). Such fatigue has been associated with a decrease in daily functioning. Cognitive impairments discussed above may also have a lasting impact on women's functional ability.

Ganz et al. (56) demonstrated the potential negative effect of chemotherapy on long-term quality of life of breast cancer survivors. In a single arm observational study, investigators identified 1,336 survivors between 5-10 years following their initial diagnosis of breast cancer (55,56). Of these 763 (57%) disease-free survivors completed a quality of life assessment with a mean follow-up of 6.3 years from diagnosis. Survivors who had received adjuvant chemotherapy or tamoxifen or both had a worse quality of life compared to those who had not received adjuvant systemic therapy with respect to physical functioning (p = 0.03), bodily pain (p = 0.01), social functioning (p=0.02) and general health (p = 0.03).



Few randomized trials have evaluated long-term impact of adjuvant chemotherapy on quality of life (35,40,47). While these studies have shown limited effects, they are problematic from several aspects: i) many of these trials evaluated uncommon types of chemotherapy for short duration (e.g., CMF x 3 months); ii) compliance with quality of life assessments was poor (< 80%); iii) quality of life was evaluated using instruments that have not been widely validated and are not currently used; and iv) specific symptoms – fatigue, vasomotor and sexual symptoms were not routinely evaluated. Recent trials comparing anthracycline-based chemotherapy regimens to 6 cycles of CMF or taxane-based regimens to anthracycline-based regimens report increasingly worse quality of life with more intensive regimens that are now widely used (65,66,69,70).

While the main hypothesis of TAILORx is that chemotherapy is unlikely to have an effect on disease-free survival in this intermediate risk group, there is a possibility that such women may achieve small benefits in reduction in recurrence, so that the impact of chemotherapy on long-term symptomatology and in particular on HRQL is relevant. Such information would be important to women and their physicians considering whether small benefits in adjuvant chemotherapy are worth any observed long-term impact on quality of life outcomes. We hypothesize that women who receive chemotherapy prior to hormonal treatment will report more endocrine symptoms and sexual dysfunction and poorer HRQL than women receiving hormonal treatment alone.

#### 1.6.5 Clinical Significance and Rationale for the Quality of Life Study Design

The PACCT-1 trial offers a unique and previously unavailable opportunity to assess patient-reported outcomes among breast cancer patients who are randomized to receive hormonal therapy alone versus chemotherapy + hormonal therapy. The randomized design will allow us to isolate and quantify the effects of chemotherapy on symptoms of interest, given equivalence between groups on disease, sociodemographic, and other characteristics which have historically confounded the interpretation of study findings. Previous studies examining breast cancer patients who received chemotherapy to those who did not were confounded by systematic differences in disease status. The use of a randomized design is methodologically superior to previous studies using cross-sectional and prospective designs, which will allow us to draw definitive conclusions regarding the role of chemotherapy in contributing to cognitive impairment. This is an important area of investigation because data on the extent to which chemotherapy compromises cognitive function may assist patients and health-care providers in their decision-making related to treatment and evaluating potential benefits versus the potential risks. Longitudinal data on the trajectory of cognitive function, fatigue, and endocrine symptoms among women who undergo chemotherapy and hormonal therapy versus those who undergo hormonal therapy alone can help to inform women with breast cancer of what to expect during and following treatment and will allow us to evaluate target symptoms

as women undergo active treatment and transition into survivorship. Longitudinal data on the trajectory of fear of recurrence can assist with determining when to best deliver interventions to address this common concern among breast cancer survivors. The collection and banking of biological specimens from TAILORx participants will allow the future investigation of genetic predictors for cognitive impairments, fatigue, and endocrine symptoms.

#### 1.6.6 Measures selected

##### 1.6.6.1 Rationale for Quality of Life Measure Selection

Cognitive function is the primary endpoint for the PACCT-1 quality of life component. Cognitive function can be assessed using multiple approaches, including neuropsychological assessment, neuroimaging, and patient self-report. Historically, neuropsychological assessment has been viewed as the “gold standard” for detecting and localizing neuropathology among individuals with traumatic brain injury or neurologic disease. However, this approach has been criticized for the lack of ecological validity (i.e. the “functional and predictive relationship between the patient's performance on a set of neuropsychological tests and the patient's behavior in a variety of real world settings,(83) particularly among individuals with intact neurological function such as individuals with breast cancer who are receiving adjuvant chemotherapy (45,93). The interpretation of neuropsychological test scores in a longitudinal design is also complicated by practice effects, or the improvement in performance over time due to increasing familiarity with the demands of the test (72). In addition, neuropsychological assessment imposes significant participant burden and due to the stringent requirements for assessment administration procedures this method is not feasible in the context of a large, multi-site clinical trial. While neuroimaging techniques have demonstrated differences between cancer patients who have received chemotherapy and oncology patients who have not received chemotherapy, as well as healthy controls, these assessment techniques are not practical for a multi-site trial given the expense of conducting imaging studies, the participant burden imposed by the length of imaging studies, and the complications inherent to ensuring comparability of imaging data and combining data collected from different imaging equipment and multiple institutions.

A number of recent studies have highlighted the utility of self-report in the assessment of individuals' perceived cognitive changes related to chemotherapy (60,63). Kohli et al. used the EORTC Cognitive Function scale to examine a sample of oncology patients undergoing

chemotherapy through participating in a cooperative group clinical trial. Participants reported more cognitive problems during and after chemotherapy in comparison to pre-chemotherapy self-report. While self-reported cognitive function has been criticized because it has tended not to be associated with actual neuropsychological performance (60,84,98), recent provocative findings suggest that in the case of mild cognitive impairment patient self-report may be more sensitive than neuropsychological testing (49,54,82).

Most research to date examining the association of chemotherapy and cognitive function has utilized neuropsychological testing to evaluate cognitive function. The use of neuropsychological testing to assess mild cognitive impairment does pose methodological limitations (e.g. ecological validity, practice effects) and numerous recent studies have demonstrated that patient self-report may be more sensitive than neuropsychological testing in detecting early cognitive decline. Neuropsychological testing is costly to administer and imposes significant participant burden. In consideration of these factors, we have selected perceived cognitive function as the primary endpoint for the quality of life study component. Given the unique opportunity to assess women with breast cancer randomized to receive chemotherapy versus no chemotherapy, this trial provides the only opportunity to date to collect comparison group data. This data will help to interpret previous research results and can also be used as comparison group data in future research.

#### 1.6.6.2 Measures to be Administered

Perceived cognitive function will be assessed using the Functional Assessment of Cancer Therapy – Cognitive Function Version 3. The FACT-Cog is the only patient-reported outcome measure to be developed based on direct input from oncology patients and expert clinicians (105,108).

The Quality of Life Co-Chair, Dr. Lynne Wagner, developed the FACT-Cog Version 3, the primary endpoint for this trial. Items for the FACT-Cog were developed based on themes that emerged from qualitative interviews with experienced oncology providers and interviews and focus groups with patients who reported cognitive impairments from chemotherapy (105,108). Within the scope of an NCI R01 project (PI: Cella), the initial version of the FACT-Cog was administered to a sample of 204 general oncology patients, which provided preliminary validation data and scale refinement (104). The FACT-Cog has been used by several investigators to assess perceived cognitive function among colorectal cancer

patients, patients undergoing bone marrow transplant, and among patients with breast and testicular cancer (99,60). FACT-Cog data from multiple institutions was combined with our own locally collected data to evaluate the dimensionality of perceived cognitive function as measured by the FACT-Cog. Those analyses supported the presence of two factors: perceived cognitive impairment and perceived cognitive abilities (64). Accordingly, the FACT-Cog Version 3 includes Perceived cognitive impairments and Perceived cognitive abilities as two distinct subscales.

The FACT-Cog is currently being validated using data collected from a sample of breast cancer patients undergoing chemotherapy. The 20-item FACT-Cog Perceived cognitive impairments subscale demonstrated excellent internal consistency at all assessment time points, including pre-, during and post-treatment (Cronbach's alpha ranged .93 - .95; unpublished data). The FACT-Cog Perceived cognitive impairments subscale was highly correlated (.75 - .87; unpublished data) with the Cognitive Difficulties Scale (CDS; 73), a 39-item self-report measure of perceived cognitive function. The Perceived cognitive impairments subscale was moderately correlated with the Hospital Anxiety and Depression Scale (HADS) Anxiety scale (.33 - .46), HADS Depression scale (.39 - .53), and the FACT-Fatigue subscale (.51-.62; unpublished data) at pre-, mid-, and post-treatment assessments.

Previous research using the FACT-Cog (Version 2) among individuals undergoing bone marrow transplant demonstrated a significant correlation with the EORTC Cognitive Function (EORTC-CF) scale and similar psychometric properties (Jacobs et al. 2007). Because the EORTC-CF scale only includes 2 items, the FACT-Cog provided greater information about the types of cognitive deficits patients were experiencing.

Secondary quality of life endpoints, specifically fatigue, fear of recurrence, endocrine symptoms and HRQL are by nature subjective experiences. Accordingly, these domains will be assessed using patient self-report measures.

Fatigue will be assessed using the Functional Assessment of Cancer Therapy – Fatigue subscale (FACT-F) (111) and the Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue 7-item Short Form. The inclusion of the PROMIS Fatigue Short Form will allow us to contribute to the validation of this tool, which will require the concurrent administration of the FACT-Fatigue subscale. Once validated, the PROMIS Fatigue Short Form will allow us to link our data with other oncology and non-oncology samples. Endocrine symptoms will be assessed using the FACT-Endocrine Symptoms subscale

(FACT-ES). The FACT-ES includes questions on vasomotor symptoms, mood, and sexual function. This scale was selected base on its previous use to evaluate the side effects of hormonal treatment in other large clinical trials (ATAC trial; Fallowfield et al. 2004). Fear of recurrence will be evaluated using the 5-item Assessment of Survivor Concerns (58). This instrument was selected because it was validated with a sample of short- and long-term cancer survivors and despite its brevity, exhibits excellent psychometric properties. The FACT-General (44) will be administered at three key time points to assess overall HRQL.

#### 1.6.6.3 Assessment Schedule

Our primary question of interest is the extent to which chemotherapy plays a causal role in the development of perceived cognitive impairments. We are interested in the causal role chemotherapy plays in fatigue and the extent to which chemotherapy contributes to endocrine symptoms associated with hormonal treatment. We seek to evaluate the extent to which chemotherapy exacerbates or attenuates fear of recurrence. We are also interested in the long-term trajectory of these symptoms throughout and following treatment among women in the Primary Study Group (Arms B and C) and women in the Secondary Study Group who receive hormonal treatment alone (Arm A) or chemotherapy followed by hormonal treatment (Arm D).

Based on these goals, the study assessment will be administered at the time of TAILORx randomization and at 3, 6, 12, 24, and 36 months post-randomization. To evaluate the effect of chemotherapy on domains of interest, the best time for an assessment is at maximal exposure to chemotherapy (ie. at the time of or immediately following the last cycle). The TAILORx protocol allows participants to receive 1 of 9 chemotherapy regimens which range in length from 8 to 24 weeks. To date, the majority of TAILORx participants enrolled are receiving 4 cycles of treatment and the most common regimens include AC 3 week cycles (29%), TC 3 week cycles (22%), and AC dose dense 2 week cycles (16%). Data collected at the 3 month assessment will be used for the primary analysis to capture most participants when they have recently completed chemotherapy or are approaching the end of their regimen.

The 6-month and 12-month assessments may provide the most clinically relevant data, because many clinicians and patients are aware of acute symptoms during chemotherapy and they are primarily interested in learning when they will return to normal or pre-treatment function. Many studies have documented that cognitive dysfunction

and fatigue can last for months or years following treatment completion. The follow-up assessments (24 and 36 months post-randomization) will provide data on long-term function and will allow us to determine whether any differences between treatment groups that emerge resolve over time. The FACT-G will only be administered pre-treatment and at 12 and 36 month follow-up assessments to minimize participant burden, while providing data on the long-term trajectory of HRQL and the effects of symptom burden on HRQL.

#### 1.7 Gender and Ethnicity

Entry to this study is restricted to female patients. Study entry is open to patients of all ethnic backgrounds. Historically, approximately 15% of patients enrolled on ECOG-ACRIN breast cancer studies are members of minority ethnic groups. It is anticipated that a similar proportion of patients on this study will be members of ethnic minorities. Based on current data, ECOG-ACRIN believes that interactions between ethnicity and genomic profiling are not expected, and accrual will not be increased to meet subgroup targets.

## 2. Objectives

In women with ER-positive and/or PR-positive, axillary node-negative breast cancer who meet standard clinical criteria for adjuvant chemotherapy in addition to hormonal therapy, the objectives of this trial are:

### 2.1 Primary

- 2.1.1 To determine whether adjuvant hormonal therapy is not inferior to adjuvant chemohormonal in women whose tumors meet established clinical guidelines for adjuvant chemotherapy and fall in the “primary study group” category (Oncotype DX Recurrence Score 11-25). The primary study endpoint is disease-free survival; other co-primary endpoints include distant recurrence free interval, recurrence free interval, and overall survival as defined in Section [6](#).
- 2.1.2 To create a tissue and specimen bank for patients enrolled in this trial, including formalin fixed paraffin embedded tumor specimens, tissue microarrays, plasma, and DNA obtained from peripheral blood. This resource will be critical for evaluating emerging Clinical Cancer Tests.

### 2.2 Secondary:

- 2.2.1 To determine whether adjuvant hormonal therapy is sufficient treatment (i.e. 10 year distant disease-free survival of at least 95%) for women whose tumors meet established clinical guidelines for adjuvant chemotherapy and who fall into the "Secondary Study Group-1" category (Oncotype DX Recurrence Score  $\leq$  10). The primary study endpoint is disease-free survival; other co-primary endpoints include distant recurrence free interval, recurrence free interval, and overall survival as defined in Section [6](#).
- 2.2.2 To compare the outcomes projected at 10 years by Adjuvant! (with outcomes projected using classical pathologic information including tumor size, hormone receptor status, and histologic grade) with those made by the Genomic Health Oncotype DX test. Classical pathologic information and outcome results will also be used to create and refine models that would use classical information instead of or in combination with genomic tests.
- 2.2.3 To estimate failure rates as a function of RS separately in the chemotherapy (arms C, D) and no chemotherapy (arms A, B) groups. The purpose of the analysis is to develop more precise estimates of the relationship between recurrence score and chemotherapy treatment effect, if any, at the upper range of the RS 11 – 25 group.
- 2.2.4 To determine the prognostic significance of the Oncotype DX recurrence score and of the individual RS gene groups (proliferation gene group, HER2 gene group, ER gene group, invasion gene group, and other genes).

Rev. 1/10

2.3 Quality of Life Objectives:

- 2.3.1 To evaluate the effects of chemotherapy + hormonal therapy vs. hormonal alone on:
- (a) perceived cognitive impairment
  - (b) fatigue
  - (c) fear of recurrence among pre-menopausal patients
  - (d) endocrine symptoms and sexual dysfunction
  - (e) overall HRQL
- 2.3.2 To determine whether perceived cognitive impairment, fatigue, fear of recurrence, endocrine symptoms and overall HRQL are similar for patients receiving chemotherapy plus hormonal therapy in secondary study group 2 as for those in the primary study group (arms D vs. C).
- 2.3.3 To determine whether perceived cognitive impairment, fatigue, fear of recurrence, endocrine symptoms and overall HRQL are similar for patients receiving hormonal therapy alone in secondary study group 1 as for those in the primary study group (arms A vs. B).
- 2.3.4 To determine whether age will be inversely associated with a fear of recurrence, independent of treatment assignment.
- 2.3.5 Among participants receiving hormonal treatment alone on Arm A and Arm B, to determine whether Oncotype DX Recurrence score will be inversely correlated with fear of recurrence.

Rev. 2/13

2.4 Determinants of Late Relapse Ancillary Study (EL112LAB)

- 2.4.1 To create a biospecimen repository including plasma, serum and CellSearch™ cassettes containing circulating tumor cells (CTC) for evaluating determinants of late relapse, including candidate biomarkers reflecting occult tumor burden (e.g., CTCs and plasma tumor DNA) and host factors (e.g., estrogen, insulin-IGF axis, inflammation, etc).
- 2.4.2 To create a biorepository of metastatic tumor samples in patients who have had a late relapse.
- 2.4.3 To determine body mass index (BMI) and comorbidity burden in patients with operable breast cancer five or more years after diagnosis.
- 2.4.4 To determine whether there is a relationship between late relapse and BMI at diagnosis and at 5 years after diagnosis, and whether BMI-associated inflammatory and/or metabolic biomarkers are associated with early and late recurrence



### 3. Selection of Patients

Each of the criteria in the following section must be met in order for a patient to be considered eligible for this study. Use the spaces provided to confirm a patient's eligibility. For each patient, this section should be photocopied, completed and maintained in the patient's chart.

Rev. 9/06

**NOTE:** This study involves a pre-registration and a registration/randomization (see Section 4). All time frames for prestudy scan and lab values and other requirements will be based on the date of pre-registration.

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

Rev. 9/07

**NOTE:** Questions regarding eligibility or treatment should be directed to the ECOG-ACRIN Study Chair (Joseph Sparano, M.D.) and/or Study Chair Liaison (Una Hopkins, R.N.) or the CTSU Help Desk at 1-888-823-5923. An email to the following email address is PREFERRED, and will be reviewed by the Study Chair and Study Chair Liaison (and other study team members); a response will be provided within 24 hours ([ecog.tailorx@jimmy.harvard.edu](mailto:ecog.tailorx@jimmy.harvard.edu)). For questions regarding patients who have been pre-registered or registered, please provide the sequence number in the subject heading and/or content of the email.

Rev. 9/06

**NOTE:** Patients enrolled on the PACCT-1 trial may be enrolled on other CTSU trials under the following conditions: (1) the treatment options in the other trials are consistent with PACCT-1-specified treatment assignment (ie, chemohormonal therapy or hormonal therapy alone) and (2) although registration on the PACCT-1 trial is required prior to registration on any other CTSU trial requiring chemotherapy, it is preferred (but not necessarily required) prior to registration on another CTSU trial not involving chemotherapy (eg, hormonal therapy, bisphosphonate therapy).

Rev. 9/07

**NOTE:** Pre-registration requires a previously determined Recurrence Score (from GHI) or tissue available for submission for *Oncotype* DX assay. See section 7.2 for submission of forms and samples associated with Recurrence Score status.

Rev. 9/06

**NOTE:** If the *Oncotype* DX Recurrence Score was previously performed by Genomic Health and the RS is 11-25, eligible patients may proceed from the pre-registration process to randomization within 24 to 72 hours after submission of the *Oncotype* DX Assay report to the ECOG-ACRIN Operations Office – Boston (see sections 3.1.3, 3.1.10 and 4.2). Pre-registration may NOT be bypassed.

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

Patient's Initials (Last, First, Middle) \_\_\_\_\_

\_\_\_\_ 3.1 Pre-Registration

\_\_\_\_ 3.1.1 Patients with operable histologically confirmed adenocarcinoma of the female breast who have completed primary surgical treatment and meet the following criteria

\_\_\_\_ 3.1.1.1 **ER and/or PR-positive:**

Estrogen and/or progesterone receptor positive disease (as defined by local pathology laboratory).

ER Status: Positive / Negative / Indeterminate Date \_\_\_\_\_  
(please circle one)

PR Status: Positive / Negative / Indeterminate Date \_\_\_\_\_  
(please circle one)

Rev. 9/06  
Rev. 8/08

\_\_\_\_ 3.1.1.2 **Negative axillary nodes:**

As assessed by a sentinel lymph node biopsy, an axillary dissection, or both, and as defined by the Sixth Edition of the AJCC staging criteria (check definition that applies):

\_\_\_\_ pN0: No regional lymph node metastases histologically, **no** additional examination for isolated tumor cells (**NOTE:** Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not great than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H& E stain. ITCs do not usually show evidence of malignant activity [eg, proliferation or stromal reaction]).

Rev. 9/07

\_\_\_\_ pN0 (i-): No regional lymph node metastases histologically; negative IHC

Rev. 9/07

\_\_\_\_ pN0 (i+): No regional lymph node metastases histologically; positive IHC, no IHC cluster greater than 0.2 mm

\_\_\_\_ pN0 (mol-): No regional lymph node metastases histologically; negative molecular findings (RT-PCR [reverse transcriptase polymerase chain reaction])

Rev. 9/07

\_\_\_\_ pN0 (mol+): No regional lymph node metastases histologically; positive molecular findings (RT-PCR)

- \_\_\_\_\_ 3.1.1.3 **Tumor size 1.1–5.0cm (or 5 mm-1.0 cm plus unfavorable histological features):**  
Unfavorable features defined as intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion.  
**NOTE:** Definition of tumor size: The tumor size used for determination of eligibility is the pathologic tumor size, which is usually determined by the size of the tumor as measured by inspection of the gross specimen. If the tumor size is measured microscopically and the tumor includes ductal carcinoma in-situ, the measurement should include only the invasive component of the tumor.
- Rev. 8/08 \_\_\_\_\_ 3.1.1.4 The tumor must be Her2/neu negative by either fluorescent in-situ hybridization (FISH) or immunohistochemistry (e.g. 0 or 1+ by DAKO Herceptest).
- \_\_\_\_\_ 3.1.2 The patient and physician must be agreeable to initiate standard chemotherapy and hormonal therapy as adjuvant therapy. The standard chemotherapy and hormonal therapy options permitted are described in [Appendix II](#) and [Appendix III](#).
- Rev. 9/06 \_\_\_\_\_ 3.1.3 A tissue specimen from the primary breast cancer has been located and is ready to be shipped to the appropriate laboratory after consent is obtained and within 3 days following pre-registration as indicated in Section [10](#).  
**NOTE:** For determination of the Oncotype Recurrence Score, tissue must be shipped to Genomic Health. If the Oncotype DX Recurrence Score was previously performed by Genomic Health (prior to pre-registration), tissue must be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility upon randomization.
- Rev. 9/06  
Rev. 9/06  
Rev. 12/14 \_\_\_\_\_ 3.1.4 Patients must be  $\geq 18$  years and  $\leq 75$  years. Patients must be less than 76 years of age because patients will be followed for up to 20 years, and because the primary study endpoints are based upon a 10 year endpoint.
- Rev. 9/06 \_\_\_\_\_ 3.1.5 Patients must have adequate organ function, including the following within 4 weeks prior to pre-registration:
- Leukocyte count  $\geq 3500/ \text{mm}^3$  and platelets  $\geq 100,000/\text{mm}^3$ .  
Leukocyte count: \_\_\_\_\_ Date of test: \_\_\_\_\_  
Platelet Count: \_\_\_\_\_ Date of test: \_\_\_\_\_
  - Serum creatinine  $\leq 1.5\text{mg/dL}$ .  
Creatinine: \_\_\_\_\_ Date of test: \_\_\_\_\_
  - Serum aspartate transaminase (AST) that is  $\leq 3$ -fold the upper institutional limits of normal.  
AST: \_\_\_\_\_ Date of test: \_\_\_\_\_  
Institutional limits of normal \_\_\_\_\_
- Rev. 9/06

	_____	3.1.6	Patients must be disease-free of prior invasive malignancies for ≥ 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma <i>in situ</i> of the cervix. Patients with a previous ipsilateral or contralateral invasive breast cancer, or with bilateral synchronous cancers, are not eligible. Patients with previous ipsilateral or contralateral DCIS are not eligible.
Rev. 9/06	_____	3.1.7	Prior Treatment
	_____	3.1.7.1	Mandatory prior surgery criteria:
Rev. 9/06		_____ 3.1.7.1.1	Patient must pre-register within 84 days from the final surgical procedure required to adequately treat the primary tumor. (Please note that if margins are not clear and a resection has to be conducted after pre-registration but before randomization, the patient will be deemed to be within the 84 day window allowed by protocol and therefore eligible).
Rev. 3/09			
Rev. 3/09		3.1.7. _____	All tumors should be removed by either a mastectomy or local excision plus an acceptable axillary procedure (i.e., sentinel lymph node biopsy, axillary dissection, or both). There must be adequate (at least 1 mm if margin width specified) tumor-free margins of resection (for invasive and ductal carcinoma in-situ) in order for the patients to be eligible. Patients with lobular carcinoma in-situ involving the resection margins are eligible.
Rev. 9/07			
	_____	3.1.7.2	Criteria re: other prior treatments:
		_____ 3.1.7.2.1	No prior chemotherapy for this malignancy.
Rev. 9/07		_____ 3.1.7.2.2	No prior radiation therapy for this malignancy. This includes no prior MammoSite Brachytherapy RT.
		_____ 3.1.7.2.3	Hormonal therapy: Patients who develop breast cancer while receiving a selective estrogen-receptor modulator (SERM; e.g., tamoxifen, toremifene, raloxifene) or an aromatase inhibitor (e.g., anastrozole, letrozole, exemestane) for breast cancer prevention or a SERM for other indications (e.g., raloxifene for osteoporosis) are <b>not</b> eligible. However, patients may have received up to 8 weeks of a SERM or aromatase inhibitor for this malignancy and still be eligible for study entry.

- \_\_\_\_\_ 3.1.8 Patients must have an anticipated life expectancy of at least 10 years. Patients with the following medical conditions should not be enrolled on the study:
- \_\_\_\_\_ 3.1.8.1 Chronic obstructive pulmonary disease requiring treatment.
  - \_\_\_\_\_ 3.1.8.2 Chronic liver disease (e.g., cirrhosis, chronic active hepatitis)
  - \_\_\_\_\_ 3.1.8.3 Previous history of a cerebrovascular accident.
  - \_\_\_\_\_ 3.1.8.4 History of congestive heart failure or other cardiac disease that would represent a contraindication to the use of an anthracycline (e.g., doxorubicin or epirubicin).
  - \_\_\_\_\_ 3.1.8.5 Chronic psychiatric condition or other condition that would impair compliance with the treatment regimen.
- \_\_\_\_\_ 3.1.9 Women must not be pregnant or breast-feeding due to the potential use of cytotoxic chemotherapy for patients participating in this trial, which is contraindicated due to the potential for chemotherapy to cause harm to the fetus or infant. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to pre-registration to rule out pregnancy. (See Section [7.1.](#))
- Female of childbearing potential? \_\_\_\_\_ (Yes or No)
- Date of negative blood or urine pregnancy test: \_\_\_\_\_
- \_\_\_\_\_ 3.1.9.1 Women of childbearing potential must be strongly advised to utilize an accepted and effective form of non-hormonal contraception (e.g. intrauterine device, condoms, diaphragm, abstinence).
- \_\_\_\_\_ 3.1.10 Patients must not have previously had the *Oncotype* DX Assay performed, with the exception of patients who have had the assay performed and have a Recurrence Score of 11-25.

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**NOTE:** A copy of the “*Oncotype* DX Patient Report” is to be faxed to the ECOG-ACRIN Operations Office – Boston (Fax: 617-582-8578, Attn: Pre-registration/PACCT-1) upon receipt of the report, or, if *Oncotype* DX Assay was previously performed, immediately following pre-registration. The protocol number (PACCT-1), and **pre-registration sequence number** MUST be indicated on the report.

**Physician’s Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

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3.2 Registration/randomization (24 to 72 hours after submission of the Oncotype DX Assay report to the ECOG-ACRIN Operations Office – Boston)

\_\_\_\_\_ 3.2.1 At the time of registration/randomization, information that will be required for proper stratification (as indicated in Section [4.2.5](#)) will include:

- Tumor Size ( $\leq 2.0$  cm vs.  $\geq 2.1$  cm):  
\_\_\_\_\_
- Menopausal Status [Post-menopausal vs. Pre- or peri-menopausal (see [Appendix III](#) for status definitions)]:  
\_\_\_\_\_
- Planned Chemotherapy (Taxane-Containing vs. Non-Taxane Containing):  
\_\_\_\_\_
- Planned Radiation Therapy [Whole breast, no boost planned vs. Whole breast, boost planned vs. Partial breast irradiation planned vs. No planned radiation therapy (for patients who have had a mastectomy)]:  
\_\_\_\_\_

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**NOTE:** Research associates may need to contact the treating physician prior to registration regarding what type of adjuvant chemotherapy is planned if that information is not available in the medical record.

\_\_\_\_\_ 3.2.2 Oncotype DX Assay result:  
Pre-registration #: \_\_\_\_\_  
RS score: \_\_\_\_\_

**Physician's Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

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3.3 Registration to Ancillary Study EL112LAB (Step 3)

All patients who meet the following criteria are eligible to participate in the ancillary study:

- 3.3.1 Patient was registered/randomized to treatment (Step 2 - Arms A, B, C, or D) at least 4.5 years (54 months) and no more than 7.5 years (90 months) prior to registration to step 3. It is preferable for patients to be registered to step 3 at 5 years (60 months +/- 6 months) after registration to step 2.
- 3.3.2 Patient is disease free, with no prior recurrence, at time of registration to Step 3.
- 3.3.3 The primary tumor tissue and peripheral blood sample were previously submitted for research studies just prior to or following registration/randomization to treatment as outlined in PACT1/TAILORx Section [10](#).

#### 4. Pre-registration and Registration/Randomization Procedures

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Data management activities for the PACCT-1 study will be performed jointly by the Cancer Trials Support Unit (CTSU) and the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN). All sites (ECOG-ACRIN and non-ECOG-ACRIN alike) will submit study data to the CTSU (with the exception of Expedited Adverse Event Reporting; please follow instructions in section 5.3 for submission of AE data), therefore, **all PACCT-1 investigators and support staff (ECOG-ACRIN and non-ECOG-ACRIN alike) must be registered members of the CTSU.** Please see the CTSU website ([www.ctsu.org](http://www.ctsu.org)) for details on registering as a CTSU member.

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**NOTE:** This study involves both a pre-registration and a registration/randomization. Please read these instructions carefully.

**NOTE:** Pre-registration is required for low risk patients and for high risk patients who will be followed in the voluntary registry.

##### 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  
E-mail: [CTSURegulatory@ctsu.coccg.org](mailto:CTSURegulatory@ctsu.coccg.org)  
(for regulatory document submission only)

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##### 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.

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3.
  - A. CTSU IRB Certification Form.  
*Or*
  - B. Signed HHS OMB No. 0990-0263 (Replace 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 link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed**

**[http://www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail [CTSUContakt@westat.com](mailto:CTSUContakt@westat.com).**

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### **Checking Your Site's Registration Status:**

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

**Patients must not start protocol treatment prior to pre-registration and registration/randomization.**

#### **4.1 Pre-Registration**

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.

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:

- 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).

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Access requirements for OPEN:

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

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

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

The following information will be requested for pre-registration:

- 4.1.1 Protocol Number
- 4.1.2 Investigator Identification
  - 4.1.2.1 Institution and affiliate name
  - 4.1.2.2 Investigator's name
- 4.1.3 Patient Identification
  - 4.1.3.1 Patient's initials (Last, First, Middle) and chart number
  - 4.1.3.2 Patient's Social Security number
  - 4.1.3.3 Patient demographics
    - 4.1.3.3.1 Sex
    - 4.1.3.3.2 Birth date (mm/yyyy)
    - 4.1.3.3.3 Race
    - 4.1.3.3.4 Ethnicity
    - 4.1.3.3.5 Nine-digit ZIP code
    - 4.1.3.3.6 Method of payment

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3.1](#). An eligibility worksheet has been appended to the protocol. A confirmation of pre-registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.1.5 Additional Requirements

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

4.1.5.2 Pathology blocks are to be submitted as follows:

- For determination of *Oncotype DX Recurrence Score*, materials **must** be submitted no later than 3 days after pre-registration as outlined in section [10.1](#). Kits for tissue submission may be ordered prior to pre-registration.

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**NOTE:** If slides, rather than blocks, are submitted for the RS assessment, additional materials are required for central review of ER/PR status as indicated in section [10.3](#).

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- If the *Oncotype DX Recurrence Score* was previously determined by Genomic Health and the score is 11-25, blocks are to be submitted for central review after randomization as indicated in Section [10.3](#).

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**NOTE:** Beginning June 2007, ECOG-ACRIN requires that all samples from patients participating in PACCT-1 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See section [10.4](#).

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4.1.5.3 Prior to registration/randomization, the institution must FAX a redacted copy of the first page of the “*Oncotype DX Patient Report*” to the ECOG-ACRIN Operations Office – Boston (617-582-8578, ATTN: Pre-Registration/PACCT-1). Indicate on the report the protocol number (PACCT-1), the patient’s initials and patient’s ECOG-ACRIN **pre-registration** sequence number.

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- If patient is having an *Oncotype DX Assay* performed by Genomic Health, Genomic Health will notify the submitting institution of the results of the *Oncotype DX Assay* within 14 working days of receipt of the sample.
- If patient has previously had an *Oncotype DX Recurrence Score* performed by Genomic Health, and the RS is 11-25, the “*Oncotype DX Patient Report*” should be FAXed to the ECOG-ACRIN

Operations Office – Boston within 24 hours following pre-registration.

- 24 hours (72 hours if a weekend or holiday) after submission of the OncoType DX Patient Report to ECOG-ACRIN, the institution may proceed to registering/randomizing the patient as outlined in Section [4.2](#).

#### 4.2 Registration/Randomization

**Patients must not start protocol treatment prior to registration/randomization.**

**Treatments should begin within 14 days after registration/randomization.**

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.

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:

- 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.

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- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

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

Institutions may register eligible patients to this study 24 hours (72 hours if weekend or holiday) after institution has Faxed a redacted copy of the first page of the "Onco<sup>type</sup> DX Patient Report" to the ECOG-ACRIN Operations Office – Boston (617-582-8578, ATTN: Pre-Registration/PACCT-1) as outlined in Section [4.1.5.3](#).

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The following information will be requested:

- 4.2.1 Protocol Number
- 4.2.2 Investigator Identification
  - 4.2.2.1 Institution and affiliate name
  - 4.2.2.2 Investigator's name
- 4.2.3 Patient Identification
  - 4.2.3.1 Patient's initials (Last, First, Middle) and chart number
  - 4.2.3.2 Patient's Social Security number
  - 4.2.3.3 Patient demographics
    - 4.2.3.3.1 Sex
    - 4.2.3.3.2 Birth date (mm/yyyy)
    - 4.2.3.3.3 Race
    - 4.2.3.3.4 Ethnicity
    - 4.2.3.3.5 Nine-digit ZIP code
    - 4.2.3.3.6 Method of payment
  - 4.2.3.4 Patient's sequence number from pre-registration (Step 1).
- 4.2.4 Classification factor  
Recurrence Score (RS)
- 4.2.5 Stratification factors
  - 4.2.5.1 Tumor Size  
≤ 2.0 cm

- 
- ≥ 2.1 cm
- 4.2.5.2 Menopausal Status  
Post-menopausal  
Pre- or peri-menopausal  
(See [Appendix III](#) for status definitions)
- 4.2.5.3 Planned Chemotherapy  
Taxane-containing (i.e., paclitaxel, docetaxel)  
Non-taxane containing
- 4.2.5.4 Planned radiation therapy  
Whole breast, no boost planned  
Whole breast, boost planned  
Partial breast irradiation planned  
No planned radiation therapy (for patients who have had a mastectomy)
- Rev. 3/09 4.2.5.5 OncoType DX Recurrence Score  
11-15  
16-20  
21-25
- 4.2.6 Additional Requirements
- 4.2.6.1 Tumor tissue must be submitted for correlative studies and banking as outlined in Section [10](#).  
**NOTE:** If tissue was submitted at pre-registration for OncoType DX RS assessment, additional materials are requested for correlative studies and banking.
- 4.2.6.2 Peripheral blood to be retained for possible future use should be submitted as outlined in Section [10](#).  
**NOTE:** Institutions outside the United States and Canada are not required to submit fresh samples because of the costs and problems associated with international shipping.  
**NOTE:** Beginning June 2007, ECOG-ACRIN requires that all samples from patients participating in PACCT-1 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See section [10.4](#).
- Rev. 9/07
- 4.3 Instructions for Patients Who Do Not Start Assigned Protocol Treatment
- Rev. 9/07 If a patient does not receive any assigned protocol treatment, all data will still be collected and submitted according to the instructions in the PACCT-1 Forms Packet.

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4.4 STEP 3: Registration to Ancillary Study EL112LAB

All patients participating PACCT-1 are eligible to participate in this the EL112LAB. Requirements for the ancillary study are outlined in [Appendix XII](#).

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**NOTE:** The ECOG-ACRIN Operations Office – Boston will provide sites a list of patients who have been identified as potential candidates for EL112LAB. The information provided will include the date range for which the patients would be eligible to participate which is dependent on the date of registration/randomization to treatment (Step 2). Routine notifiers will also be utilized to serve as reminders to sites regarding the timeline of a patient’s potential eligibility.

The following information will be collected at time of registration to step 3

4.4.1 Protocol Number

4.4.2 Investigator Identification

- Institution and affiliate name
- Investigator’s name
- NCI investigator ID

4.4.3 Patient Identification

4.4.3.1 Patient’s initials and chart number

4.4.3.2 Patient’s Social Security number

4.4.3.3 Patient demographics

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

4.4.4 Additional Requirements

4.4.4.1 Patients must provide a signed and dated, written informed consent form to participate in EL112LAB. The model consent for this ancillary study is provided in [Appendix I-A](#)

4.4.4.2 Forms and biological materials are to be submitted as outlined in [Appendix XII](#). A summary is provided in Section [7.4](#).

**NOTE:** ECOG-ACRIN requires all samples submitted to be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See section [10.4](#).

## 5. Treatment Plan

**NOTE:** All questions regarding treatment or dose modifications should be directed to the ECOG-ACRIN Study Chair.

**NOTE:** Systemic treatment (chemotherapy or hormonal therapy) should be initiated within 14 days after registration/randomization. For patients randomized or assigned to receive chemotherapy, chemotherapy should be administered first; hormonal therapy should begin within 4 weeks after the last dose of chemotherapy, and should not be given concurrently with chemotherapy. Hormonal therapy may be initiated more than 4 weeks after completion of chemotherapy (or more than 2 weeks after registration if receiving hormonal therapy alone) if the treating physician elects to begin hormonal therapy after completion of radiation therapy. It is recommended that hormonal therapy be given concurrently with radiation therapy, but may be delayed until after completion of irradiation at the discretion of the treating physician (and should begin within 4 weeks of completing irradiation).

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### 5.1 Treatment Arms

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**NOTE:** Patients enrolled on the PACCT-1 trial may be enrolled on other CTSU trials under the following conditions: (1) the treatment options in the other trials are consistent with PACCT-1-specified treatment assignment (ie, chemohormonal therapy or hormonal therapy alone) and (2) although registration on the PACCT-1 trial is required prior to registration on any other CTSU trial requiring chemotherapy, it is preferred (but not necessarily required) prior to registration on another CTSU trial not involving chemotherapy (eg, hormonal therapy, bisphosphonate therapy).

Secondary Study Group-1 (RS ≤ 10): Patients will receive hormonal therapy of the treating physician's choice (see [Appendix III](#) for guidelines)

5.1.1 Primary Study Group (RS 11-25): Patients will be randomized at the time of registration to receive chemotherapy plus hormonal therapy or hormonal therapy alone (see [Appendix II](#) and [Appendix III](#) for guidelines).

5.1.2 Secondary Study Group-2 (RS ≥ 26): Patients will receive chemotherapy (see [Appendix II](#)) and hormonal therapy (see [Appendix III](#)) of the treating physician's choice.

For patients with a RS ≥ 26 who do not register on another CTSU study, the enrolling site is asked to provide baseline and follow-up information on a voluntary basis. Requested information will include the following: (1) a baseline case report form, (2) a report of disease relapse event (as defined in Section [6](#)), and/or second primary cancer, and/or death (if any of these events occur), (3) and a report of disease and survival status 5 years after registration.



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## 5.2 Radiotherapy

Patients who have had breast conservation surgery will be treated with radiotherapy. Guidelines for radiation therapy are as follows:

Radiation should begin within 4-8 weeks of registration for patients receiving hormonal therapy alone or within 4-8 weeks after completion of chemotherapy (or sooner if the patient has adequately recovered from chemotherapy-associated toxicity).

Radiation treatment should be delivered using one of the following:

- (a) External beam irradiation to the whole breast to a dose of 45-50 Gy using daily fractions of 1.8-2.0 Gy, 5 days per week. A boost dose to the primary tumor bed is recommended to bring the total dose to 60-66 Gy.
- (b) External beam irradiation to the whole breast using accelerated fractionation of 42.56 Gy in 16 daily fractions, 5 days per week. A boost dose to the primary tumor bed is recommended.
- (c) Patients may receive accelerated partial breast irradiation (APBI), if they are participating in the randomized NSABP/RTOG APBI trial or the randomized RAPID APBI trial. Accelerated partial breast irradiation (APBI), including Mammosite brachytherapy, is otherwise not permitted, either before or after pre-registration, if not on a randomized radiation study. APBI on study may be given before chemotherapy if indicated.
  - Breast radiation should not be given concurrently with chemotherapy. It is recommended that hormonal therapy be given concurrently with radiation therapy, but may be delayed until after completion of irradiation at the discretion of the treating physician (and should begin within 4 weeks of completing irradiation).

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## 5.3 Quality of Life Assessments

All PACCT-1 participants will be eligible to participate in the QOL assessment. The primary QOL objectives pertain to participants in the Primary Study Group and those randomly assigned to Arms B and C. Secondary analyses will also examine women in the Secondary Study Group (1 and 2) and treated on Arms A or D.

### 5.3.1 Assessment Instruments

Study participants will complete the following patient-reported outcomes measures:

Scale	Number of items	Estimated administration time
FACT-Cog Version 3	37	10 minutes
FACT-Fatigue subscale	13	3 minutes
PROMIS Fatigue 7-item Short Form	7	2 minutes
Assessment of Survivor Concerns	5	2 minutes
FACT-Endocrine subscale	19	4 minutes

TOTAL	81	21 minutes
FACT-General*	27	7 minutes
TOTAL: 12 and 36 month assessments	108	28 minutes

\*The FACT-G will only be administered at baseline, 12 and 36 months in an attempt to minimize participant burden.

The FACT-Cog Version 3 consists of four subscales: Perceived cognitive impairments (20 items), Perceived cognitive abilities (9 items), Comments from others (4 items) and Impact on quality of life (4 items). Subscales are scored and interpreted independently and are not combined to create a single score. The Perceived cognitive impairment subscale will be used for the primary analysis.

Demographic and medical characteristics will also be obtained from participants, including comorbid illnesses, current medications (including treatments for menopausal symptoms), height and weight, and level of physical activity. This information is not currently being collected from TAILORx participants. We will develop a brief set of questions to capture this data.

### 5.3.2 Assessment Schedule

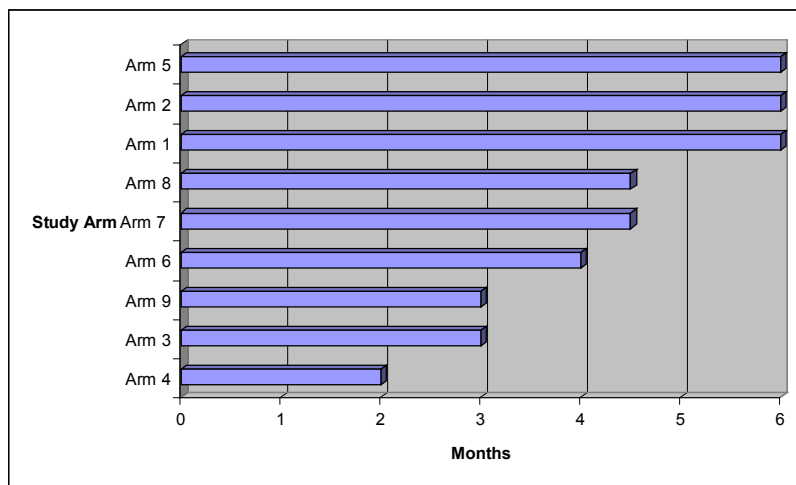
Participants will be assessed according to the following schedule:

- 1) Baseline\* (at the time they are assigned to the Primary or Secondary Study Groups)
- 2) 3 months
- 3) 6 months
- 4) 12 months\*
- 5) 24 months
- 6) 36 months\*

\*The FACT-G will only be administered at baseline, 12 and 36 months

The proposed assessment time points correspond to TAILORx study visits and the probable timing of routine care clinic visits to minimize participant burden. The table below displays the length (in months) of all 9 chemotherapy regimens allowable per the TAILORx protocol. The majority of participants are receiving treatment on Arms 3, 4 and 9. As indicated in the table, these regimens are completed at 3 months. The 3 month assessment will be used for the primary analysis to assess differences between treatment arms following the maximal exposure to chemotherapy.

### Length of chemotherapy regimens for each treatment arm



\*Study arm numbers refer to the Regimen code, see table in [Appendix II](#)

### 5.3.3

#### QOL Instrument Administration Instructions

5.3.3.1 The questionnaires must be administered at the timepoints listed above. The patient should be instructed to respond to the questionnaires in terms of his/her experience during the time frame specified on each questionnaire.

5.3.3.2 The CRN/CRA should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

5.3.3.3 Whenever possible, the HRQL assessment should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed and before test results are shared with the patient. In the event that the questionnaires are not administered at the clinic visit, the HRQL data can be collected by telephone or mail as backup methods provided that HRQL data is captured prior to initiation of treatment.

5.3.3.4 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on his/her own (e.g. difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and the type of assistance given.

5.3.3.5 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked

about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's responses.

- 5.3.3.6 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If the patient has marked more than one answer per question, ask the patient which answer best reflects how they are feeling. If the patient has skipped a question or questions, the patient should be asked if he/she would like to answer it. If the patient refuses, it should be indicated on the questionnaire that he/she declined to answer the item.
- 5.3.3.7 If the patient refuses or cannot complete the questionnaire at any time point, he or she should be asked to do so at the next scheduled HRQL assessment.
- 5.3.3.8 The patient may decline to complete the HRQL assessment for any reason. The reason must be documented on the Assessment Compliance Form.
- 5.3.3.9 If a patient misses an appointment on the scheduled date, the questionnaires may be completed by telephone on the appointed date or they may be completed at the time the appointment is rescheduled. If the missed scheduled date is on a treatment date, the quality of life assessment will be done when the patient comes for the rescheduled treatment.
- 5.3.3.10 If a patient cannot complete the quality of life questionnaires because he/she is too sick, this should be documented on the Assessment Compliance Form.

#### 5.4 Adverse Event Reporting Requirements

Identify the type of event and grade using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

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6/14

##### 5.4.1 **Reporting procedure**

**Arms A, B, C and D** - 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 NCI (301-897-7497)

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 faxed to ECOG-ACRIN (617 632 2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) 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 [ncictephhelp@ctep.nih.gov](mailto:ncictephhelp@ctep.nih.gov) or by phone at 1-888-283-7457 or 301-840-8202.

5.4.2 **Other recipients of adverse event reports**

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

Adverse events determined to be reportable 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.

5.4.3 **Expedited reporting for PACCT-1 protocol**

Attribution	Grade 5 <sup>a</sup>	
	Unexpected	Expected
Possible, Probable, Definite	7 calendar days	7 calendar days
<b>7 Calendar Days:</b> Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.		
<p><b>a</b> This includes all deaths within 30 days of the last dose of treatment regardless of attribution.</p> <p><b>NOTE:</b> Any death that occurs &gt; 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.</p>		

Rev. 10/13, 11/13

5.4.4 **Reporting second primary cancers**

All cases of second and secondary malignancies [including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)], regardless of attribution, that occurs following treatment on NCI-sponsored trials must be reported as follows:

1. Fax a completed TAILORx Second Primary Form within 30 days to the CTSU by fax at 301-545-0406.

**NOTE:** A TAILORx CTSU Data Transmittal Form should accompany all forms and reports submitted to the CTSU.

**NOTE:** The TAILORx Second Primary Form should not be used to report recurrence or development of metastatic disease.

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

## 6. Measurement of Effect

**NOTE:** Recurrence must be documented by biopsy and/or evidence of disease on radiologic studies. Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Whenever possible, histologic proof of recurrence should be obtained.

### 6.1 Ipsilateral Breast Tumor Recurrence (IBTR)

Recurrence occurring within the ipsilateral breast in a patient who has had prior breast conserving therapy (ie, lumpectomy). Patients who develop an IBTR must continue to be followed for other sites of recurrence, which must be reported if they occur. Development of invasive disease in the ipsilateral breast should be reported as IBTR, not as a new primary cancer. New sites of ductal carcinoma in situ (DCIS) should be reported, but will not be considered an IBTR and follow-up for IBTR should continue.

### 6.2 Local/Regional Recurrence (LRR)

One or both of the following: (a) nodal relapse: recurrence in regional lymph nodes (e.g., ipsilateral axillary, supraclavicular, or internal mammary lymph nodes), and/or (b) recurrence in the skin and/or chest wall in a patient who has had a prior mastectomy or breast conserving surgery. Patients who develop an LRR must continue to be followed for other sites of recurrence, which must be reported if they occur.

### 6.3 Distant Recurrence (DR)

The development of a distant recurrence of breast cancer, including distant organs (eg, brain, liver, lungs, bone, etc) and/or non-regional lymph nodes (eg, mediastinal, cervical, contralateral axilla, etc). Patients who develop a distant recurrence must continue to be followed for survival; other sites of recurrence/progression do not need to be reported.

### 6.4 Second Primary Breast Cancer

Evidence of invasive breast cancer in the contralateral breast. Histologic confirmation of second primary breast cancers is required. New sites of DCIS should be reported, but are not to be considered an event for purposes of analysis, and patients with DCIS should continue to be followed for development of invasive disease. Patients who develop a second primary breast cancer must continue to be followed for other sites of breast cancer recurrence, which must be reported if it occurs.

### 6.5 Second Primary Cancer (non-breast)

Any non-breast invasive cancer except squamous or basal cell carcinoma of the skin. New in situ cancers at any site (except breast) should not be reported. Patients who develop a second primary cancer must continue to be followed for breast cancer recurrence, which must be reported if it occurs.

6.6 Disease-Free Survival (DFS)

Date of randomization or registration to the date of ipsilateral breast tumor recurrence, local/regional recurrence, distant recurrence, second primary cancer (breast or non-breast), or death from any cause.

6.7 Distant Recurrence-Free Interval (DRFI)

Date of randomization or registration to the date of distant recurrence of breast cancer, as defined in Section [6.3](#), or of death with distant recurrence, if death is the first manifestation of distant recurrence.

6.8 Recurrence-Free Interval (RFI)

Date of randomization or registration to the date of first recurrence of breast cancer (IBTR, LRR, or DR) or to the date of death with recurrence, if death is the first manifestation of recurrence.

6.9 Overall Survival

Date of randomization or registration to date of death from any cause.

6.10 Cause-specific Survival

Date of randomization or registration to date of death from breast cancer.

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6.11 Quality of Life

Quality of life endpoints will be measured using patient-reported outcomes questionnaires. Domains to be assessed and instruments to be administered include perceived cognitive impairments (FACT-Cog), fatigue (FACT-Fatigue and PROMIS Fatigue SF), fear of recurrence (Assessment of Survivor Concerns), endocrine symptoms (FACT-ES) and HRQL (FACT-General).

## 7. Study Parameters

### 7.1 Therapeutic Parameters

Prestudy CBC (with differential and platelet count) and all required prestudy chemistries (as outlined in Section 3) should be done ≤ 4 weeks before pre-registration.

Rev. 9/07 [Deleted NOTE in Addendum #2]

	<u>Pre-Registration</u>	<u>Registration/ Randomization</u>	<u>Follow-up<sup>4</sup></u>
Rev. 9/07			Between every 3- 6 months x 5 years, then annually thereafter
	X		X <sup>1</sup>
	X		
	X		
	X <sup>2</sup>		
	X <sup>2</sup>		
Rev. 9/07	X <sup>3</sup>		Annual
	X		
Rev. 9/07, 7/10	BIOLOGICAL MATERIAL SUBMISSIONS and related documents: See section 10		
Rev. 9/07	X <sup>6</sup>	X <sup>7</sup>	
Rev. 9/07		X <sup>8</sup>	
Rev. 9/07		X <sup>7</sup>	
Rev. 3/09	X <sup>10</sup>		
Rev. 1/10	See Section 7.3		

1 The following events must be reported to ECOG-ACRIN within 30 days that they are known to have occurred: death from any cause, recurrence (ipsilateral breast tumor recurrence, local/regional recurrence, or distant recurrence, as defined in Section 6), or second primary cancer; if these events have not occurred, follow-up at the time points indicated for history and physical exam is required to confirm that they have not occurred.

Rev. 9/06 2 Obtained within 4 weeks prior to pre-registration

Rev. 9/07 3 Mammogram and/or Breast MRI obtained as part of the original diagnosis, biopsy and surgical treatment will suffice and need not be repeated.

4 Follow-up for up to 20 years

Rev. 9/07, 7/10 5 Oncotype DX assay (RS score) is performed by Genomic Health (see Sections 4 and 10 and Appendix V). Fax a redacted copy of the first page of the "Oncotype DX Patient Report" to the ECOG-ACRIN Operations Office Boston

Rev. 9/06 (617-582-8578, ATTN: Pre-Registration/PACCT-1). Registration/randomization may proceed 24 hours and up to 72 hours (if weekend or holiday) after submission of the Oncotype DX Patient Report to ECOG-ACRIN.

Rev. 9/07 6 MANDATORY from patients with no RS score determined prior to pre-registration. Samples must be submitted to Genomic Health, Inc for Oncotype Dx assessment. See section 10.1.

Rev. 9/07 7 Required for central review and, if patient consents, banking for future research. See section 10.3.

Rev. 9/07 8 For patients who consent to future use. See section 10.3.

9 Bilateral breast MRI alone is acceptable if mammography could not be performed.

Rev. 3/09 10 All females of childbearing potential must have a blood test or urine study within 2 weeks prior to pre-registration to rule out pregnancy.



Rev. 9/07

7.2 [Submission of Biological Materials Removed in Addendum #2]

All sample submission information can be found in section [10](#).

Rev. 1/10

7.3 Timepoints for QOL Assessments<sup>1,2</sup>

<u>Scale<sup>3</sup></u>	Baseline (Randomization)	3 months.	6 months	12 months	24 months	36 months
FACT-Cog Version 3	X	X	X	X	X	X
FACT-Fatigue subscale	X	X	X	X	X	X
PROMIS Fatigue 7-item short form	X	X	X	X	X	X
Assessment of Survivor Concerns	X	X	X	X	X	X
FACT-Endocrine Subscale	X	X	X	X	X	X
FACT-General	X			X		X

1. Assessment at randomization must be completed before treatment is initiated. All follow-up assessments should be completed on the target date or as close to the target date as possible. For follow-up assessments, QOL should be administered + two weeks of the target date.
2. All assessments are to be administered by the site and mailed back to the ECOG-ACRIN Operations Office – Boston at:  

ECOG-ACRIN Operations Office – Boston  
Attn: Data  
900 Commonwealth Avenue  
Boston, MA 02215
3. Please see PACCT-1 forms packet for QOL assessment forms.

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7.4 Requirements for Ancillary Study EL112LAB (Step 3 registration)

For all patients who have registered to Step 3, forms and samples are to be submitted as outlined in [Appendix XII](#). A schedule summary is provided below.

Kits for sample collection and shipment are available for sites in the United States and Canada. Complete the KIT ORDER FORM (Appendix XIV) and fax to Zemotak-International at (800) 815-4675. Institutions outside the United States

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and Canada who wish participate in this ancillary study are to contact the ECOG-ACRIN CBPF to discuss the logistics of specimen submissions.

**NOTE:** ECOG-ACRIN requires all samples submitted to be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See section [10.4](#).

Rev.10/13

	Registration to EL112LAB	At 1, 2, 3, 4, & 5 years after registration to EL112LAB	Tumor recurrence
Health Questionnaires	X	X	
FASTING Blood samples <sup>1</sup>	X		X
Tumor sample			X

1. Fasting draws are strongly encouraged. Provide time of last caloric intake in STS.

## 8. Drug Formulation and Procurement

### 8.1 Cyclophosphamide

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

#### 8.1.1 Other Names

Cytoxan, Neosar, CTX, CPM, NSC #261037.

#### 8.1.2 Classification

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

#### 8.1.3 Mode of Action

Cyclophosphamide metabolites are thought to disrupt cell division primarily by cross-linking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

#### 8.1.4 Storage and Stability

Tablets and injectable powder are stored at room temperature 25°C (77°F). The temperature is not to exceed 30°C (90 F°). Reconstituted parenteral solutions are stable for 24 hours at room temperature for 6-14 days if refrigerated.

#### 8.1.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

##### 8.1.5.1 Dosage in Renal or Hepatic Failure

Cyclophosphamide dosage adjustment for patients with renal or hepatic failure has not been adequately evaluated.

#### 8.1.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

#### 8.1.7 Administration

May be given orally, IV push, or by IV infusion.

#### 8.1.8 Compatibilities

Numerous compatibility studies have been published. For specific details refer to handbook on injectable drugs by Lawrence A. Trissel.

8.1.9 Availability

Cyclophosphamide is commercially available as 25 mg and 50 mg tablets and for parenteral injection as 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.

8.1.10 Side Effects

Side effects vary significantly based on the specific dose and duration of cyclophosphamide.

8.1.10.1 Incidence More Frequent (>5%)

1. Anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills)
2. Thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising; black tarry stools; blood in urine or stools; pinpoint red spots on skin). Nadir counts usually occur 7 to 12 days after administration and recovery usually complete by day 17 to 21.
3. Alopecia
4. Anorexia, nausea and vomiting
5. Gonadal suppression (azoospermia, missed menstrual periods) resulting in infertility. Return of normal gonadal function and fertility occurs with time in many younger men and women.
6. Hemorrhagic cystitis

8.1.10.2 Incidence Less Frequent (1-5%)

1. Stomatitis

8.1.10.3 Incidence Rare (1%)

1. Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat)
2. Flushing or redness of face
3. Diarrhea
4. Skin rash
5. Pneumonitis or interstitial pulmonary fibrosis
6. Syndrome of inappropriate antidiuretic hormone (siadh)
7. Chemical phlebitis (redness, swelling or pain at site of injection)
8. Secondary malignancies
9. Blurred vision, cardiac toxicity presenting as congestive heart failure
10. Hemorrhagic myocarditis

11. Cardiac necrosis
12. Pericarditis (seen with high dose regimens used with bone marrow transplantation)

#### 8.1.11 Drug Interactions

##### 8.1.11.1 Digoxin

Several studies conducted in lymphoma patients receiving combination chemotherapy including cyclophosphamide revealed a 20–50% reduction in digoxin absorption when digoxin tablets were administered. When digoxin capsules were administered no significant decrease in digoxin absorption occurred. To avoid decreased serum digoxin levels the use of digoxin in liquid form (liquid or capsules containing liquid digoxin) instead of tablets is recommended.

##### 8.1.11.2 Pentostatin

Two case reports describe fatal cardiac toxicity in patients receiving CTX 6.4 g/m<sup>2</sup> over 4 days and pentostatin 4 mg/m<sup>2</sup> over 4 hours on day 3. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

##### 8.1.11.3 Succinylcholine

Cyclophosphamide may prolong the effects of succinylcholine by irreversibly inhibiting the enzyme pseudocholinesterase. Limited clinical observations and *in vitro* studies suggest that prolonged apnea might result when succinylcholine is administered to some patients also receiving cyclophosphamide. Management options include avoiding concurrent therapy or if concurrent therapy can not be avoided, to monitor for prolonged succinylcholine effect in patients receiving both drugs. If cyclophosphamide has been administered within 10 days of succinylcholine, extreme caution should be used after succinylcholine administration. The anesthesiologist should be informed of the potential for succinylcholine-induced apnea and appropriate precautions and monitoring should be implemented.

##### 8.1.11.4 Trastuzumab

In early clinical trials the concurrent administration of cyclophosphamide and trastuzumab increased the incidence and severity of cardiac dysfunction. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended.

8.1.12 Nursing Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm<sup>3</sup> and increased risk of bleeding with platelet counts less than 20,000 cells/mm<sup>3</sup>. Advise patients to call the clinic if they develop a fever above 101°F or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters above normal intake for 72 hours after administration. Instruct patients to void more frequently to minimize occurrence of hemorrhagic cystitis. For high-dose therapy MESNA may be used.
4. Premedicate with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.1.13 References

American Hospital Formulary Service 99 – Drug Information; 832-837.

Cytosan Package Insert, Princeton, NJ: Mead Johnson Oncology Products 1998; July Micromedex Inc. Vol. 101; 1999.

USPDI Volume 1 1999; 1128-1134.

Trissel L.A, Handbook on injectable drugs (8<sup>th</sup> Ed), Bethesda, MD: American Society of Hospital Pharmacists, 1994, Pp. 287-295.

Cazin B, Gorin NC, Laporte JP. Cardiac complications after bone marrow transplantation: A report of a series of 63 consecutive transplants. *Cancer* 1986; 57:2061-2069.

Gryn *et. al.* Pentostatin increases the acute toxicity of high dose cyclophosphamide. *Bone Marrow Transplantation* 1993; 12:217-220.

Pedersen-Bjergaard J, Ersboll J, Sorenson HM. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for Non-Hodgkin's lymphoma. *Ann Intern Med* 1985; 103:195-200.

Stillwell TJ, Benson RJ. Cyclophosphamide-induced hemorrhagic cystitis: A review of 100 patients. *Cancer* 1988; 61:451-457.

Zuccherro FJ, Ed. Evaluation of drug interactions. St. Louis: Professional Drug Systems, 1997; 2/35, 12/21.

Hansten Pd, Ed. Drug interactions analysis and management. Applied Therapeutics, Inc., Vancouver, WA 1998; 185-186.

Trastuzumab Package Insert, South

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## 8.2 Methotrexate

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

### 8.2.1 Other Names

#### 8.2.1.1 Chemical Name

N-[4-[[[(2,4-Diamino-6-pteridiny)]methyl]]  
methylamino]benzoyl]-L-glutamic acid

#### 8.2.1.2 Synonyms

Methotrexate sodium, MTX, Mexate, Mexate-AQ, Folex,  
Folex PFS, Abitrexate, Rheumatrex, Amethopterin, NSC  
#740

### 8.2.2 Classification

Antimetabolite

### 8.2.3 Mode of Action

Methotrexate inhibits the enzyme dihydrofolate reductase, thereby blocking the conversion of folic acid to its active form, tetrahydrofolic acid. Inhibition of this enzyme reduces purine synthesis and the conversion of deoxyuridylate to thymidylate which inhibits the synthesis of DNA, RNA and proteins.

### 8.2.4 Storage And Stability

Store at room temperature protected from light. Reconstituted solutions are stable at room temperature for at least 1 week. Solutions (50 mg/100 mL) in PVC bags of 5% dextrose may be frozen at -20°C for at least 30 days when thawed in 2 minutes by microwave radiation. There is no loss of potency after 5 freeze-thaw cycles.

### 8.2.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

### 8.2.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

### 8.2.7 Administration

Usually administered by IV bolus (< 100 mg), or slow IV infusion over 30 minutes or longer (> 100 mg). Has also been given intrathecally, intra-muscularly, orally, intra-arterially, intraperitoneally and intravesicularly.

8.2.8 Compatibilities

Compatible with sodium bicarbonate, cytarabine, cephalothin, mercaptopurine, vincristine sulfate, hydrocortisone, leucovorin, furosemide, and amino acids. At the "Y-site," compatible with fluorouracil, cisplatin and heparin.

8.2.9 Incompatibilities

Incompatible in solution with bleomycin, fluorouracil, prednisolone sodium phosphate, droperidol, metoclopramide, and ranitidine. Aspirin, probenecid, and nonsteroidal anti-inflammatory drugs may prolong methotrexate clearance and increase toxicity. They should not be given to patients receiving larger doses of methotrexate (for 48 hours after a dose).

8.2.10 Availability

Commercially available as a lyophilized powder for injection (20, 50, 100, 250, and 1000 mg/vial), as a 25 mg/mL preservative free isotonic solution for injection (50, 100, 200 and 250 mg/vial), as a 2.5 mg/mL (5 mg vial) and 25 mg/mL (50 and 250 mg vials) preservative protected isotonic solution for injection and as a 2.5 mg tablet.

8.2.11 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia: dose-related, more likely with prolonged drug exposure; anemia.
2. Dermatologic: Skin erythema and/or rash, sometimes pruritic; alopecia; photosensitivity; furunculosis; depigmentation or hyperpigmentation; acne; telangiectasia; skin desquamation (exfoliative dermatitis) and bullae formation; folliculitis.
3. Gastrointestinal: Nausea and vomiting, uncommon with conventional doses, and usually mild; stomatitis, common, dose- and infusion duration- related and highly variable; diarrhea; anorexia; hematemesis; melena.
4. Genitourinary: Renal dysfunction: dose-related, more likely to occur in patients with already compromised renal function, dehydration, or on other nephrotoxic drugs, manifested by increased creatinine, hematuria.
5. Hepatic: Increased SGOT, mild and transient; hepatic fibrosis and cirrhosis, more likely to occur in patients receiving long-term continuous or daily methotrexate treatment.
6. Neurologic: Encephalopathy, more commonly with multiple intrathecal doses and in patients who have received cranial irradiation; tiredness, weakness, confusion, ataxia, tremors, irritability, seizures, coma. Acute side effects of intrathecal methotrexate may include: dizziness, blurred vision, headache, back pain, nuchal rigidity, seizures, paralysis, hemiparesis.
7. Allergic: Fever and chills; rash; urticaria; anaphylaxis.
8. Ocular: Conjunctivitis; excessive lacrimation; cortical blindness has occurred with high doses.



9. Pulmonary: Pneumonitis, pulmonary fibrosis, cough, dyspnea.
10. Other: Malaise; osteoporosis (aseptic necrosis of the femoral head); hyperuricemia; reversible oligospermia.

#### 8.2.12 Nursing Implications

1. Administer antiemetics as indicated.
2. Monitor for hematologic toxicity.
3. Observe for gastrointestinal toxicity (stomatitis, diarrhea); offer symptomatic care.
4. For patients who are to begin methotrexate therapy at a dose of 1 g/m<sup>2</sup> or greater: Proper functioning of kidneys must be documented. Proper hydration and alkalinization of urine must be maintained.
5. Instruct patient to use sunscreen lotion or cream when exposed to the sun.
6. Scheduling for methotrexate serum levels may be necessary in high dose situations.
7. Time of administration of infusions may be critical - should be carefully monitored. An infusion pump may be necessary.
8. High dose methotrexate (see route of administration) must be given with leucovorin rescue. Educate patient and significant other about importance of compliance with medication schedule. There may be financial implications due to the high cost of the drug.

#### 8.2.13 References

- Alkins SA, Byrd JC, Morgan SK *et al.* Anaphylactoid reactions to methotrexate. *Cancer* 1996; 77:2123-2126.
- Anon: Drugs of choice for cancer chemotherapy. *Med Lett Drugs Ther* 1997; 39:21-28.
- Anon: NCI Investigational Drugs Pharmaceutical Data. National Cancer Institute, Bethesda, MD, 1988.
- Athanikar N, Boyer B, Deamer R *et al.* Visual compatibility of 30 additives with a parenteral nutrient solution. *Am J Hosp Pharm* 1979; 36:511-513.
- Benvenuto JA, Anderson RW, Kerkof K *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; 38:1914-1918.
- Bleyer WA: The clinical pharmacology of methotrexate. *Cancer* 1978; 41:36.
- Evans WE, Crom WR, Abromowitch M *et al.* Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. *N Engl J Med* 1986; 314(8):471-477.
- Jolivet J, *et al.* The pharmacology and clinical use of methotrexate. *N Engl J Med* 1983; 309: 1094-1104.

McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; 33: 1010-13.

Product Information: Methotrexate. Immunex Corporation, Seattle, WA, 1998.

Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; 3: 1-13.

### 8.3 Fluorouracil (Infusional)

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

#### 8.3.1 Other Names

5-Fluorouracil, 5-FU, Adrucil, Efudex. NSC #19893.

#### 8.3.2 Classification

Antimetabolite.

#### 8.3.3 Mode of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

#### 8.3.4 Storage and Stability

Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

#### 8.3.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

#### 8.3.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

#### 8.3.7 Administration

The drug will be given by protracted venous infusion.

#### 8.3.8 Incompatibilities

Incompatible with doxorubicin and other anthracyclines. When giving doxorubicin IV push or through a running IV, flush line before giving

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fluorouracil. May form precipitate with fluorouracil in some concentrations.

8.3.9 Availability

Commercially available in 500 mg/10 mL ampules and vials, and 1 g/20 mL, 2.5 g/50 mL, and 5 g/100 mL vials.

8.3.10 Side Effects

1. Hematologic: Leukopenia, thrombocytopenia, anemia, can be dose limiting; less common with continuous infusion.
2. Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.
3. Gastrointestinal: Nausea, vomiting, anorexia, diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.
4. Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia).
5. Cardiac: Angina, noted with continuous infusion.
6. Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.
7. Hepatic: Hepatitis with hepatic infusion.

8.3.11 Nursing Implications

1. Monitor CBC, platelet counts.
2. Administer antiemetics as indicated.
3. Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.
4. Assess for stomatitis - oral care recommendations as indicated.
5. Monitor for neurologic symptoms (headache, ataxia).
6. Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.
7. Inform patient of potential alopecia.

8.3.12 References

Hansen R, Quebbeman E, Ausman R, et al. Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. *J Surg Oncol* 40:177-181, 1989.

Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. *Cancer* 61:36-45, 1988.

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8.4 Doxorubicin

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.4.1 Other Names

Adriamycin, Rubex, Adriamycin RDF, Adriamycin PFS, hydroxydaunorubicin, hydroxydaunomycin, ADR, NSC #123127.

8.4.2 Classification

Anthracycline antibiotic.

8.4.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.4.4 Storage and Stability

Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

8.4.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

8.4.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

8.4.7 Administration

Intravenously, either as a bolus injection or as a continuous infusion through a central venous line.

8.4.8 Incompatibilities

Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

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8.4.9 Compatibilities

Stable with vincristine in normal saline for 5 days at room temperature protected from light. Also compatible in solution with cyclophosphamide.

8.4.10 Availability

Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/mL solution for injection in 10, 20, 50, and 200 mg vials.

8.4.11 Side Effects

1. Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.
2. Dermatologic: Alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.
3. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule.
4. Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with total doses > 550 mg/m<sup>2</sup>, mediastinal irradiation pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.
5. Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity.
6. Local effects: Vesicant if extravasated; flush along vein, facial flush.

8.4.12 Nursing Implications

1. Monitor CBC, platelet counts.
2. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
3. Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete.
4. Advise patient of red discoloration of urine for 24 hours after administration of the drug.
5. Administer antiemetics as indicated.
6. Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection.
7. Be aware of "Adria" flare - most common reaction consists of an erythematous streak up the vein. It is associated with urticaria

and pruritus. Occasionally the use of corticosteroids and/or antihistamines has been useful.

8. Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

#### 8.4.13 References

Speth PA. Clinical pharmacokinetics of doxorubicin. Clin Pharmacokinetics 1988; 15:51-31.

Von Hoff DD, *et al.* Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91:710-717.

Lum BL, *et al.* Doxorubicin: Alteration of dose scheduling as a means of reducing cardiotoxicity. Drug Intell Clin Pharm 1985; 19:259-264.

### 8.5 Paclitaxel

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

#### 8.5.1 Other Names

Taxol, Onxol, Nov-Onxol, Paclitaxel Novaplus, NSC# 125973

#### 8.5.2 Classification

Antimicrotubule agent.

#### 8.5.3 Mode of Action

Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

#### 8.5.4 Storage and Stability

The intact vials may be stored under refrigeration or at room temperature. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/mL in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.

#### 8.5.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

#### 8.5.6 Preparation

Preparation of standard regimens should follow site standards.

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For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

8.5.7 Administration

Usually administered as an intravenous infusion over 3 to 24 hours with an in-line 0.22 micron filter. One-hour intravenous bolus infusions have been used in Phase I studies.

8.5.8 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole may inhibit paclitaxel metabolism, based on *in vitro* data.

8.5.9 Availability

A concentrated solution of 6 mg/mL in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% is commercially available in 5 mL vials. 100 mg/16.7 mL and 300 mg/50 mL vials are also available.

8.5.10 Side Effects

1. Hematologic: Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia).
2. Hypersensitivity: Thought to be caused by the Cremophor vehicle. Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and tachycardia. More severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.
3. Cardiovascular: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication -- Dexamethasone) may also occur.
4. Neurologic: Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).
5. Dermatologic: Alopecia (universal, complete and often sudden, between days 14-21); injection site reactions

(erythema, induration, tenderness, skin discoloration);  
infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare);  
radiation recall; and rash.

6. Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
7. Hepatic: Increased AST, ALT, bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.
8. Other: Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

#### 8.5.11 Nursing Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and stomatitis.
3. Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.
4. Advise patients of possible hair loss.
5. Cardiac monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.
6. Monitor liver function tests.
7. Advise patient of possible arthralgias and myalgias which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.
9. Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorsEL vehicle for this drug can cause tissue damage.
10. In-line filtration with a 0.22 micron filter should be used.

#### 8.5.12 References

Rowinsky EK, Casenave LA, Donehower RC. Taxol: A novel investigational microtubule agent. J Natl Cancer Inst 1990; 82:1247-1259.



Gregory RE, DeLisa AF. Paclitaxel: A new antineoplastic agent for refractory ovarian cancer. *Clin Pharm* 1993; 12:401-415.

Rowinsky EK, Eisenhauer EA, Chaudry V, *et al.* Clinical toxicities encountered with paclitaxel. *Semin Oncology* 1993; 20:1-15.

Walker FE. Paclitaxel: Side effects and patient education issues. *Semin Oncology Nurs* 1993; 9 (suppl 2):6-10.

## 8.6 Epirubicin

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

### 8.6.1 Other Names

Ellence®, 4'epidoxorubicin hydrochloride, IMI-28, ADR 143, NSC #256942

### 8.6.2 Classification

Anthracycline antibiotic.

### 8.6.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Epirubicin also inhibits topoisomerase II.

### 8.6.4 Storage and Stability

This product is available as a solution and should be stored under refrigeration.

### 8.6.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

### 8.6.6 Preparation

Preparation of standard regimens should follow site standards.

For patients receiving regimens on CTSU protocols, protocol specific preparation must be followed.

### 8.6.7 Administration

Intravenously into the side arm of a freely flowing solution of normal saline or D5W over 3-5 minutes. If the patient has a venous access device, epirubicin may be diluted further for infusion.

### 8.6.8 Incompatibilities

Heparin and dexamethasone are incompatible. Alkaline solutions (pH > 8) cause decomposition of epirubicin and result in a color change of the drug from red to blue-purple.

8.6.9 Availability

Commercially available in 50 mg /25 mL and 200 mg/100 mL vials for injection from Pfizer Oncology.

8.6.10 Side Effects

1. Hematologic: Severe myelosuppression, dose limiting, with nadir of WBC about 12-15 days after treatment; modest thrombocytopenia with nadir 8-11 days after treatment.
2. Gastrointestinal: Significant nausea and vomiting, diarrhea, mucositis, anorexia.
3. Dermatological: Alopecia, regional phlebitis, nail pigmentation (rare), vesicant.
4. Cardiovascular: Previous radiation of marrow-producing bones and/or preventive chemotherapy with anthracene or anthracycline drugs lowers the cumulative dose that may cause the development of CHF. Cardiotoxicity, manifested as tachycardia, premature ventricular beats, or flattening T-waves, may occur with cumulative doses > 700 mg/m<sup>2</sup>. With cumulative doses > 1000 mg/m<sup>2</sup>, left ventricular failure may occur (clinical CHF).
5. Neurological: Asthenia (rare).
6. Other: Fever, development of secondary AML or MDS.

8.6.11 Nursing Implications

1. Check CBC, differential, and platelets, and bilirubin before treatment.
2. Give supportive care for nausea and vomiting; administer antiemetic therapy.
3. Monitor for development of congestive heart failure (basilar rales, S<sup>3</sup>, gallop dyspnea).
4. Advise patient regarding risk of infection and bleeding.
5. If extravasation occurs, treat with ice for 30 minutes 3-4 times daily.

8.6.12 References

Cersosimo RJ, Hong WK. Epirubicin: A review of the pharmacology, clinical activity and adverse effects of an Adriamycin analogue. *J Clin Oncol* 1986; 4:425.

Ganzina F. 4'-epi-doxorubicin, a new analogue of doxorubicin: A preliminary overview of preclinical and clinical data. *Cancer Treat Rev* 1983; 10:1-22.

Robustelli D, Cuna G, *et al.* Clinical evaluation of 4'-epi-doxorubicin in advanced solid tumors. *Invest New Drugs* 1983; 1:349-353.

Walde D, *et al.* High dose epirubicin in previously untreated patients with advanced metastatic cancer: A phase I study. *Proc Am Soc Clin Oncol* 1988; 7:73.

## 8.7 Docetaxel

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

### 8.7.1 Other Names

Taxotere, RP 56976, NSC #628503.

### 8.7.2 Classification

Antimicrotubule agent.

### 8.7.3 Mode of Action

Docetaxel, a semisynthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

### 8.7.4 Storage and Stability

Docetaxel is stored at 4°C protected from light. The solvent vials may be stored at room temperature or at 4°C. The premix solution is stable for 8 hours at room temperature (15°- 25°C) or refrigerated (at 2°- 8°C). The final dilution is also stable for 8 hours. (Please note that the company is no longer recommending that the final product be placed in PVC bags).

### 8.7.5 Dose Specifics

Please refer to [Appendix II](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

If treating physician elects to use regimen other than those specified in [Appendix II](#), please contact study chair.

### 8.7.6 Preparation

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 15 seconds. Allow to stand for 5 minutes at room temperature, and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Please note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in D5W or NS. The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.9 mg/mL. Non-PVC-containing intravenous infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

### 8.7.7 Administration

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Docetaxel has been administered as a 1 to 24 hour infusion. A peristaltic infusion pump is recommended.

8.7.8 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexy] phthalate). No further information available.

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8.7.9 Availability

Docetaxel is commercially available in single-dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) docetaxel (anhydrous).

8.7.10 Side Effects

1. Cardiac: arrhythmias, pericardial effusions, palpitations.
2. Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, hypernatemia.
3. Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.
4. Neurologic: reversible dyesthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.
5. Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
6. Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.
7. Hepatic: increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction.
8. Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions.
9. Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites, flu-like symptoms, fever.

8.7.11 Nursing Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and mucositis.
3. Advise patients of possible hair loss.
4. Monitor for signs and symptoms of hypersensitivity reactions. Insure that recommended premedications are given.
5. Monitor liver function tests.

6. Evaluate site regularly for signs of infiltration.
7. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs of fluid retention and cutaneous reactions.

#### 1.1.1 References

Investigator's Brochure: Docetaxel. Rhone-Poulenc Rorer, June 14, 1995.

Pazdur R, *et al.* Phase I trial of Taxotere; Five-day schedule. *J Natl Cancer Inst* 84:1781-8, 1992.

Pazdur R, *et al.* Phase I trial of Taxotere (RP56976). *Proc Am Soc Clin Oncol* 11:111, 1992.

Burris H, *et al.* A phase I clinical trial of Taxotere as a 6-hour infusion repeated every 21 days in patients with refractory solid tumors. *Proc Am Soc Clin Oncol* 11:137, 1992.

Bissett D, *et al.* Phase I study of Taxotere (RP56976) given as a 24-hour infusion. *Proc Am Assoc Cancer Res* 33:526, 1992.

Bruno R, *et al.* Clinical pharmacology of Taxotere (RP56976) given as a 1-2 hour infusion every 2-3 weeks. *Proc Am Assoc Cancer Res* 33:261, 1992.

DeValeriola D, *et al.* Phase I pharmacokinetic study of Taxotere (RP56976) administered as a weekly infusion. *Proc Am Assoc Cancer Res* 33:1563, 1992.

## 8.8 Tamoxifen

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

### 8.8.1 Other Names

Nolvadex, tamoxifen citrate, NSC# 180973

### 8.8.2 Classification

Hormone antagonist (antiestrogen).

### 8.8.3 Mode of Action

Tamoxifen and its metabolites possess antiestrogenic activity due to their ability to compete with estradiol for binding to receptors in the cells of tumors that contain high amounts of estrogen receptors (such as breast cancer). The tamoxifen-estrogen receptor complex is translocated from the cytoplasm of cancer cells to the nucleus where it reduces DNA synthesis and cellular responses to estrogen. Tamoxifen also displays mild estrogenic activity and induces secretion of transforming growth factor beta (TGF-beta), which has inhibitory effects on many types of epithelial cells.

### 8.8.4 Storage and Stability

Tamoxifen is stored at room temperature protected from light.

### 8.8.5 Dose Specifics

Please refer to [Appendix III](#) for standard regimen dose and schedule.

If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule.

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If treating physician elects to use regimen other than those specified in [Appendix III](#), please contact study chair.

8.8.6 Preparation

Not applicable, tablet is ready for administration.

8.8.7 Administration

Oral.

8.8.8 Incompatibilities

Tamoxifen is a potent inhibitor of hepatic cytochrome P450 mixed function oxidases (MFO). The effect of tamoxifen on the metabolism and excretion of other drugs requiring MFO for activation is unknown. Phenobarbital decreased tamoxifen serum level significantly in one patient. Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen levels. Tamoxifen may potentiate the anticoagulant effects of warfarin.

8.8.9 Availability

Tamoxifen is commercially available in 10 mg and 20 mg tablets.

8.8.10 Side Effects

1. Hematologic: Thrombocytopenia, usually mild and transient, leukopenia, anemia.
2. Dermatologic: Rash, erythema.
3. Gastrointestinal: Nausea, vomiting, anorexia (may lead to weight loss), diarrhea or constipation, distaste for food.
4. Genitourinary: Vaginal bleeding or discharge, menstrual changes (amenorrhea, menstrual irregularities), pruritus vulvae.
5. Hepatic: Increased liver enzymes, cholestasis, increased bilirubin, and fatty changes in the liver.
6. Neurologic: Depression, dizziness, lightheadedness, headache, confusion, lassitude, and syncope.
7. Cardiovascular: Hot flashes, thrombophlebitis, thromboembolism, pulmonary embolism, fluid retention and edema. Thrombotic events, DVT, clotting factor abnormalities.
8. Ocular: Retinopathy, corneal opacity, slight increased risk of cataracts; corneal scarring and retinal changes have been reported.
9. Metabolic: Hypercalcemia.
10. Other: Tumor "flare" may occur in the first month of therapy, manifested as an increase in tumor-related symptoms, such as bone pain, increase in tumor size, erythema. Weight gain, fluid retention, and edema.

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11. Effects in pregnancy: classified as Category D; women should not become pregnant while taking tamoxifen.
  12. Secondary cancers: Tamoxifen increases the risk for uterine cancer and the possibility of death from this disease. Patients receiving tamoxifen should have routine gynecologic exams and report any menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge and/or pelvic pain or pressure. Tamoxifen may possibly increase the risk for gastrointestinal cancers.
- 8.8.11 Nursing Implications
1. Monitor carefully for tumor flare reactions.
  2. Teach patients and families to recognize signs and symptoms of hypercalcemia.
  3. Advise patient of potential vaginal bleeding and menstrual changes, hot flashes.
- 8.8.12 References
- Legha SS. Tamoxifen in the treatment of breast cancer. *Ann Intern Med* 1988; 109:219-228.
- Love RR. Tamoxifen therapy in primary breast cancer: Biology, efficacy and side effects. *J Clin Oncol* 1989; 7:803-815.
- Kaiser-Kupfer MI, Lippman ME. Tamoxifen retinopathy. *Cancer Treat Rep* 1978; 62:315-320.
- Lipton A, Harvey HA, Hamilton RW. Venous thrombosis as a side effect of tamoxifen treatment. *Cancer Treat Rep* 1984; 68:887-889.
- 8.9 Exemestane
- NOTE:** Please refer to package insert for complete prescribing and toxicity information.
- 8.9.1 Other names
- Aromasin®, NSC# 713563
- 8.9.2 Classification
- Steroidal aromatase inhibitor.
- 8.9.3 Mode of Action
- Exemestane irreversibly inhibits aromatase activity (approximately 98%) and reduces plasma estrone, estradiol and estrone sulphate levels by 85-95%. Exemestane is 150-times more potent than aminoglutethimide in inhibiting aromatase. Maximal aromatase suppression occurs at exemestane doses of 10-25 mg.
- 8.9.4 Storage and Stability
- Exemestane is stored at room temperature protected from light.
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- 8.9.5 Dose Specifics  
Please refer to [Appendix III](#) for standard regimen dose and schedule. If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule if this drug is used.
- 8.9.6 Preparation  
Not applicable
- 8.9.7 Administration  
Exemestane is administered orally with food.
- 8.9.8 Incompatibilities  
No clinically relevant changes in the results of clinical laboratory tests have been observed. There are no known drug-drug interactions reported.
- 8.9.9 Availability  
Exemestane is commercially available as a 25 mg tablet..
- 8.9.10 Side Effects
1. Gastrointestinal: nausea, vomiting, abdominal pain, anorexia, diarrhea.
  2. Hematologic: lymphocytopenia
  3. Dermatologic: Hot flushes, rashes.
  4. Hepatic: Increased GGT, SGOT (AST), SGPT (ALT).
  5. Neurologic: Headache, dizziness, insomnia, depression, anxiety, fatigue.
  6. Pulmonary: Cough
  7. Cardiovascular: thrombophlebitis.
  8. Musculoskeletal: bone pain, back pain, arthralgia, limb pain
  9. Other: Hair thinning, sweating.
- 8.9.11 Nursing/Patient Implications  
Inform patients of potential side effects (joint/bone pain, diarrhea, asthenia, headache, hot flushes, nausea).
- 8.9.12 References  
<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=exemestane>
- 8.10 Anastrozole
- NOTE:** Please refer to package insert for complete prescribing and toxicity information.
- 8.10.1 Other names  
Arimidex®, NSC# 719344



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- 8.10.2 Classification and Chemical Information  
Non-steroidal aromatase inhibitor.
- 8.10.3 Mode of Action  
Anastrozole selectively inhibits aromatase and lowers serum estradiol concentrations without affecting adrenal corticosteroids or aldosterone. Many breast cancers have estrogen receptors, and growth of these tumors can be stimulated by estrogens. In postmenopausal women, the principal source of circulating estrogen is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissue, with further conversion of estrone to estradiol.
- 8.10.4 Storage and Stability  
Stored at room temperature and protected from light.
- 8.10.5 Dose Specifics  
Please refer to [Appendix III](#) for standard regimen dose and schedule. If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule if this drug is used.
- 8.10.6 Preparation  
Not applicable.
- 8.10.7 Route of Administration  
Oral.
- 8.10.8 Availability  
Commercially available, Anastrozole is supplied as 1mg film-coated tablets.
- 8.10.9 Side Effects
1. Gastrointestinal: diarrhea, nausea, vomiting, abdominal pain, anorexia.
  2. Hematologic: Anemia, leukopenia (2-5%).
  3. Dermatologic: Hot flushes, rashes.
  4. Hepatic: Increased GGT, SGOT (AST), SGPT (ALT).
  5. Neurologic: Headache, pain, back pain, dizziness, insomnia, anxiety.
  6. Pulmonary: Increased cough, dyspnea, sinusitis, bronchitis, rhinitis.
  7. Cardiovascular: Hypertension, thrombophlebitis.
  8. Musculoskeletal: bone pain, back pain, arthralgia, limb pain
  9. Other: hair thinning, sweating.
-

8.10.10 Drug Interactions  
Anastrozole does not appear to cause significant inhibition of cytochrome p450 mediated metabolism. Anastrozole did not alter the pharmacokinetics or activity of warfarin in a study of 16 male volunteers (Center For Drug Evaluation 2001).

8.10.11 Nursing/Patient Implications  
Inform patients of potential side effects (joint/bone pain, diarrhea, asthenia, headache, hot flushes, nausea).

8.10.12 References  
<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=anastrozole>

8.11 Letrozole

**NOTE:** Please refer to package insert for complete prescribing and toxicity information.

8.11.1 Other names  
Femara®, NSC# 719345

8.11.2 Classification and Chemical Information  
Non-steroidal aromatase inhibitor.

8.11.3 Mode of Action  
Letrozole is an orally active highly selective, non-steroidal competitive inhibitor of the aromatase enzyme system. It binds to the P-450 portion of the aromatase enzyme to lower serum estradiol concentrations with no clinically relevant effect on progesterone or corticosteroidal synthesis. Aromatase inhibitors block the aromatase enzyme, consequently lowering estrogen levels and thereby deprive the tumor of its growth stimulus.

8.11.4 Storage and Stability  
Stored at room temperature and protected from light.

8.11.5 Dose Specifics  
Please refer to [Appendix III](#) for standard regimen dose and schedule. If patient is participating in another CTSU trial, please refer to protocol specified regimen and schedule if this drug is used.

8.11.6 Preparation  
Not applicable.

8.11.7 Route of Administration  
Oral.

8.11.8 Availability  
Commercially available, Letrozole is supplied as 2.5 film-coated tablets.

8.11.9 Side Effects

1. Gastrointestinal: nausea, constipation, diarrhea, vomiting, anorexia, dyspepsia, and abdominal pain.
2. Hematologic: Anemia, leukopenia.
3. Dermatologic: Hot flushes, rashes.
4. Hepatic: Increased GGT, SGOT (AST), SGPT (ALT).
5. Neurologic: Headache, dizziness, insomnia, anxiety.
6. Pulmonary: Dyspnea, cough, chest wall pain.
7. Cardiovascular: Hypertension, thrombophlebitis.
8. Musculoskeletal: bone pain, back pain, arthralgia, limb pain
9. Other: Hair thinning, sweating.

8.11.10 Drug Interactions

Co-administration of tamoxifen and letrozole decreases serum letrozole concentration by 38%.

8.11.11 Nursing/Patient Implications

Inform patients of potential side effects (joint/bone pain, diarrhea, asthenia, headache, hot flushes, nausea).

8.11.12 References

<http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=letrozole>

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## 9. Statistical Considerations

This section incorporates major changes made to the statistical design in November 2008. The revised design parallels the original design, but the design was updated to reflect a substantially higher rate of non-adherence with the treatment assignment than allowed in the original design, leading to an increase in the accrual goal for the randomized cohort from 4,390 to 6,860 patients. The null and the alternative hypotheses and the type I error and the power are the same as in the original design. The assumptions on the distribution of OncoType DX Recurrence Scores (RS) and on the accrual rates were also updated to reflect the experience with the study so far. The difference that could be detected in the low RS stratum (arm A) was also modified to reflect lower accrual to this group than originally expected.

The primary endpoint is invasive disease-free survival (DFS), defined to be time from randomization to first event, where the first event is any of ipsilateral breast tumor recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers), or death without evidence of recurrence (as defined in reference 4). DFS is used for the primary endpoint rather than distant relapse-free interval (DRFI, as defined in Section 6), which was used as the primary endpoint in the development of the assay, because DFS is the standard endpoint for evaluating adjuvant treatments for breast cancer, and the important question here, as in other treatment studies, is whether chemotherapy results in an overall DFS benefit of sufficient magnitude to justify its use. Patients will be followed for distant failure following local recurrence. (Note: In various presentations, the primary endpoint of the analyses of the assay in the B-20 and B-14 studies was called DRFS, and it was called 'distant recurrence' in the NEJM paper, but the definition used is the same as DRFI here.) DRFI is a key secondary endpoint, and RFI and OS as defined in Section 6 will also be analyzed.

Patients being considered for this study will have their RS evaluated, either after pre-registration (most cases) or prior to initial registration. Patients with an RS of 11 – 25 will be randomized. The randomization will be stratified on tumor size ( $\leq 2$  cm vs.  $> 2$  cm), menopausal status (pre vs. post), planned chemotherapy (taxane containing or not), planned radiation therapy [whole breast, no boost planned vs. whole breast, boost planned vs. partial breast irradiation planned vs. no planned radiation therapy (for patients who have had a mastectomy)], and RS group (11-15 vs. 16-20 vs. 21-25, added mid-study), as described in Section 4.

The overall DFS hazard rate on the tamoxifen + CMF arm of B-20 was .025 / year, which under an exponential distribution, gives 5-year and 10-year DFS rates of approximately 88% and 78%. In the preliminary results, the 5-year and 10-year DRFIs in the RS 11 – 25 group on tamoxifen+chemo are 97% and 94%, and the 5-year and 10-year DFS rates are 91% and 76%. For purposes of the calculations here, we assume exponential failure distributions with 5-year and 10-year DFS rates of 90% and 81% and 5-year and 10 year DRFI rates of 97% and 94% with chemo+hormonal therapy for the RS 11 – 25 group.

This study uses a non-inferiority design to determine whether patients with Recurrence Score (RS) between 11 and 25 derive benefit from adjuvant chemotherapy. Studies have indicated that patients with a low RS receive little if any benefit from chemotherapy and patients with a high RS receive a substantial benefit. This is biologically plausible, since the RS is driven primarily by genes reflecting cell proliferation. The test of non-

inferiority here uses a null hypothesis of no difference, as when testing for superiority, but with a larger type I error (one-sided 10%) and smaller type II error (5%) than usual. A decrease in the 5-year DFS rate from 90% with chemotherapy to 87.0% or lower on hormonal therapy alone would be considered unacceptable. This difference corresponds to a 32.2% increase in the DFS failure hazard rate from not giving chemotherapy (the hazard ratio for hormones alone / chemo + hormones is 1.322). DFS will be compared using a stratified log rank test, with the test stratified on the same factors used in the randomization (including on RS group 11-15 vs. 16-20 vs. 21-25, which was not added to the stratification until midway through the study). The primary analysis will compare treatment groups defined by the randomized treatment assignment. Patients not meeting the protocol eligibility criteria will be excluded from the primary comparison. The local lab's assessment of hormone receptor status and Her2 status will be used to determine eligibility. A secondary analysis comparing groups defined by treatment received will also be performed. Both the primary assigned treatment and secondary as treated comparisons need to be non-significant for a clear conclusion of non-inferiority of hormonal therapy alone.

It is possible that not all patients will receive their assigned therapy. Since the primary analysis will compare the randomized treatment groups, treatment non-adherence will dilute the treatment effect and reduce the power of this study. Based on data available as of October 30, 2008, it is estimated that 17% of the patients assigned to hormonal therapy plus chemotherapy are not receiving chemotherapy, and 7% of the patients randomized to hormonal therapy alone are receiving chemotherapy. To adjust the sample size to maintain adequate power for the primary comparison with these rates of non-adherence, an increase of 73% in the number of patients randomized relative to a design with 100% adherence is needed (based on the Lachin-Foulkes correction).

The design assumes randomization of 6,860 patients with RS of 11 – 25 over 3.81 years (1800/year), of which it is assumed up to 5% may be ineligible for this study (so at least 6,517 eligible patients will be enrolled). Full information corresponds to 835 DFS events in the subset of eligible patients. This is expected to occur in summer 2014 (at a median follow-up of about 5.8 years) if the 5-year DFS rates are 90% with chemotherapy and 87% without, and in spring/summer 2015 (at a median follow-up of about 6.7 years) if the 5-year DFS rates are 90% in both arms. These projections take into account a 2.5% early lost to follow-up rate (based on the number of patients withdrawing consent). Allowing time for data submission and review, actual analysis times could be as much as a year later. Based on information available on this study through October 7008, 61% of the pre-registered patients have RS 11-25 and are randomized, 13% have RS < 11 and are registered to arm A, 16% have RS > 25 and are registered to arm D, and 10% are not enrolled on any of the arms. Thus up to 11,246 patients may need to be screened to give the required number of randomizations.

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. The first interim analysis will be performed at the first DMC meeting when at least 25% of the total planned number of DFS events (209 events in the primary analysis subset) has been reported. Interim analyses will be performed for each subsequent DMC meeting until either the criteria for early stopping are met or the total planned number of DFS events has been reported, except that a scheduled interim analysis will not be performed if the increment in the information since the previous interim analysis is less than 10% of the total planned information. At each interim analysis (and at the final analysis), the stratified log rank test statistic will be computed. The stopping boundary for rejecting non-inferiority will be based on a truncated version

of the Lan- Demets error spending rate function corresponding to an O'Brien-Fleming shaped boundary with an overall one-sided type I error of 10%. At early analyses, the boundary will be truncated at a level corresponding to a one-sided nominal significance of 0.002. The boundary function will be computed to maintain the type I error rate adjusting for the effects of the truncation and the effects of the early stopping in favor of non-inferiority, discussed below. If the boundary is crossed at an interim analysis or at the final analysis, then the hypothesis of non-inferiority will be rejected. If the criteria for rejecting the hypothesis of non-inferiority are not met, then it will be concluded that hormonal therapy alone is not inferior to combined chemo+hormonal therapy.

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To allow for early stopping in favor of non-inferiority, this study will also be monitored using conditional power for the primary assigned treatment comparison above and using repeated confidence interval (RCI) methodology. At each interim analysis, the conditional power of the logrank test for the primary comparison at a type I error rate of 10% (one-sided) will be computed using simulations (incorporating the estimated distribution of treatment non-adherence). The two-sided 95% RCI on the log hazard ratio (for received hormones alone vs. received chemo + hormones), will also be computed.

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Since ITT and as treated analyses have well-known potential biases in the presence of treatment non-adherence, the hazard ratio in the subpopulation that would receive the assigned treatment if assigned to either arm will be estimated using a full mixture likelihood approach (Cuzick et al, JRSSB, 69:565-588, 2007) and the RCI obtained by inverting the corresponding likelihood ratio test. The RCI will use the critical value from the O'Brien-Fleming error spending rate function with an overall one-sided 2.5% error rate. If the conditional power of the assigned treatment analysis is < 10% and the upper limit of the RCI lies below the minimum unacceptable log ratio of  $\log(1.322)$ , then the study will be stopped in favor of non-inferiority. This monitoring rule has deliberately been chosen to be conservative, since the results must be convincing that the conclusion of non-inferiority is based on an adequate amount of information rather than on an underpowered comparison.

Accrual rates, the distribution of Recurrence Scores and treatment adherence rates will continue to be closely monitored throughout the study. If there are significant deviations from the assumptions stated above, then design modifications to ensure that adequate power will be available will be considered by the Steering Committee. If the modifications needed are not feasible, then early termination of this study will be discussed with the Steering Committee, the Breast Intergroup and CTEP. These rates will also be reported to the DMC at every DMC meeting while this study is ongoing, and the DMC may also recommend changes to the design or early termination of this study.

At the time of the final analysis, DRFI will also be compared using a stratified log rank test with one-sided type I error of 10%. Under the accrual, follow-up and adherence assumptions given above, the DRFI test will have 95% power to detect a difference in DRFI corresponding to 5-year DRFI rates of 97% on chemo+hormonal therapy vs. 95.2% on hormonal therapy alone. This analysis requires 284 DRFI failures in the subset of eligible patients. Note that in this analysis, patients who die without developing distant (breast cancer) metastases are censored at the time of death, and other intervening DFS events (eg local-regional recurrence) are ignored. While ideally this study would include an early stopping rule based on differences in DRFI, the expected number of events during the accrual period is too low to provide a meaningful stopping rule, and once accrual is completed, the release of results will be based on the primary endpoint.

Survival will also be compared. Using a stratified log rank test with one-sided type I error of 10%, at a time when 443 deaths have been observed, there would be 95% power to detect a difference in survival corresponding to 5-year survival rates of 95% on chemo+hormonal therapy vs. 92.8% on hormonal therapy alone.

Because of the high non-adherence with treatment assignment, estimated effects from the assigned treatment analyses will be biased towards no difference. Multiple analyses will be performed to estimate the actual effects of chemotherapy. These analyses will include comparing groups by treatment received (the as treated analysis), comparing treatments excluding the patients not receiving their assigned treatments (per protocol analysis), and newer statistical methods for estimating causal effects of treatment. Cox proportional hazards models stratified on the randomization stratification factors (including on RS group 11-15 vs. 16-20 vs. 21-25, which was not added to the stratification until midway through the study) will be used to estimate the treatment hazard ratios for the as treated and per protocol analyses. Details of the causal inference methods will be given in the statistical analysis plan for the study.

The interaction of the treatment effect with RS will also be examined for each of the endpoints within the various estimation methods. Smoothing spline methods (34) will be used to estimate the treatment hazard ratio as a function of RS and to test for treatment by RS interaction. One analysis will just analyze the patients in the randomized group (RS 11 – 25). A second analysis will be done estimating the failure rates as a function of RS separately in the chemo and no chemo groups. This analysis will use patients from Arms A and B to estimate the relationship without chemotherapy and patients from arms C and D to estimate the relationship with chemotherapy. This analysis should lead to more precise estimates of the relationships at the extremes of the intermediate group than the analysis limited to the RS 11 – 25 group. However, the question of whether there could be different patient selection in the three groups, potentially leading to biases in the second analysis, will also need to be considered.

Another secondary objective is to validate whether patients with Recurrence Scores <11 (Arm A) have failure rates that are low enough that adjuvant chemotherapy is unlikely to be of much absolute benefit. Based on experience through October 7008, 13% of the pre-registered entries are RS < 11 and are being enrolled for follow-up on arm A. Assuming 11,284 patients are pre-registered and 95% of the registered patients are eligible, then 1,394 eligible patients would be expected to be enrolled and followed on arm A. Based on data from NSABP B-20 and B-14, it is expected that the 10-year DRFI rate will be about 95% and the 10-year DFS rate will be between 80% and 85%. The null hypothesis of a 10-year DRFI rate of 95% will be tested by fitting an exponential model and using the Wald test statistic for the log hazard rate. With 1,394 eligible patients entered over 3.81 years and 3.5 years of additional follow-up, a one-sided test with type I error 2.5% will have power of at least 85% for the alternative that the 10-year DRFI rate is 93%. Full information for this test is 75 distant recurrence failures.

All patients with an elevated Recurrence Score > 25 (Arm D) who are assigned to receive chemotherapy will also be followed for relapse and survival. This will provide an extremely valuable resource for further correlative studies, and will be required for achieving the second primary objective (2.1.2) of evaluating emerging "Cancer Clinical Tests" as they develop. Identifying patients with a high Recurrence Score (>25) who relapse despite adjuvant chemotherapy will be just as informative as identifying patients with a low RS (<11) who relapse without chemotherapy. The ability to evaluate emerging future "Cancer Clinical Tests" will only be possible if outcome data is collected for all patients enrolled in all arms (A-D) of the trial.

For objective 2.2.4, the prognostic significance of the genomic variables (overall RS and the individual gene group scores for proliferation, HER2, ER, invasion, and other genes) will be evaluated by fitting proportional hazards regression models containing standard factors such as tumor size, hormone receptor status and tumor grade in addition to the genomic variables. The endpoint for the primary analyses will be DRFI, and models where the log hazard ratio is linear in the genomic variables will be used for the primary test of significance. For each genomic variable, the model will be fit using the standard factors and the genomic variable and the significance of the genomic variable will be determined. Additional analyses will be done to explore the functional form of the relationships using penalized spline methods and other exploratory modeling techniques. Joint models combining the gene group variables will also be fit to evaluate whether the different gene groups are of independent prognostic significance.

ER, PgR and Her2 will be centrally evaluated. Study eligibility (and hence whether cases are included in the primary analysis) will be determined by the results from the local labs. Secondary analyses excluding cases that are ER and PR negative on central review and excluding cases that are Her2 positive on central review will be performed to examine the sensitivity of the results to possible misclassification of these factors by the local labs.

Another objective of this study is to compare the prognostic and predictive power of Adjuvant! with the GHI RS and to determine if the classical information reflected in Adjuvant! adds significantly to RS. The Adjuvant! continues to undergo refinement and enhancement, but roughly it begins by estimated 10-year breast cancer specific mortality (BCSM) from SEER data based on tumor size, grade, nodal status and ER status. The benefit of treatment is estimated from the Oxford overview, and the effects of competing risks are factored in based on age and co-morbidities. Following the methodology in John Bryant's presentation at St. Gallen (2005), the Adjuvant! 10-year BCSM will be used to rank the risk level of the patients enrolled in this study. The Adjuvant! risk rankings (ARR) will then be analyzed in a similar way to the GHI RS. In the group of patients who do not receive chemotherapy (both the randomized group and the RS  $\leq$  10 cohort), models for DFS and DRFI will be fit containing RS and ARR separately and together to compare the prognostic power of these variables separately and in combination with other factors. Models with both RS and ARR will be used to determine whether either adds significant prognostic information to the other. A similar analysis will be done in the cohort of chemotherapy treated patients. Within the randomized group, analyses examining interaction of the ARR and the effect of chemotherapy, similar to those for RS, will also be performed.

Return of Research Results: The results of correlative science studies, including genomic studies, will require mature clinical results with at least five years of clinical followup, or longer. Since the research results are not anticipated to have clinical relevance to either the patient or their family members, these results will not be disclosed to the patient. If, unexpectedly, results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting is required. Research data will not be shared with individual patients when the data are generated. Sharing of research data with individual patients may occur when data have been validated by multiple studies, and testing done in CLIA-approved laboratories. The results of the research relative to objective 2.11 (the primary clinical objective) and 2.21 (a secondary clinical objective) will be released by the ECOG-ACRIN Data Monitoring Committee (DMC) in accordance with the ECOG-ACRIN DSMC Policies and Procedures



and with the criteria stipulated in the statistical section of the protocol. Use of tissue and clinical information for objective 2.12 (specimen bank) will require review by the PACCT Correlative Science Committee (as described in [Appendix- VIII](#)). Release of data regarding secondary objectives (2.21, 2.22, and 2.23) will require that a sufficient amount of time elapsed to achieve the primary objective, that the data analysis and review has been completed, and that the ECOG-ACRIN statistician has written a technical report describing the results. Standard procedures described in the ECOG-ACRIN DSMC Policies and Procedures will be followed in order to safeguard against the inadvertent release of data.

Based on previous data from E2197, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	256	0	256
Not Hispanic or Latino	10992	0	10992
<b>Ethnic Category: Total of all subjects</b>	11248	0	11248
Racial Category			
American Indian or Alaskan Native	27	0	27
Asian	151	0	151
Black or African American	857	0	857
Native Hawaiian or other Pacific Islander	4	0	4
White	10209	0	10209
<b>Racial Category: Total of all subjects</b>	11248	0	11248

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

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#### Quality of Life Analysis Plan

Perceived cognitive function as assessed by the FACT-Cog Version 3 will be used as the primary quality of life endpoint. The primary question for the Quality of Life component is to assess differences in perceived cognitive impairment among women randomized to receive hormonal treatment alone (Arm B) versus chemotherapy + hormonal treatment (Arm C). Participants receiving treatment on Arms A and D will also complete the Quality of Life assessment. Secondary analyses will examine whether participants assigned to the Secondary Study Group are similar to participants receiving comparable treatment through the Primary Study Group with regard to patient-reported outcomes measures. We will allow total accrual of 1,000 participants to the Quality of Life component of this trial. To ensure that we have adequate power to examine differences between Arms B and C, we will monitor accrual to the Primary Study Group to ensure an adequate sample size. If needed, we will close the Quality of Life component to accrual from participants on Arms A and D if we do not achieve anticipated accrual to the Primary Study Group.

Primary endpoint:

- Comparison of FACT-Cog Perceived cognitive impairment scores between participants on Arm B and Arm C at 3 month assessment

Secondary endpoints:

- Comparison of FACT-Cog scores between Arms B and C at 3, 12, 18, 24 and 36 months
- Differences in FACT-Cog change scores from randomization to 3, 6, 12, 18, 24 and 36 months
- Differences between Arms B and C on other patient-reported outcomes measures
- Differences between participants receiving hormonal treatment alone (Arm B versus Arm A) on patient-reported outcomes measures
- Differences between participants receiving chemotherapy followed by hormonal treatment (Arm C versus Arm D) on patient-reported outcomes measures

FACT-Cog summary scores, Version 3 scoring

		N	Mean	SD	Median
Pre-tx (n = 80)	FACT-Cog Perceived Cognitive Impairments (0-80)	78	64.57	12.16	67.2
	FACT-Cog Impact on QOL (0-16)	78	13.95	3.58	16
	FACT-Cog Comments from Others (0-16)	78	14.85	1.85	16
	FACT-Cog Perceived Cognitive Abilities (0-36)	74	26.25	6.22	26.4
Cycle 4 Day 1 (n = 79)	FACT-Cog Perceived Cognitive Impairments (0-80)	77	57.56	16.18	62.2
	FACT-Cog Impact on QOL (0-16)	76	12.89	4.25	15
	FACT-Cog Comments from Others (0-16)	77	14.46	2.10	16
	FACT-Cog Perceived Cognitive Abilities (0-36)	75	26.04	7.07	27
6 month post-T1 (n = 64)	FACT-Cog Perceived Cognitive Impairments (0-80)	64	58.26	14.63	60.6
	FACT-Cog Impact on QOL (0-16)	64	13.48	3.83	15
	FACT-Cog Comments from Others (0-16)	63	14.24	2.76	16
	FACT-Cog Perceived Cognitive Abilities (0-36)	64	28.18	5.67	28.3

**NOTE:** Data not available for 5 newly created items (2 perceived cognitive function, 1 comments from others, 2 perceived cognitive

As of November 3, 2009, 5408 of the planned 6860 patients have been randomized, leaving 1452 remaining to be randomized to arms B (hormonal therapy alone) and C (chemo + hormonal therapy) in the TAILORx primary study group. At the current rate, the accrual goal should be reached in early August, 2010. During that period, it is projected that an additional 800 patients should be enrolled in the secondary study groups. The potential number of participants in the QOL evaluation will depend on how quickly the amendment is activated and approved by IRBs.

The primary analysis will compare arms in the 'per-protocol' population, with cases not adhering to the chemo assignments excluded. Secondary analyses comparing all patients as treated and all patients as assigned (ITT) will also be examined. Current data suggest 17% of the patients assigned to chemo are not receiving it and 7% of the patients assigned to hormones alone are receiving chemo. Since enrollment and baseline assessment for the cognitive and QoL evaluations will occur before chemo

adherence status is definitively known, the enrollment requirements will be increased by a factor of  $1/0.85=1.176$ . So far, 62% of the randomized participants are post-menopausal and 38% are pre-menopausal.

The primary analysis to determine the effects of chemotherapy will use linear mixed models (as implemented for example in SAS PROC MIXED) to perform repeated measures regression analysis of the follow-up evaluations, with the baseline evaluation included as a covariate. Initially, a model allowing separate means for each treatment at each assessment will be used, but more parsimonious models for the changes over assessments will be considered. One particular model that will be examined is a piecewise linear model allowing a change in slope at the end of chemo. The primary analysis will treat missing data as missing at random, but sensitivity analyses using selection models to allow for various assumptions about the relationship between probability of missing data and cognitive function will also be analyzed. Power calculations will be based on ordinary t-tests without considering the adjustment for the baseline evaluation. This should give a conservative approximation to the analysis adjusting for baseline levels, if there is a reasonable degree of correlation between the baseline and follow-up levels and if missing follow-up information is missing at random.

The primary endpoint of cognitive function at 3 months will be evaluated using the FACT-COG. The primary FACT-COG evaluation will be the difference in the 3-month 'Perceived Cognitive Impairments' scale. In the pilot data in the table above, there was an average drop of 6-7 points from baseline to cycle 4 of chemotherapy and to 6 months, with an average population standard deviation of about 15. The correlation between the baseline and follow-up evaluations was also 0.5 to 0.6. With 235 patients per arm, a t-test comparing the 3-month evaluations will have 90% power for a mean difference of 4.5 points (0.3 standard deviations), allowing a two-sided type I error of 5%. Within the postmenopausal and premenopausal subsets, there will be 90% power to detect a mean difference of 5.7 and 7.35 points (0.38 and 0.49 standard deviations), respectively. Because of the correlation of the baseline and 3-month evaluations, the regression adjustment for the baseline evaluation should increase the power of these comparisons. We assume up to 10% of the cases may have incomplete information through the 3 month evaluation, so 522 patients are needed to give 235/arm analyzable. ECOG-ACRIN has demonstrated experience in E1Z03 in collecting a longitudinal data set with over 94% adherence with submitting data. This study took an active approach with sites being reminded in advance of scheduled assessment times.

Assuming there is significantly larger cognitive impairment or perceived cognitive impairment at 3 months for patients treated with chemo, a major secondary objective is investigating whether this difference persists, and if not, how long it takes to recover from the effects of chemo. Assuming an additional 5% drop out (giving 223/arm in the per-protocol analysis), a 5%-level two-sample t-test comparing the 12-months post randomization evaluations will have 90% power to detect mean differences in the FACT-COG Perceived Cognitive Impairment scale of 4.65, 5.85 and 7.50 points (0.31, 0.39, and 0.50 population standard deviations) in the overall, postmenopausal and premenopausal groups. The question of the duration of chemo-related impairment (or perceived impairment) will be investigated through modeling the assessments as a function of time in the repeated measures model. Simultaneous confidence intervals for differences over time will be determined from a model where the effects are allowed to vary smoothly over time which gives a reasonable fit to the data.

The impact of other variables, such as baseline characteristics and demographic factors will be evaluated by including them as covariates in the repeated measures regression

analysis. The relationship of cognitive function to outcomes in other domains, such as symptoms of depression and anxiety (assessed by the Hospital Anxiety and Depression Scale) and fatigue (assessed by the FACT fatigue scale) will be evaluated by including the values as (time-dependent) covariates in the longitudinal models.

Allowing up to 15% of those participating in the cognitive and QOL components to be non-adherent with the chemotherapy assignment, and hence excluded from the primary per-protocol analysis, a total of 614 patients need to be enrolled from the primary study group. At current rates, it is expected that 64% of the patients entering the primary and secondary study groups will be randomized in the primary study group. Thus participation by a total of 1000 patients should be sufficient to meet the objectives of this project.

#### Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

Rev. 9/07 **10. Tissue and Blood Specimens**

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Rev. 12/14

**NOTE:** REQUIREMENTS FOR PATIENTS PARTICIPATING IN EL112LAB (REGISTERED TO STEP 3). SEE [Appendix XII](#).

This section provides guidelines for the submission of biological materials as follows:

- Section [10.1](#): **For patients who have not had the Recurrence Score previously** determined, outlines sample and form submissions associated with request for the *Oncotype* DX assay. Submissions are during pre-registration.
- Section [10.2](#): **Applicable to all patients.** Reporting of Recurrence Score results; required for all patients prior to registration/randomization.
- Section [10.3](#): **Applicable to all patients.** Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility, for purposes of central review and, with patient consent, banking for future research. Review and banking objectives for the CBPF are summarized [Appendix VIII](#).

As of June 2007, ECOG-ACRIN requires all samples submitted from patients participating in PACCT-1/TAILORx be logged into the ECOG-ACRIN Sample Tracking System (STS) [see section [10.4](#)].

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

10.1 Pre-Registration Submissions

This section outlines the submission of original diagnostic tumor tissue to establish the *Oncotype* DX Recurrence Score (RS status). This is MANDATORY for patients with unknown Recurrence Scores (most patients). For submissions required after registration/randomization from all patients, proceed to Section [10.3](#).

All residual material from tissue submitted to GHI during pre-registration will be forwarded to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF). Requests for return of tissue blocks for purposes of patient management must be directed to the CBPF.

10.1.1 Ordering the *Oncotype* Specimen Kit

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

If the kit is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration. The kit will be shipped overnight and will contain instructions, a shipping kit (includes cryotubes and slide cassette), a mailer, and a requisition form containing barcode labels to place on the submitted materials. One *Oncotype* Specimen Kit and Requisition form should be completed per patient.

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

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Summary submission guidelines, including a draft requisition form, are provided in [Appendix V](#). Oncotype DX information provided in the packet is located in [Appendix X](#).

### 10.1.2 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 PACCT-1 /TAILORx trial. Participating sites will correspond directly with GHI, not via STS. The CBPF will log receipt of materials from GHI into the STS. Due to the size of the trial, receipt logging will not occur in real time. For more information on the STS, see Section [10.4](#).

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Material	Report/Forms	Required	Ship to:
Primary Tumor Tissue	<ul style="list-style-type: none"> <li>Oncotype DX Requisition Form</li> <li>ECOG-ACRIN Generic Specimen Submission Form (#2981)</li> </ul>	Identify all submitted materials with ECOG-ACRIN case# AND study# (PACCT-1 / TAILORx), as well as a bar code from the kit	Customer Service Genomic Health, Inc. 301 Penobscot Drive Redwood City, CA 94063 Telephone: 866-662-6897
Concurrent forms submission to CBPF	<ul style="list-style-type: none"> <li>Pathology Report with immunologic studies, if available</li> <li>Surgical Report</li> <li>Copy of Oncotype DX Requisition Form</li> <li>ECOG-ACRIN Generic Specimen Submission Form (#2981)</li> </ul>	Send forms to CBPF at the time tissue is sent to GHI.  Identify all forms with ECOG-ACRIN case# AND Oncotype DX Requisition#	<b>Fax (preferred) to:</b> 713-563-6506 Attn: Rebecca Haas  <b>Or Send to:</b> 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
Concurrent forms submission to CTSU Houston Office	<ul style="list-style-type: none"> <li>Pathology/Surgical Reports</li> </ul>	Pathology and/or Surgical Reports to the CTSU Houston Office should be accompanied by the TAILORx Source Document Tracking Form and TAILORx CTSU Data Transmittal Form.	Fax to 301-545-0406

- Residuals will be forwarded from GHI to ECOG-ACRIN CBPF for correlative studies and banking. If CBPF determines insufficient materials are available for correlative studies, an additional block will be required. In this case, your site will be notified by CBPF.

### 10.1.3 Notification of Results

Genomic Health will notify the institution of the recurrence score (RS) via the mechanism selected on the Oncotype Requisition Form within 14 days of receipt of the tissue by Genomic Health. If you do not receive an RS 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.

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## 10.2 Submitting the RS to the ECOG-ACRIN Operations Office – Boston

The site must report the RS to the ECOG-ACRIN Operations Office – Boston prior to registration/randomization. The following instructions apply to all patients (patients with no RS before pre-registering, as well as patients with a known RS prior to pre-registration).

- Make a copy of the first page of the form with the patient's name blacked out (redacted) and replaced by initials (last initial, first initial). Make sure the patient's ECOG-ACRIN sequence number appears on the form. For a sample form, please see [Appendix X](#) of the protocol.
- Fax the first page of the form to the ECOG-ACRIN Operations Office – Boston, ATTN: TAILORx Pre-Study, 617-582-8578. Include the patient's sequence number and initials on the cover sheet.
- ECOG-ACRIN Operations Office – Boston staff will enter the score in a database table. Please allow 24 hours on weekdays, 72 hours on weekends (please also make allowances for holidays) before registering your patient to step 2.

## 10.3 Registration/Randomization Submissions (All Patients)

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Samples are submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Primary tumor tissue is required for central review including validation of diagnosis, histopathology evaluation and testing of ER, PR, and Her2/neu status as outlined in [Appendix VIII](#). If slides were submitted to GHI during pre-registration for RS score determination OR if the RS score was determined PRIOR to pre-registration, tissue submission for the central evaluation is MANDATORY. For all patients, if any submitted materials are deemed inadequate for the required diagnostic studies, submission of additional pathology materials will be required.

Submissions for future research: Additional tissue (including frozen tissue, if available) is requested to be submitted from patients who answer "yes" to "My tissue may be kept for use in future research to learn about, prevent, or treat cancer". Blood samples are to be submitted from patients who answer "yes" to "I give permission for samples of my blood to be drawn and sent to ECOG-ACRIN to be kept for use in future research to learn about, prevent, or treat cancer."

All shipments are to be logged into the ECOG-ACRIN STS to allow tracking of sample submissions on the PACCT-1/TAILORx trial.

### 10.3.1 Kits

The kits contain blood collection tubes and shipping supplies to allow combined or split frozen/ambient submissions.

To order the kit, complete the PACCT-1 Peripheral Blood Collection and Shipping Kit Order Form ([Appendix VI](#)) (include the ECOG-ACRIN patient case number) and fax to Zemotak-International at 800-815-4675.

It is recommended that the kits be requested within one day after pre-registration, and prior to registration/randomization. Do not request kits prior to pre-registration.

10.3.2 Sample Submission Summary

Biological Materials	Shipping note: (Section <a href="#">10.3.4</a> )	Report/Forms	Expectancy of submissions
Rev. 12/14 Primary Tumor Tissue <sup>1</sup>	ECOG-ACRIN CBPF (Section <a href="#">10.3.3</a> ) Ambient temp, batch shipping acceptable	<ul style="list-style-type: none"> <li>Pathology Report<sup>1</sup></li> <li>Surgical Report</li> <li>Immunologic studies, if available</li> <li>STS-generated shipping manifest or ECOG-ACRIN Generic Specimen Submission Form (#2981)</li> </ul> <p>Copies of these reports and the completed form must be sent with each tumor tissue submission.</p>	<p>An additional block or acceptable alternative material is requested (not required) if</p> <ol style="list-style-type: none"> <li>Patient consented to banking</li> </ol> <p>AND</p> <ol style="list-style-type: none"> <li>Tissue block submitted to GHI after pre-registration (most patients will be in this category).</li> </ol> <p>A tissue block or acceptable alternative material is <u>required</u> if</p> <ol style="list-style-type: none"> <li>Patient had obtained an RS of 11-25 prior to pre-registration</li> </ol> <p>OR</p> <ol style="list-style-type: none"> <li>Residual material from GHI submission was insufficient for correlative studies. ECOG-ACRIN CBPF will contact the site in this circumstance.</li> </ol>
Rev. 12/14 Frozen Tumor Tissue (if available) <sup>1,2,3</sup>	Ship to CBPF using collection and shipping kit <sup>2</sup>	<ul style="list-style-type: none"> <li>Pathology Report</li> <li>Surgical Report</li> <li>Immunologic studies, if available</li> <li>STS-generated shipping manifest or ECOG-ACRIN Generic Specimen Submission Form (#2981)</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>TAILORx Virtual Frozen Tissue Bank Form (#2675).</li> </ul>	<p>If available AND patient has consented to banking of samples for possible future use:</p> <ol style="list-style-type: none"> <li>Submit frozen material to ECOG-ACRIN CBPF with indicated forms</li> </ol> <p>OR</p> <ol style="list-style-type: none"> <li>Retain frozen tissue on site and submit TAILORx Virtual Frozen Tumor Form (#2675) to CBPF.</li> </ol>
Rev. 12/14 Plasma, EDTA purple top <sup>2</sup>	Ship to CBPF on dry ice (preferred) or frozen packs. May be batch shipped.	<p>If logged in Sample Tracking System (STS), include STS shipping manifest. If STS unavailable, include TAILORx Material Submission Form (#2539) or ECOG-ACRIN Generic Specimen Submission Form (#2981)<sup>4</sup></p>	<p>Submit if patient has consented to banking. Samples are drawn after registration/randomization and prior to start of therapy.</p>
Rev. 12/14 Serum, SST <sup>2</sup>			
Rev. 12/14 Peripheral blood, citrate CPT <sup>2</sup>	Ship to CBPF at ambient temp, day of collection		
Rev. 12/14 Peripheral blood PAXgene DNA <sup>2</sup>			

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1. Fax: Pathology report with TAILORx Source Document Tracking Form and TAILORx CTSU Data Transmittal Form.



2. Collection and shipping kits ordered by faxing PACCT-1 Collection and Shipping Kit Order Form ([Appendix-VI](#)) to Zemotak-International at 800-815-4675.
- Rev. 12/14 3. If frozen tissue will be retained at the local site, submit a completed TAILORx Virtual Frozen Tissue Bank Form (#2675) to the ECOG-ACRIN CBPF (fax to 713-563-6506, Attn: Rebecca Haas)
- Rev. 8/08 4. In this event, a copy of the Material Submission Form must be faxed to the CTSU with a TAILORx CTSU Data Transmittal Form. Refer to [Appendix XI](#)

### 10.3.3 Tumor Tissue

Tissue is to be submitted within two weeks following registration/randomization. Do not submit tissue from patients who have not pre-registered to the PACCT-1 /TAILORx trial.

#### 10.3.3.1 Fixed Tissue

One (1) paraffin block of the primary cancer. Submit with forms as noted in the table 10.3.2. This will be required for some patients, and is requested for others, as follows:

- Pre-registration of patient with known RS score (no samples submitted to GHI on protocol):  
MANDATORY
- Pre-registration of patient with unknown RS score (materials submitted per protocol section [10.1](#), above. Most patients will be in this category):
  - If slides, rather than a block, were submitted to Genomic Health: Submission of tissue to CBPF is MANDATORY
  - Blocks submitted to Genomic Health: additional materials are requested to be submitted to the ECOG-ACRIN CBPF. Be aware that if the material forwarded to the CBPF by Genomic Health is inadequate for the required diagnostic studies, submission of additional pathology materials will be required

If an institution will not allow block release, the institution MUST contact the ECOG-ACRIN CBPF (Tel: 844-744-2420, Email: [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org)) to request alternative submission requirements.

Samples are to be shipped at ambient temperature within two weeks following registration/randomization. If possible, ship with peripheral blood samples.

#### 10.3.3.2 Frozen Tissue

If available, submit from patients consenting to banking. Submit with forms as noted in the table 10.3.2.

Tissue **must remain frozen** during the shipment. Ship overnight **on dry ice**, Sunday through Thursday only. Do not ship the day before a holiday.

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Frozen tissue may be batched and shipped with the frozen plasma and serum samples.

If the STS is unavailable on the day of the shipment, complete an ECOG-ACRIN Generic Specimen Submission Form (#2981) and fax to the ECOG-ACRIN CBPF at 713-563-6506.

**NOTE:** Available frozen tissue may remain at local sites until requested by the ECOG-ACRIN CBPF. If materials will be retained until requested, submit a completed TAILORx Virtual Frozen Tissue Bank Form (#2675) to the ECOG-ACRIN CBPF.

#### 10.3.4 Blood samples

Submit from patients consenting to banking.

Samples are drawn after registration/randomization and prior to start of therapy. Collect Sunday through Thursdays preferred. Samples collected on a Friday must be submitted as a split shipment (see 10.3.5, Part B). Do not collect on the day before a holiday.

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All blood samples are shipped via OVERNIGHT delivery using the airbill provided in the kit. If STS is unavailable on the day of the shipment, complete an ECOG-ACRIN Generic Specimen Submission Form (#2981) and fax to the ECOG-ACRIN CBPF at 713-563-6506.

- Samples shipped at ambient temperature must be sent on the day of collection. In hot weather, please include a cool pack but wrap/insulate samples so the samples cannot freeze.
- Frozen samples are to be shipped on dry ice (preferred) or frozen cool packs. Multiple patient samples may be batched and shipped monthly. Ship on Sunday through Thursday only. Do not ship the day before a holiday.

All blood samples are to be submitted with an STS shipping manifest or a completed ECOG-ACRIN Generic Specimen Submission Form (#2981) if STS is unavailable.

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**NOTE:** These guidelines are for the U.S., Hawaii, Puerto Rico and proximal Canadian sites only. International sites must contact the ECOG-ACRIN CBPF to make special arrangements.

Ship Frozen

1. Serum: **SST red/grey marble top** vacutainer
  - a. Draw peripheral blood into vacutainer.
  - b. Allow blood to coagulate 20 minutes, then centrifuge at 25°C, 1500xg (2700-3000 rpm) for 15 minutes.
  - c. Pipette the serum into 4 cryotubes provided in the kit.
  - d. Store frozen, below -20°C (-70 °C preferred), until shipped

Ship Ambient

2. Peripheral Blood: **citrate CPT** (blue/black top)

- |              |    |  |
|--------------|----|--|
|              |    | <ul style="list-style-type: none"> <li>a. Draw 8mL peripheral blood into vacutainer and gently invert 8-10 times.</li> <li>b. Within 20 minutes of collection, centrifuge at 1500xg (2700-3000 rpm) for 20 minutes.</li> <li>c. Resuspend cells within the tube by gently inverting 1 time.</li> <li>d. Ship at ambient temperature the day of collection.</li> </ul>  |
| Ship Frozen  | 3. | <p>Plasma: <b>EDTA purple top tube</b></p> <ul style="list-style-type: none"> <li>a. Draw peripheral blood into vacutainer and gently invert 8-10 times.</li> <li>b. Within 20 minutes of collection, centrifuge at 1500xg (2700-3000 rpm) for 15 minutes.</li> <li>c. Pipette the plasma into <b>4 cryotubes</b> provided in the kit and store frozen, below <math>-20^{\circ}\text{C}</math> (<math>-70^{\circ}\text{C}</math> preferred), until shipped</li> <li>d. Remaining Cells: <b>EDTA purple top tube</b></li> </ul> |
| Ship Ambient |    | <ul style="list-style-type: none"> <li>e. Replace the stopper on the EDTA tube containing the cells and ship ambient the day of collection</li> </ul>  |
| Ship Ambient | 4. | <p>Peripheral blood: one <b>PAXgene DNA tube</b></p> <ul style="list-style-type: none"> <li>a. Draw peripheral blood into vacutainer, then gently invert tube 8-10 times.</li> <li>b. Ship at ambient temperature the day of collection.</li> </ul>  |

### 10.3.5 Shipping Guidelines

These guidelines are for the U.S., Hawaii, Puerto Rico and proximal Canadian sites only. International sites must contact the ECOG-ACRIN CBPF to set up special arrangements.

All blood and frozen tissue samples are shipped via OVERNIGHT delivery using the airbill (FedEx account number **212898813-PACCT**) provided in the kit. If frozen tissue is submitted, the frozen samples MUST be shipped on DRY ICE.

Log the shipment into the ECOG-ACRIN STS the day of shipment. If STS is unavailable at time of shipment, complete an ECOG-ACRIN Generic Specimen Submission Form (#2981) and fax to the ECOG-ACRIN CBPF at 713-563-6506. Once STS is available, retrospectively log the submissions using the actual collection and shipping dates.

Fixed, paraffin embedded tissue samples are to be packaged to prevent breakage and shipped no later than two weeks following registration/randomization. Samples may be submitted with the ambient blood shipment.

**A. Combination Shipment:** Shipping Both Frozen and Ambient Samples Together.

For shipments with blood draws performed Monday through Thursday ONLY.

- Line the styrofoam containers with enough absorbent material to absorb any contents that may leak.
- Each frozen sample must be in its own cryovial or sealed container. The frozen samples are then placed into a biohazard bag, sealed and placed into the large styrofoam container.
- Add DRY-ICE or Frozen Brick into large styrofoam. Use enough of DRY ICE to last 4 days. Cover the Styrofoam.
- Place room temp samples (PaxgeneDNA, CPT and EDTA cell tube) into small styrofoam/cardboards provided. Fixed tissue blocks may be submitted with these samples.
- Place the styrofoam containers into large cardboard box.
- Affix IATA labels (UN3373, Biohazard, and DRY-ICE label if dry-ice is used) on the cardboard box. Sites outside of US borders must include CDCP permit label on shipment.
- Place documents (STS Shipping manifest or Material Submission Form) on top, then seal box.

**B. SPLIT SHIPMENT FOR FRIDAY COLLECTION**

For blood specimens drawn on Friday and/or before holidays, ambient shipments **MUST** be mailed the day of collection. Keep frozen plasma and serum at  $-20^{\circ}\text{C}$  or colder until next business day to ship. Package in the individual styrofoam containers as outlined above and ship in separate cardboard boxes.

Affix IATA labels (UN3373, Biohazard, DRY ICE if applicable) on the cardboard boxes. Sites outside of US borders must include CDCP permit label on shipment.

**Ship to:** 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 (713-745-4440 Local or International Sites)  
Fax: 713-563-6506  
Email: [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org)

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10.4 ECOG-ACRIN Sample Tracking System

Rev. 2/13

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, 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>.

Rev. 11/07

Important: 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.

A shipping manifest must be generated and shipped with all sample submissions.

Rev. 2/13

For the EL112LAB Ancillary Study, if STS is unavailable at time of sample submission, a completed Generic Specimen Submission Form (#2981) is to be faxed to the receiving laboratory and included with the sample shipment. When STS becomes available, the submissions must be retroactively logged into the system, using actual submission dates and tracking numbers. Indicate on the submission for the appropriate Lab:

- ECOG-ACRIN CBPF
- FCCC Clinical Protocol Support Lab

Please direct your questions or comments pertaining to the STS to

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[ecog-acrin.tst@jimmy.harvard.edu](mailto:ecog-acrin.tst@jimmy.harvard.edu).

#### 10.5 ["Processing of Specimen in ECOG-ACRIN Central Biorepository and Pathology Facility" Deleted in Addendum #2]

Processing information is available in [Appendix VII](#).

#### 10.6 Banking

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. Residual materials from any laboratory studies, including the Oncotype DX 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 ECOG-ACRIN CBPF.

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#### 10.7 Lab Data Transfer Guidelines

Rev. 12/14

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.

#### 10.8 Sample Inventory Submission Guidelines

Rev. 12/14

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 ECOG-ACRIN Translational Science Team.

## 11. Records to Be Kept

Rev. 9/07 Please refer to the PACCT-1 Forms Packet for the forms submission schedule and copies of all forms. The PACCT-1 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (<http://www.ecog.org>) or CTSU website ([www.CTSU.org](http://www.CTSU.org)).

Data management activities for the PACCT-1 (TAILORx) study will be performed by the Cancer Trials Support Unit (CTSU). For this reason, investigators and study support staff involved in the collection and reporting of study data must be registered members of the CTSU. Please see the CTSU website ([www.ctsu.org](http://www.ctsu.org)) for details on registering as a CTSU member.

Rev. 1/10 Data management activities for the QOL portion of the study will be done by the ECOG-ACRIN Operations Office – Boston.

### Data Completion and Submission Guidelines

Rev. 9/06  
Rev. 11/07 All ECOG-ACRIN and non-ECOG-ACRIN sites are required to submit patient data via the CTSU (with the exception of Expedited Adverse Event Reporting and the AML/MDS/ALL Report Form; please follow instructions in section 5.3 for submission of AE data).

Rev. 1/10 **NOTE:** All ECOG-ACRIN and non-ECOG-ACRIN sites are required to submit the QOL data directly to the ECOG-ACRIN Operations Office – Boston.

Sites that are pre-selected by ECOG-ACRIN to participate in the CTSU RDC system should take special note of the RDC instructions in the CTSU appendix of this protocol ([Appendix XI](#)). The CTSU help desk is available to answer questions about data submission at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

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

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

## 12. Patient Consent and Peer Judgment

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

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**Appendix I**

**Informed Consent Template [Deleted in Update #7]**

**INFORMED CONSENT INTENTIONALLY REMOVED FROM  
PROTOCOL DOCUMENT**

**Appendix I was removed from the protocol document in Update #7 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines**

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**Appendix I-A**

**EL112LAB: North American Breast Cancer Groups Biospecimen  
Bank for Determinants of Late Relapse in Operable Breast Cancer  
Suggested Patient Consent Form [Deleted in Update #7]**

**INFORMED CONSENT INTENTIONALLY REMOVED FROM  
PROTOCOL DOCUMENT**

**Appendix I-A was removed from the protocol document in Update #7 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines**

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**Appendix II**

**Chemotherapy Regimens**

Regimen Code	Regimen Name	Regimen Dose/Schedule	Regimen Schedule	No. of Cycles
1	Oral CMF	C 100 mg/m <sup>2</sup> /day PO x 14 days M 40 mg/m <sup>2</sup> IV days 1, 8 F 600 mg/m <sup>2</sup> IV days 1, 8	Every 4 weeks	6
2	IV CMF	C 600 mg/m <sup>2</sup> IV M 40 mg/m <sup>2</sup> IV F 600 mg/m <sup>2</sup> IV	Every 3 weeks	6-8
3	Standard AC	A 60 mg/m <sup>2</sup> IV C 600 mg/m <sup>2</sup> IV	Every 3 weeks	4
4	Dose dense AC	A 60 mg/m <sup>2</sup> IV C 600 mg/m <sup>2</sup> IV Plus G-CSF	Every 2 weeks	4
5	Standard AC - T	A 60 mg/m <sup>2</sup> and C 600 mg/m <sup>2</sup> IV every 3 weeks x 4 cycles ⇒ T 175 mg/m <sup>2</sup> every 3 weeks x 4 cycles	Every 3 weeks	8
6	Dose dense AC - T	A 60 mg/m <sup>2</sup> and C 600 mg/m <sup>2</sup> IV plus G-CSF every 2 weeks x 4 cycles ⇒ T 175 mg/m <sup>2</sup> plus G-CSF every 2 weeks x 4 cycles	Every 2 weeks	8
7	FEC	F – 500 mg/m <sup>2</sup> IV E – 50-100 mg/m <sup>2</sup> IV C – 500 mg/m <sup>2</sup> IV	Every 3 weeks	6
8	TAC	T - 75 mg/m <sup>2</sup> A - 50 mg/m <sup>2</sup> C - 500 mg/m <sup>2</sup> <b>NOTE:</b> TAC should be used only in women ≤/ = 70 years of age	Every 3 weeks	4-6
9	TC	T - 75 mg/m <sup>2</sup> C - 600 mg/m <sup>2</sup>	Every 3 weeks	4
10	Other protocol-specified regimens	Participating in other CTSU trials including chemotherapy	As specified in protocol	As specified in protocol

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Rev. 9/06	11	Other regimens not protocol-specified	<b>Contact study chair:</b> Not participating in other CTSU trials; treating physician elects to use regimen other than regimens 1-9; contact study chair, Joseph Sparano, M.D.		
Rev. 9/06	<p>Abbreviations:</p> <p>C – cyclophosphamide;  A – doxorubicin (Adriamycin);  M – methotrexate;  F – 5-fluorouracil;</p> <p>T - paclitaxel (Taxol) in AC-T regimens (regimen codes 5 or 6), or docetaxel (Taxotere) in TC and TAC regimens (regimen codes 8 and 9)  E - epirubicin; G-CSF – granulocyte colony stimulating factor (or pegfilgrastim);  IV - intravenous</p>				

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**Appendix III**

**Hormonal Therapy Regimens**

**Years 1- 5**

Regimen Code	Menopausal Status	Regimen
A	Pre, Peri, or Post	Tamoxifen 20 mg PO daily
B	Post	Anastrozole (Arimidex) 1 mg PO daily
C	Post	Letrozole (Femara) 2.5 mg PO daily
D	Post	Exemestane (Aromasin) 25 mg PO daily
E	Pre or Peri	Participating in another CTSU study; as specified in treatment protocol
F	Post	Participating in another CTSU study; as specified in treatment protocol
G	Pre or Peri	Ovarian suppression (surgery, irradiation, or Gn RH analogue) may be used in conjunction with tamoxifen or an aromatase inhibitor, and may continue beyond 5 years.

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**NOTE:** Patients who are intolerant of one hormonal regimen may switch to another regimen.

**Years 6-10**

Regimen Code	Menopausal Status at year 6	Treatment during years 1-5	Treatment years 6-10
1	Pre or Peri	Tamoxifen 20 mg PO daily	No further treatment
2	Post	Tamoxifen 20 mg/ PO daily	Any aromatase inhibitor
3	Post	Any aromatase inhibitor	No further treatment
4	Post	Any aromatase inhibitor	May continue aromatase inhibitor
5	Pre or Peri	Any treatment	Participating in CTSU study; as specified in protocol
6	Post	Any treatment	Participating in CTSU study; as specified in protocol

**Definition of Menopausal Status:**

Menopausal will be defined according to the following criteria:

**Post-menopausal:**

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)
- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4 IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

**Pre- or peri-menopausal:**

Not meeting definition for postmenopausal outlined above

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**Appendix IV**

**Submission of Biological Materials and Related Documents**

**[Removed in Addendum #2]  
See Section [10](#)**

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
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**Appendix V**

**Pathology Submission Guidelines**

The following items are included in [Appendix V](#):

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1. Checklist for PACCT-1 Material Submissions
2. Guidelines for Submission of Pathology Materials  
(instructional sheet for Clinical Research Associates [CRAs])
3. Instructional memo to submitting pathologists
4. Copy of Genomic Health *Oncotype* DX Requisition Form with study-specific instructions

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Rev. 12/14

**NOTE:** Pathology Submission Form (#638 v04.2) is no longer required for this protocol. If the ECOG-ACRIN Sample Tracking System (STS) is unavailable at the time of specimen submission, a completed ECOG-ACRIN Generic Specimen Submission Form (#2981) is to serve as the shipping manifest. Retroactively enter all submissions into STS using actual submission dates.



Rev. 9/07 Checklist for PACCT-1 Material Submissions:

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). See section [10.4](#).

Rev. 7/10 **A. Pre-registraton: MANDATORY if Oncotype DX Recurrence Score NOT previously performed**

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

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

DO NOT MIX BARCODE LABELS BETWEEN PATIENTS.

**Submit to GENOMIC HEALTH:** (see [Appendix X](#))

\_\_\_\_\_ Primary 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)

Rev. 12/14 \_\_\_\_\_ Completed ECOG-ACRIN Generic Specimen Submission Form (#2981)

\_\_\_\_\_ Completed Oncotype DX Requisition Form

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

- For the “PROCESSING CODE” **enter the protocol number and the ECOG-ACRIN patient case number** assigned at pre-registration (e.g. PACCT-1-10001).
- Method of payment (section III): Complete with patient’s insurance information.
- ADDITIONAL PHYSICIAN (section V): Enter the contact information of the Institutional CRA coordinating the PACCT-1 study.
- COMMENT, section VII (REQUIRED): Enter the protocol number “PACCT-1” and the patient’s ECOG-ACRIN case number.
- **“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 ECOG-ACRIN CBPF.
  - BLOCK RETURN CONTACT = ECOG-ACRIN Central Biorepository and Pathology Facility
  - BLOCK RETURN ADDRESS = MD Anderson Cancer Center, Department of Pathology, Unit 085, Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586, 1515 Holcombe Blvd
  - CITY = Houston, STATE = TX, ZIP = 77030

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- BLOCK RETURN PHONE NUMBER = 844-744-2420

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**Submit to the ECOG-ACRIN CBPF and the CTSU:**

- \_\_\_ Pathology and surgical reports, including immunological studies if performed.
- \_\_\_ Copy of completed ECOG-ACRIN Generic Specimen Submission Form (#2981) with GHI barcode
- \_\_\_ Shipping Manifest from Sample Tracking System (STS) to ECOG-ACRIN CBPF only

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**B. Registration/Randomization (STEP 2)**

Rev. 12/14

The required materials are to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility after pre-registration, but no later than two weeks following patient registration/randomization to the PACCT-1/TAILORx trial.

**NOTE:** Frozen tumor tissue is requested on all registered/randomized patients consenting to banking. See Section [10.3](#) for kit requests, sample preparation, and shipping guidelines.

There are two registration scenarios for submission:

1. Oncotype DX Recurrence Score (score 11-25) performed PRIOR to pre-registration.

- \_\_\_ Primary Tumor Tissue Block - **Submission is MANDATORY**
  - \_\_\_ Additional Primary Tissue Block, if available and patient consented to banking
- Include the following with ALL pathology submissions:

Rev. 12/14

- \_\_\_ Pathology and surgical reports, including immunological studies if performed.
- \_\_\_ Copy of completed ECOG-ACRIN Generic Specimen Submission Form (#2981)
- \_\_\_ Shipping Manifest from Sample Tracking System (STS)

2. Oncotype DX Recurrence Score performed after pre-registration, prior to registration/randomization

Rev. 2/13

- A. If SLIDES were sent to GHI
- \_\_\_ Primary Tumor Tissue Block - **Submission is MANDATORY**
  - \_\_\_ Additional Primary Tissue Block, from patients who consented to banking
  - \_\_\_ Frozen tissue, if available and patient consented to banking
- Include the following with ALL pathology submissions:

Rev. 12/14

- \_\_\_ Pathology and surgical reports, including immunological studies if performed.
- \_\_\_ Copy of completed ECOG-ACRIN Generic Specimen Submission Form (#2981)
- \_\_\_ Shipping Manifest from Sample Tracking System (STS)

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- B. If Tissue Block was sent to GHI, submit the following from patients who consented to banking their tissue

**NOTE:** If the residual material from GHI submission was insufficient for correlative studies, submission of additional tumor tissue is mandatory. ECOG-ACRIN CBPF will contact the site in this circumstance

Additional Primary Tissue Block

Frozen tissue, if available

Include the following with ALL pathology submissions:

Pathology and surgical reports, including immunological studies if performed.

Copy of completed ECOG-ACRIN Generic Specimen Submission Form (#2981)

Shipping Manifest from Sample Tracking System (STS).

Rev. 2/13 **C. Registration (STEP 3) To Ancillary Study EL112LAB**

Tumor tissue samples, blocks preferred, from recurrence biopsy are to be submitted. See [Appendix XII](#).

### Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)
- Shipping Manifest from Sample Tracking System (STS)

These are also requested for samples submitted to Genomic Health on PACCT-1

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#### Instructions:

1. Provide the following information to the pathologist.

- Patient's name (last, first)
- Protocol number
- Protocol case number (the patient's ECOG-ACRIN sequence number)
- Patient's hospital number
- Institution
- Affiliate (if appropriate)

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Rev. 12/14 2. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material, to the appropriate pathologist.

Rev. 12/14 3. The pathologist should return to you the required pathologic samples and surgical pathology reports, along with the completed ECOG-ACRIN Generic Specimen Submission Form (#2981). If any other reports are required, they should be obtained from the appropriate department at this time.

Rev. 9/07 4. Keep a copy of the ECOG-ACRIN Generic Specimen Submission Form (#2981) for your records.  
Rev. 12/14

Rev. 9/07 5. Double check that ALL required forms, reports, and pathology samples are included in the package to send to the Central Biorepository and Pathology Facility or Genomic Health.  
Rev. 12/14

**Pathology specimens submitted for a patient WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.**

Rev. 9/07 6. Tissue to be submitted for the determination of Oncotype Recurrence Score is to be shipped as outlined in section [10.1](#).

Customer Service  
Genomic Health, Inc.  
301 Penobscot Drive  
Redwood City, CA 94063

To order specimen kits and requisition forms, contact Genomic Health Customer Service (866-662-6897).

- Rev. 9/07 7. Mail all pathology reports, surgical reports, and pathology materials for additional laboratory  
Rev. 12/14 studies and banking to:

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

If you have any questions concerning the above instructions, or if you anticipate any problems in meeting the pathology material submission deadline of 72 hours for the Recurrence Score assessment, or within two weeks following registration/randomization for banking samples, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility at Tel: 844-744-2420 or email [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org).

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- Rev. 9/07 8. Copies of submitted pathology reports must be submitted to CTSU as indicated in [Appendix XI](#).

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**MEMORANDUM**

**TO:** (Submitting Pathologist)

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

**DATE:**

**SUBJECT:** Submission of Pathology Materials for Program for the Assessment of Clinical Cancer Tests (PACCT-1): *Trial Assigning Individualized Options for Treatment*. The TAILORx Trial.

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The patient named on the attached ECOG-ACRIN Generic Specimen Submission Form (#2981) has been entered onto an ECOG-ACRIN protocol by \_\_\_\_\_ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for determination of Onco<sup>type</sup> DX Recurrence Score (RS), pathology review, laboratory studies, and banking.

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For submission of tissue to Genomic Health for RS assessment, complete the Onco<sup>type</sup> DX Requisition Form provided in the Onco<sup>type</sup> DX Specimen Kit. On the requisition form, the PROCESSING CODE must be completed with the protocol number PACCT-1, and the patient's ECOG-ACRIN case number. Complete the BLOCK RETURN section with the ECOG-ACRIN CBPF information as indicated on page 2 of [Appendix V](#). 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 ECOG-ACRIN CBPF.

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.

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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-ACRIN CBPF upon written request for purposes of patient management.

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Questions may be directed to Genomic Health Customer Service (650-556-9300) or the ECOG-ACRIN CBPF (Tel: 844-744-2420 or email: [Eacbpf@mdanderson.org](mailto:Eacbpf@mdanderson.org)).


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

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

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

Thank you.

**THIS IS AN EXAMPLE REQUISITION FORM  
PLEASE DO NOT USE**



# TAILORx Study

## How To Order The Oncotype DX® Breast Cancer Assay

*The TAILORx clinical trial is sponsored by the National Cancer Institute and administered by the Eastern Cooperative Oncology Group.*



1. Complete the Oncotype DX Requisition Form and 638 Form. The Requisition Form can be ordered by calling Genomic Health's Customer Service at 866-ONCOTYPE (866-662-6897). For the Requisition Form, include the following:
  - Five digit PACCT-1 patient number ("PACCT-1/#####") in the Study Name/Code section
  - Select option 1 ("No Investigation Required") under the Benefits Investigation section
  - Select the Specimen Retrieval option:
    1. I want Genomic Health® to request the specimen:
      - Select option 1 in the Specimen Retrieval section.
      - Please fax a) Requisition Form, b) 638 Form, and c) insurance card and/or face sheet to Genomic Health at 866-444-0640.
    2. I will arrange to have the specimen sent:
      - Please fax a) Requisition Form, b) 638 Form, and c) insurance card and/or face sheet to Pathology.
      - The face sheet should be included in the specimen kit when shipped.



2. Within 10 to 14 days of receiving the specimen, Genomic Health will return the Oncotype DX results via fax, overnight mail, or secure online access. It is the responsibility of the CRA to fax the Recurrence Score® result to ECOG at 617-582-8578, Attention: Pre-registration PACCT-1.



3. Genomic Health will submit an insurance claim. Some insurance companies require a prior authorization from the ordering physician as part of the reimbursement process. In such cases, Genomic Health will contact the physician directly for this information. It is important to know that Genomic Health will not contact patients pertaining reimbursement. Patients may receive an EOB (explanation of benefits) from their insurance company, acknowledging receipt of a claim from Genomic Health, however, patients who participate in this trial will have *no financial responsibility* for the Oncotype DX test.



4. The patient's tumor block and 638 Form will be shipped to ECOG's Pathology Coordinating Office (PCO) in Chicago for future studies in the NCI PACCT program. For special consideration regarding processing and use of residual materials, contact the PCO directly at 312-503-3384.

**For information about the Oncotype DX Breast Cancer Assay, please contact Genomic Health Customer Service:**

301 Penobscot Drive  
Redwood City, CA 94063 USA  
customerservice@genomichealth.com  
866-ONCOTYPE (866-662-6897)  
Fax: 866-GHI-0640 (866-444-0640)

**For protocol and general information, please contact:**



Clinical Trials Support Unit (CTSU)  
ctscontact@westat.com  
www.ctsu.org  
888-823-5923



www.genomichealth.com  
www.oncotypedx.com

THIS IS AN EXAMPLE REQUISITION FORM  
PLEASE DO NOT USE

In the Processing Code section of the Requisition Form, enter the Protocol # and Case "PACCT-1/#####."





Genomic Health, Inc.  
301 Penobscot Drive  
Redwood City, CA 94063 USA  
Tel (866) ONCOTYPE (866) 662-6887  
www.oncotypedx.com

**Oncotype DX® Requisition Form and  
Statement of Medical Necessity  
(BENEFITS INVESTIGATION FORM)**

All Oncotype DX® reports will include ER, PR and HER2 Scores. Please see [www.oncotypedx.com](http://www.oncotypedx.com) for details.  
**PATHOLOGY: Time Sensitive — Please Expedite**

First Submission     Resubmission — Associated Requisition    Study Name / Code: **PACCT-1/#####**

**PATHOLOGY: Attach Specimen Barcode Here** 

**Fax (866) 444-0640**

---

**I. ORDERING PHYSICIAN INFORMATION**

PRACTICE \_\_\_\_\_

ORDERING PHYSICIAN NAME \_\_\_\_\_

CONTACT NAME \_\_\_\_\_

PHONE \_\_\_\_\_ FAX \_\_\_\_\_

**II. ADDITIONAL PHYSICIAN (Name will appear on report)**

ADDITIONAL PHYSICIAN / RECIPIENT NAME (Optional) \_\_\_\_\_

ADDRESS \_\_\_\_\_

CITY \_\_\_\_\_ STATE \_\_\_\_\_ ZIP \_\_\_\_\_ COUNTRY \_\_\_\_\_

PHONE \_\_\_\_\_ FAX \_\_\_\_\_

**CRA Contact Info Required** →

**CRA Name** \_\_\_\_\_

**CRA Shipping Address** \_\_\_\_\_

**CRA Phone #** \_\_\_\_\_ **CRA Fax #** \_\_\_\_\_

**III. PATIENT INFORMATION**

PATIENT NAME: Last, First MI \_\_\_\_\_

DOB (MM/DD/YYYY) \_\_\_\_\_ SEX  Female  Male

MEDICAL RECORD / PATIENT NUMBER \_\_\_\_\_ SSN \_\_\_\_\_

ADDRESS 1 \_\_\_\_\_

ADDRESS 2 \_\_\_\_\_

CITY \_\_\_\_\_ STATE \_\_\_\_\_ ZIP \_\_\_\_\_ COUNTRY \_\_\_\_\_

HOME PHONE \_\_\_\_\_ WORK PHONE \_\_\_\_\_

CELL PHONE \_\_\_\_\_

---

**IV. BILLING INFORMATION**

SUBMITTING DIAGNOSIS \_\_\_\_\_ ICD-9 CODE \_\_\_\_\_

PRIVATE INSURANCE (Attach Front/Back copy of insurance card.)

Primary \_\_\_\_\_ MEMBER ID \_\_\_\_\_

Secondary \_\_\_\_\_ MEMBER ID \_\_\_\_\_

For Authorization # \_\_\_\_\_

MEDICARE (Complete additional information below.)  
All Medicare patients will have an eligibility check and may be contacted during the process.

Hospital Inpatient (> 24 hour stay)  
Discharge Date \_\_\_\_\_

Hospital Outpatient

Non-hospital Patient

MEDICAID (Attach Front/Back copy of insurance card.)

PATIENT SELF-PAY Check (US), certified funds, money order, or credit card

Name on Credit Card \_\_\_\_\_

Credit Card # \_\_\_\_\_

Expiration Date (MM/YY) \_\_\_\_\_

BILL PATHOLOGY ACCOUNT Restricted to contracted accounts on file at Genomic Health

---

**V. BENEFITS INVESTIGATION — SERVICE OPTIONS (SELECT ONE)**

1.  No Investigation Required.    2.  YES Investigate — Proceed with test and REPORT RESULTS.    3.  YES Investigate — Proceed with test and HOLD FINAL PROCESSING pending patient approval. (May extend turn-around-time for report results.)

STATEMENT OF MEDICAL NECESSITY (Please state why the patient needs this test and any past experiences using Oncotype DX to support treatment decisions.) \_\_\_\_\_

---

**VI. SPECIMEN RETRIEVAL — SERVICE OPTIONS (SELECT ONE)**

1.  I want Genomic Health to request the specimen. (COMPLETE the information below.)    2.  I will arrange having the specimen sent. (FAX this form to Pathology.)

LOCATION OF SPECIMEN \_\_\_\_\_ PHONE \_\_\_\_\_ FAX \_\_\_\_\_ CONTACT NAME \_\_\_\_\_

---

**VII. PHYSICIAN SIGNATURE**

ORDERING PHYSICIAN SIGNATURE \_\_\_\_\_ DATE \_\_\_\_\_

**X** \_\_\_\_\_

PRINT NAME \_\_\_\_\_

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. Please read Section VII on the reverse side for full details.

By signing this form you are stating that either 1) the patient is a newly diagnosed female, with Stage I, II, or III (T3, N1), ER-Positive breast cancer OR 2) If the patient does not meet these criteria, that you have entered the reason(s) in the Exception Criteria space provided. A Genomic Health representative will contact you should your patient not meet these criteria.

EXCEPTION CRITERIA \_\_\_\_\_

Node Status (Select One):  
 Node Negative     Micromets (pN1mi: 0.2 – 2.0mm)     Node Positive

---

**VIII. PATHOLOGY INFORMATION**

ACCOUNT \_\_\_\_\_

SUBMITTING PATHOLOGIST NAME \_\_\_\_\_

PHONE \_\_\_\_\_ FAX \_\_\_\_\_

SPECIMEN ID: The OncotypeDX assay will be completed on the specimens in the order listed below.  
Only one specimen is typically required.    MULTIPLE PRIMARIES:  Yes  No

1) \_\_\_\_\_ 3) \_\_\_\_\_

2) \_\_\_\_\_ 4) \_\_\_\_\_

DATE OF SURGERY (MM/DD/YYYY) \_\_\_\_\_ DATE BLOCK PULLED FROM ARCHIVE (Required for Medicare) \_\_\_\_\_

BLOCK RETURN LOCATION (if different than the Pathology Account listed above) \_\_\_\_\_ PHONE \_\_\_\_\_ CONTACT NAME \_\_\_\_\_  
ECOG Pathology Coordinating Office, Northwestern University, Olson Pavilion Rm 8471, 710 N. Fairbanks Ct., Chicago, IL 60611    (312) 503-3384





**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

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**Appendix VI**

**PACCT-1 and EL112LAB Peripheral Blood Collection and Shipping Kit Order Form**

**FAX Completed form to Zemotak-International at (800) 815-4675.**

**NOTE:** Kits for EL112LAB patients may be ordered within one month prior to visit, including that for patients who are potentially eligible to step 3 but not yet consented. EL112LAB1 kits are not protocol or patient specific and can be interchanged between patients and trial. Protocol # requested for tracking purposes.

**Date:** \_\_\_\_\_

Rev. 12/14 **# of EL112LAB1 CBPF Sample Submission Kits:** PACT1 \_\_\_\_\_ E5103 \_\_\_\_\_  
For collection of Plasma (CTAD, PST, PPT), Cells (CTAD) and Serum (RST)

**# CellSave (CTC) Kit [E5103 ONLY]** \_\_\_\_\_  
For collection of CellSave (CTC) Whole Blood at time of first EL112LAB blood draw, Submission to Fox Chase Cancer Center

Kits to be shipped to:

Institution Contact: \_\_\_\_\_

Phone number for contact: \_\_\_\_\_

E-mail for contact: \_\_\_\_\_

Institution Address: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

Rev. 12/14 Sample Submission Schedule Summary Information

Protocol	Receiving Lab	At time of Step 3 registration**	Years 1,2,3,4 and 5 from step 3 registration	Relapse**
PACT1	CBPF	EL112LAB1 Kit		EL112LAB1 Kit
E5103	CBPF	EL112LAB1 Kit	EL112LAB1 Kit	EL112LAB1 Kit
	Fox Chase	CellSave (CTC)		

\*\*Tissue to be submitted per protocol.

**NOTE:** Questions are to be directed to the ECOG-ACRIN CBPF, Attn: Adekunle Raji  
Tel: (844) 744-2420, E-Mail: [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org)

**Comments (please note Protocol # and relevant ECOG-ACRIN patient IDs):**

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
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The TAILORx Trial**

**Appendix VII**

Rev. 2/13

**PACCT-1 Shipment Notification Form - REMOVED**

**All samples submitted from patients participating in PACCT-1 must be logged into the online ECOG-ACRIN Sample Tracking System (see Section [10.4](#)). In the event that STS is not available at time of sample shipment, use the Generic Specimen Submission Form (#2981) found in the forms packet. When STS is available, shipments must be logged retroactively into the system, indicating the actual dates of collection and shipment.**

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix- VIII**

**Correlative Science for the PACCT-1 Trial**

**Background:** The clinical trial design of the PACCT-1 trial is based the Genomic Health analysis of NSABP B20 described in the preliminary data section. To summarize, the low risk group receiving tamoxifen alone experienced an event rate of five relapses out of 135 cases (4%). In the intermediate group there were eight relapses out of 45 cases (18%). In the high risk group there were 18 relapses out of 47 cases (38%). These estimates were validated with samples from the tamoxifen arm of the B14 trial. On the chemotherapy plus tamoxifen arm of NSABP B20, the event rates were, 5%, 10% and 11% respectively. The advantage for chemotherapy was only statistically significant in the high risk group RR 0.258 (0.126-0.528). The design of the PACCT-1 trial is essentially a prospective trial to confirm these findings in the context of contemporary practice.

Even if the risk estimates provided by the B14 and B20 analysis are replicated, there remain areas for assay improvement, for example:

1. The registry design will allow study of patients in the low risk group who relapse (5%) since they were misclassified as low risk. Identifying the molecular signatures of the tumors that do unexpectedly poorly would allow additional biomarkers to be added to the model to ensure that as few patients as possible are under-treated.
2. The registry design will also allow the study of patients in the intermediate and high risk groups who relapse despite tamoxifen and chemotherapy. If patients with treatment resistant tumors can be prospectively identified they could be singled out for more effective treatment.
3. There are too few cases in the intermediate group to be certain what the chemotherapy benefit is seen within this group. The randomization of patients with intermediate risk scores to chemotherapy versus observation in the PACCT-1 study is designed to answer this question. If chemotherapy is shown to provide benefit, the over treatment problem will remain substantial for the intermediate group because overall the risk status is still favorable. Alternative risk models or a modification of the assay will be a critical focus for further investigation.

**Procedures for accessing samples:** A large number of samples will be accrued during the conduct of the PACCT-1 trial. These samples will be used for independent analyses using alternative approaches and statistical models proposed by academic or industry investigators. An important consideration is that the PACCT-1 research must be conducted in an “open source” environment as the best models may, in the end, involve a synthesis of a number of different biomarker approaches. The following research outlines are not intended to be specific or inclusive, but are designed to inform institutional review boards, patients and investigators of the scope of the research that is likely to be undertaken. The samples will be banked at ECOG-ACRIN (FFPE, plasma, serum, cells, DNA, RNA and frozen tumor from the virtual tumor bank) and access will depend on further approval. The only correlative science aims that are considered

“embedded” are tests for ER, PgR by IHC and HER2 FISH using whole sections, the construction of a TMA and a centralized histopathology grading exercise. Activating a new analysis requires the development of a concept sheet (using the standard TBCI form) with the active collaboration of the PACCT-1 correlative science committee (CSC) to ensure all the relevant components of an application have been provided and the proposal has high scientific merit (this is mandatory). The concept will then be submitted to the TBCI correlative science committee for approval (see <http://ctep.cancer.gov/resources/tbci/>). An approved concept will lead to a PACCT-1 sub-protocol that will be approved by the CIRB and CTEP. Institutional IRB approval of sub-protocols involving sample analysis will only have to be sought from institutions that will receive samples for analysis. All samples will be stripped of identifiers and the marriage of clinical and research data will use an honest broker approach to prevent the identity of a patient being divulged to laboratory investigators or individual laboratory results inappropriately communicated to physicians or patients.

**Summary of approved banking procedures for PACCT-1.** The following banking procedures are intrinsic to this protocol and are embedded aspects of the study.

1. The procurement of five 4 micron sections for H+E, ER IHC, PgR IHC, HER2 FISH and one spare for assay failures.
2. TMA construction with three cores.
3. Baseline plasma and serum banking
4. Genomic DNA banking from peripheral blood
5. RNA “left over” from the Genomic Health Assay.
6. Consent for the acquisition of samples from the “virtual frozen tumor bank”.

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The following considerations provide the rationale for these banking procedures:

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**Processing of blocks:** The FFPE blocks will be accessed on an ongoing basis at the ECOG-ACRIN CBPF. A cutting schema will be in place for 5 sections for ER IHC, PgR IHC, HER2 FISH, Standard H+E and one spare for assay failure problems. The H+E will be reviewed for “block mapping” and central grade assignment and 3 or more cores will be removed for TMA construction. The remaining specimen will then be banked until they are ready to be accessed for further analysis through approved sub-protocols.

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If the institution demands the return of the block, after sampling for the tissue microarray cores, ten 10 micron sections will be cut and stored in microfuge tubes at -70°C (macrodissection will have to be performed at this time if required) and additional 20 five micron sections will be cut and mounted on charged slides for storage before returning the blocks. Whole sections will be stored at 4°C in oxidation free storage boxes

**Tissue Microarray (TMA) Construction:** The goal of the TMA construction will be a resource that can be used to study additional biomarkers in a format that preserves resources to the greatest possible extent.

**Tumor RNA banking:** We anticipate that there will be RNA remaining from a significant proportion of the specimens after the *Oncotype* assay has been performed. This RNA will be sent in a timely manner in batches to ECOG-ACRIN for storage. Sub-protocols will be encouraged that test alternative risk models based on mRNA profiling have been developed and present alternative solutions to the problem of outcome prediction in early stage breast cancer. These assays, like *Oncotype DX*, will typically also be based on q RT PCR, although other RNA analysis techniques such as microarray analysis

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Rev. 12/14 could also be entertained. For those cases that RNA is not available, three 10 micron sections (six 10 micron sections if macro dissected) of the tissue submitted to the CBPF will be processed to extract total RNA for correlative science studies.

**Tumor and adjacent normal tissue DNA.** RNA expression profiling reflects the effect of somatic mutation, most obviously through gene over-expression as a result of gene amplification. However other somatic mutations such as deletions and single nucleotide mutations probably play an important role in determining the eventual clinical outcome. The ability to identify these abnormalities is amenable to high-throughput techniques such as DNA sequencing and array-based comparative genomic hybridization.

Rev. 9/07 **Baseline plasma and serum banking:** Considerable advances in proteomic techniques have taken place in the last several years. These techniques may ultimately prove valuable in defining patients with low volume residual disease through the presence of circulating tumor products or through certain immune responses to the presence of malignant cells. These techniques could prove very valuable in the area of prognosis, which is essentially an exercise in the identification of patients with metastatic spread of tumor. These samples could also be used to study steroid hormone level and other risk factors for the development of breast cancer.

**Baseline Genomic DNA banking:** When clinical data become available from the PACCT-1 study, studies of genetic variation can be focused on the impact of genetic variation in the efficacy and safety of adjuvant endocrine and chemotherapy treatment. For example an Aromatase SNP has already been linked to the outcome of AI therapy for advanced disease. Colomer et al recently reported that advanced disease patients with the aromatase polymorphism rs4646 had markedly better time to progression upon treatment with letrozole in comparison with those with a “normal” gene.

Rev. 9/06 **Virtual frozen tumor bank.** Frozen samples from tumors are reasonably often banked under institutional banking protocols. The consent form of the PACCT-1 trial includes language that requests permission to access these samples to address specific questions that have been approved through the process outlined above. If patients provide consent to future research, frozen tumor tissue that has been collected at the local institution will be submitted after registration/randomization or, if retained at the local site until requested, will be considered part of the “Virtual Tumor Bank”. In the MA27 clinical trial a virtual tumor bank was piloted. In the initial cohort of over 1000 patients, approximately 10% of cases were recorded to have frozen tumor banked at the institution and that the patient had given permission for the tissue to be sent to another institution for analysis. Thus in a large trial, such as PACCT-1, a relatively large number of frozen tumors will be accrued. ACOSOG will conduct a targeted effort to increase the number of tumors banked and available for analysis through this mechanism.

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**Central testing of ER, PR, Her2/neu:**

In order to validate the performance of the Oncotype Dx assay, ER, PR, and HER2 centrally assayed by ECOG-ACRIN CBPF using tissue microarray sections. ER and PR will be assayed with FDA approved Dako PharmDx kits and scored using Allred Scoring system. HER2 amplification will be evaluated using Vysis PathVysion FISH assay.

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**Web based pathology review:**

**H&E slides will be scanned with ScanScope (or other web enabled pathology image archiving system) to post the images on the web to the pathology community to develop consensus review of histologic grade and mitotic activity index that will eventually be incorporated for Adjuvant! Evaluation.**

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix IX**

**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 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 clinical trial. Many questions remain unanswered in cancer. With the help of people like you who participate in this research, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. Your physician and research staff will maintain very close contact with you. This will allow your physician 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 Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

---

**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix X**

**Oncotype DX Assay Information**

Rev. 9/06 This appendix contains **examples** of the “Oncotype DX Patient Report” and information sheets (provided in the Oncotype DX Specimen Kit) distributed by Genomic Health.

For patients without determined Recurrence Scores:

To order the “Oncotype Specimen Kit” contact Genomic Health Customer Service (866-662-6897). Kit should be ordered prior to pre-registration. 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.

As outlined in [Appendix V](#), materials are submitted AFTER pre-registration to Genomic Health. An example of the “Oncotype DX Requisition Form” and instructions on how the requisition form MUST be completed are in [Appendix V](#).

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

Recurrence Scores determined prior to or during pre-registration:

Rev. 7/10 After pre-registration, **fax** a redacted copy of the first page of the “Oncotype DX Patient Report” (labeled with protocol number (PACCT1), patient initials and case number) to the ECOG-ACRIN Operations Office (FAX: 617-582-8578, Attn: Pre-registration/PACCT-1).

Registration/randomization may proceed 24 to 72 hours after submission of the report the ECOG-ACRIN Operations Office.




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**1. REDACT**

**2. Add Pt Initials**

Genomic Health, Inc.  
301 Penobscot Drive  
Redwood City, CA 94063  
Tel (866) ONCOTYPE (866-662-6897)  
www.oncotypedx.com



**PATIENT REPORT**

<p>Patient: Doe, Jane <b>D,J</b></p> <p>Sex: Female</p> <p>DOB: 01/01/1950</p> <p>Medical Record/Patient #: 556677771</p> <p>Date of Surgery: 11/23/2004</p> <p>Specimen ID: SURG-0001</p>	<p>Requisition: R00003G</p> <p>Date Received: 12/01/2004</p> <p>Date Reported: 12/01/2004</p> <p>Client: Community Medical Center</p> <p>Treating Physician: Dr. Harry D Smith</p> <p>Submitting Pathologist: Dr. John P Williams</p> <p>Additional Physician: Dr. Sally M Jones</p>
--	--

**PACCT1/#####**

**ASSAY DESCRIPTION**

CR to determine the expression of a panel of 21 genes in tumor tissue. A clinically validated test to determine the individual Recurrence Score™. The Recurrence Score range is from 0-100.

**3. ADD PROTOCOL# AND CASE:**  
**PACCT1/#####**

**DO NOT REDACT**

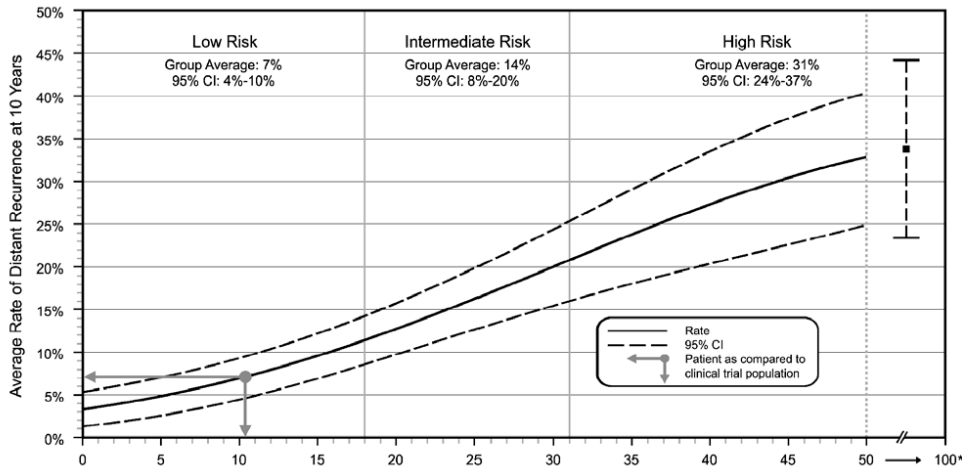
Recurrence Score = **10**

Test results should only be used in populations consistent with the clinical trial experience outlined below.

**Patients with a Recurrence Score of 10 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **7%** (95% CI: 5%-9%)**

**CLINICAL EXPERIENCE**

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



**4. FAX REDACTED COPY OF REPORT (labeled as above) TO 617-582-8578, ATTN: PACCT1/Pre-registration**

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been approved or cleared by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. These results are adjunctive to the ordering physician's workup.

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypedx.com  
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GHI004 Rev006 01/10/2005

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## PATHOLOGY GUIDELINES FOR BLOCKS

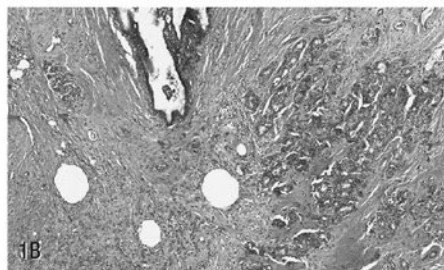
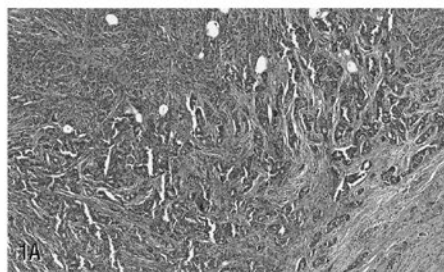
### RECOMMENDATIONS FOR SELECTING THE MOST REPRESENTATIVE BLOCK

Select the paraffin-embedded tumor block with the greatest amount of invasive carcinoma that is morphologically consistent with the submitting diagnosis.

- A. Choose the one block with both the greatest amount / area of invasive carcinoma and associated stroma.
- B. Hemorrhage, necrosis, and adipose tissue do not need to be minimized. They contain little RNA and thus do not significantly impact this assay.
- C. A pathologist at Genomic Health will review the H&E slide and, if necessary, perform manual microdissection consistent with clinical trial experience.
- D. For breast carcinoma submissions, microinvasive carcinomas (one or more foci < 0.1 cm) are not acceptable samples.

#### BREAST

##### SATISFACTORY SPECIMENS

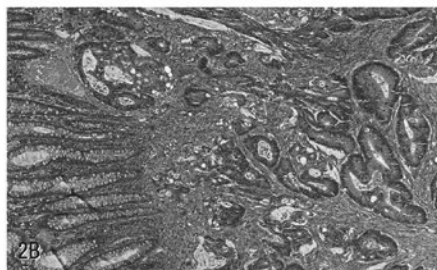
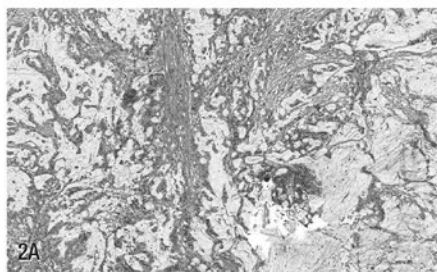


**Figure 1A.** The invasive carcinoma comprises the majority of the tissue section.

**Figure 1B.** The invasive carcinoma is adjacent to a biopsy cavity requiring manual microdissection by GHI pathology. (H&E A  $\times 40$  and B  $\times 40$ )

#### COLON

##### SATISFACTORY SPECIMENS



**Figure 2A.** The invasive carcinoma comprises the majority of the tissue section.

**Figure 2B.** The invasive carcinoma infiltrates around normal colonic epithelium requiring manual microdissection by GHI pathology. (H&E A  $\times 40$  and B  $\times 40$ )

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

## PREPARATION INSTRUCTIONS FOR BLOCKS

### SPECIMEN PREPARATION INSTRUCTIONS FOR BLOCKS

#### 1. Materials and equipment

- A. Fixed paraffin-embedded (FPE) cancer tissue block
- B. *OncoType* DX® Specimen Collection and Transportation Kit Box ("OncoType DX Specimen Kit")
- C. *OncoType* DX Cancer Assay Requisition Form ("OncoType DX Requisition Form")
- D. Frozen 3 oz. ice pack (provided with *OncoType* DX Specimen Kit, chilled in freezer overnight)

**NOTES:** The ice pack included with the kit should be frozen overnight for best use. Follow your laboratory's standard practice guidelines for the processing of FPE tissue.

#### 2. To submit a tumor block:

- A. Apply one S barcode label, obtained from the inner top lid of the *OncoType* DX Specimen Kit, to each block. (See Figure 3)
- B. Place the tumor block in the small plastic bag and seal the bag.
- C. Please do not submit an H&E slide when you are submitting tumor blocks. Genomic Health will prepare an H&E slide on site.

#### 3. Complete the *OncoType* DX Requisition Form.

- A. One *OncoType* DX Specimen Kit and Requisition Form should be completed 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.
- B. Before shipping, make a copy of the *OncoType* DX Requisition Form and retain it for your records.

#### 4. Place the *OncoType* DX Requisition Form and relevant patient insurance materials in the *OncoType* DX Specimen Kit, between the box and the large secondary containment bag.

- 5. Place a frozen ice pack on top of the foam, inside the large secondary containment bag (before it is sealed).
- 6. Seal the large secondary containment bag and close the box using the tab.



Figure 3

**REIMBURSEMENT:** Genomic Health is prepared to bill insurance plans directly on behalf of insured patients in the US whose physicians order the *OncoType* DX Assay.

### DOMESTIC SHIPPING INSTRUCTIONS

#### 1. Materials and equipment

- A. *OncoType* DX Specimen Kit containing the patient specimen and *OncoType* DX Requisition Form
- B. FedEx® US Airbill pre-printed with Genomic Health shipping information
- C. FedEx® Clinical Pak, Large — a plastic over wrap used to ship the specimen to Genomic Health
- D. FedEx® adhesive airbill pouch for the FedEx® Airbill

**NOTE:** To order additional kits please e-mail Customer Service at [customerservice@genomichealth.com](mailto:customerservice@genomichealth.com) or call 866-ONCOTYPE (866-662-6897).

- 2. Place the *OncoType* DX Specimen Kit into the FedEx® Clinical Pak.
- 3. Complete the FedEx® US Airbill.
- 4. Seal the Clinical Pak by removing the plastic adhesive protector from the white strip and secure.
- 5. Place the package in the designated FedEx® pickup location at your site.
- 6. If your site does not have standard FedEx® pickup, please call 800-GO FEDEX (800-463-3339) to arrange for pick up.

**NOTE:** For International specimens, please call 001-650-569-2080 to speak with a Customer Service representative or visit [www.oncotypedx.com](http://www.oncotypedx.com).

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

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PATHOLOGY GUIDELINES FOR UNSTAINED SLIDES

RECOMMENDATIONS FOR SELECTING THE MOST REPRESENTATIVE TUMOR BLOCK

Select the paraffin-embedded tumor block with the greatest amount of invasive carcinoma that is morphologically consistent with the submitting diagnosis.

- A. Choose the one block with both the greatest amount / area of invasive carcinoma and associated stroma.
- B. Hemorrhage, necrosis, and adipose tissue do not need to be minimized. They contain little RNA and thus do not significantly impact this assay.
- C. A pathologist at Genomic Health will review the H&E slide and, if necessary, perform manual microdissection consistent with clinical trial experience.
- D. For breast carcinoma submissions, microinvasive carcinomas (one or more foci < 0.1 cm) are not acceptable samples.

BREAST

SATISFACTORY SPECIMENS

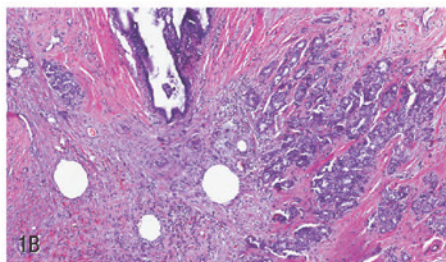
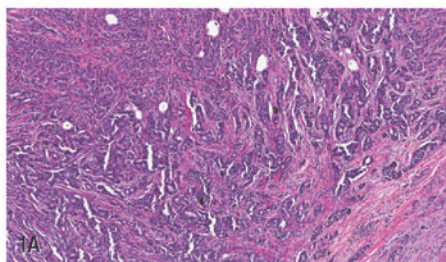


Figure 1A. The invasive carcinoma comprises the majority of the tissue section.

Figure 1B. The invasive carcinoma is adjacent to a biopsy cavity requiring manual microdissection by GHI pathology. (H&E A x40 and B x40)

COLON

SATISFACTORY SPECIMENS

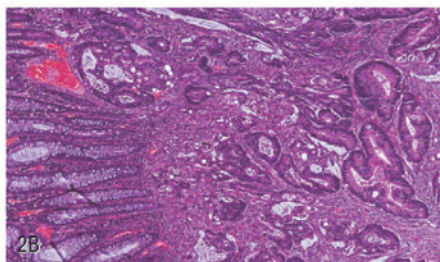
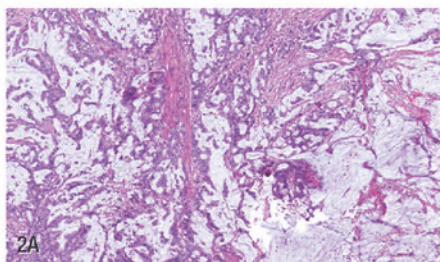


Figure 2A. The invasive carcinoma comprises the majority of the tissue section.

Figure 2B. The invasive carcinoma infiltrates around normal colonic epithelium requiring manual microdissection by GHI pathology. (H&E A x40 and B x40)

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

## PREPARATION INSTRUCTIONS FOR UNSTAINED SLIDES

### SPECIMEN PREPARATION INSTRUCTIONS FOR UNSTAINED SLIDES

#### 1. Materials and equipment

- Fixed paraffin-embedded (FPE) cancer tissue block
- Oncotype DX® Specimen Collection and Transportation Kit Box ("Oncotype DX Specimen Kit")
- Oncotype DX Cancer Assay Requisition Form ("Oncotype DX Requisition Form")
- Glass slides
- Slide carriers

**NOTES:** 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.

#### 2. Prepare fifteen 5µm serial unstained slides with one 5µm serial section on each slide.

- Ensure the sections on each slide are oriented similarly.
- Allow the slides to air dry. Do not place the slides on a hot plate.
- Do not place cover slips on the unstained slides.

#### 3. Label the slides as follows:

- Apply one S barcode label, obtained from the inner top lid of the Oncotype DX Specimen Kit, to each slide. (See Figure 3)
- Hand number the serially sectioned unstained slides (1-15) to indicate the order in which they were cut.

#### 4. 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.



Figure 3

#### 5. Complete or print the Oncotype DX Requisition Form.

- Please complete one Oncotype DX Specimen Kit and Requisition Form for each patient, and for 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 / primary tumor.
- Before shipping, make a copy of the Oncotype DX Requisition Form and retain it for your records.

#### 6. Place the Oncotype DX Requisition Form and relevant patient insurance materials in the Oncotype DX Specimen Kit, between the box and the large secondary containment bag.

#### 7. Seal the large secondary containment bag and close the box using the tab.

**REIMBURSEMENT:** Genomic Health is prepared to bill insurance plans directly on behalf of insured patients in the US whose physicians order the Oncotype DX Assay.

### DOMESTIC SHIPPING INSTRUCTIONS

#### 1. Materials and equipment

- Oncotype DX Specimen Kit containing the patient specimen and Oncotype DX Requisition Form
- FedEx® US Airbill pre-printed with Genomic Health shipping information
- FedEx® Clinical Pak, Large — a plastic over wrap used to ship the specimen to Genomic Health
- FedEx® adhesive airbill pouch for the FedEx® Airbill

**NOTE:** To order additional kits please e-mail Customer Service at [customerservice@genomichealth.com](mailto:customerservice@genomichealth.com) or call 866-ONCOTYPE (866-662-6897).

#### 2. Place the Oncotype DX Specimen Kit into the FedEx® Clinical Pak.

#### 3. Complete the FedEx® US Airbill.

#### 4. Seal the Clinical Pak by removing the plastic adhesive protector from the white strip and secure.

#### 5. Place the package in the designated FedEx® pickup location at your site.

#### 6. If your site does not have standard FedEx® pickup, please call 800-GO FEDEX (800-463-3339) to arrange for pick up.

**NOTE:** For International specimens, please call 001-650-569-2080 to speak with a Customer Service representative or visit [www.oncotypedx.com](http://www.oncotypedx.com).

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

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix XI**

**Cancer Trials Support Unit (CTSU) Participation Procedures**

**REGISTRATION/RANDOMIZATION**

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. 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 registered member Web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Rev. 12/14

Each CTSU 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. All forms and documents associated with this study can be downloaded from the PACCT-1 Web page on the CTSU registered member Web site (<http://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

**Requirements for PACCT-1 site registration:**

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet

**Pre-study requirements for patient enrollment on PACCT-1:**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed (including tumor, blood, and plasma samples).
- Contact Genomic Health Customer Service (866-662-6897) and request the “Oncotype Specimen Kit” for mandatory submission of one tumor block for the determination of the Oncotype DX Recurrence Score. If the kit is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration. Materials must be submitted no later than 3 days after pre-registration as outlined in section [10.1](#).

[If patient previously had an Oncotype DX Recurrence Score performed by Genomic Health, and the RS is 11-25, blocks should be submitted for central review following registration as outlined in section [10.3](#).]

Rev. 9/07

**CTSU Procedures for Patient Enrollment**

Rev. 7/10

Please see Section [4](#) of the protocol for instructions on using the OPEN registration system.

Rev. 8/08,  
7/10

*Reminder: If the "Oncotype Specimen Kit" is not available at time of pre-registration, it must be ordered within 24 hours following pre-registration.*

Rev. 7/10

### **Oncotype DX Assay and Recurrence Scoring**

Rev. 9/06

- If patient previously had an Oncotype DX Recurrence Score performed by Genomic Health, and the RS is 11-25, a redacted copy of the first page of the Oncotype DX Patient Report should be FAXed to the ECOG-ACRIN Operations Office – Boston (617-582-8578, ATTN: Pre-registration/PACCT-1) within 24 to 72 hours (if weekend or holiday) of pre-registration. Indicate on the report the protocol number (PACCT-1), and patient's ECOG-ACRIN pre-registration sequence number.

Rev. 9/06

- If patient is having an Oncotype DX Assay performed by Genomic Health, Genomic Health will notify the submitting site of the assay results within 14 working days of receipt of the sample. Once received, FAX a redacted copy of the first page of the "Oncotype DX Patient Report" to the ECOG-ACRIN Operations Office – Boston prior to registration/randomization (617-582-8578, ATTN: Pre-registration /PACCT-1). Indicate on the report the protocol number (PACCT-1), and patient's ECOG-ACRIN pre-registration sequence number.

Rev. 9/06,  
9/07

#### Important notes:

- In all cases, the first page of the "Oncotype DX Patient Report" must be faxed to the ECOG-ACRIN Operations Office – Boston prior to proceeding to registration/randomization.
- It will take 24 hours and up to 72 hours (if weekend or holiday) for ECOG-ACRIN to enter the Oncotype DX Patient Report results in their system, therefore CTSU CANNOT register/randomize a patient until this time has lapsed.

### **Registration/Randomization**

Important: It will take 24 hours and up to 72 hours (if weekend or holiday) for ECOG-ACRIN to enter the Oncotype DX Patient Report results in their system, therefore CTSU CANNOT register/randomize a patient until this time has lapsed.

Rev. 8/08,  
7/10

*Patients must not start protocol treatment prior to registration/randomization.*

*Treatments should begin within 14 working days after registration/randomization.*

### **DATA SUBMISSION**

All documentation associated with this study may be downloaded from the PACCT-1 Web page located on the CTSU registered member Web site (<http://members.ctsu.org>). CTSU investigators must use the current version of all documents and forms and adhere to the PACCT-1 schedule for data submission.

Rev. 8/08

#### **Submission via Hard Copy**

Original and amended post-enrollment CRFs (including Specimen Submission forms), clinical reports and responses to query and delinquency letters must be faxed directly to the CTSU Data Operations Center accompanied by a properly completed TAILORx CTSU Data Transmittal Form. Copies of clinical reports must also be accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533). Please remember to include the Patient ID and protocol number on all pages of the report and redact the patient's name.

---

A TAILORx CTSU Data Transmittal Form must accompany all data submissions. Data submitted with an improperly completed TAILORx CTSU Data Transmittal Form or without a TAILORx CTSU Data Transmittal Form will be returned to the site for corrective action without being processed. **Fax documents to 301-545-0406.**

### **Submission via Remote Data Capture**

**(These instructions are ONLY for pre-selected RDC sites. These sites were selected by ECOG-ACRIN and will submit patient data via CTSU's RDC system.)**

All participating sites are required to submit patient data via the CTSU's Remote Data Capture (RDC) system. The CTSU Remote Data Capture system allows sites to enter patient data into an Oracle Clinical ® (OC) database over a secure Internet connection. The RDC system also allows for data correction at the point of entry, and is used to communicate and resolve issues relating to discrepant data. Sites can connect to the OC-RDC application via the Remote Data Capture link on the CTSU member website.

Rev. 9/06  
Rev. 9/06,  
8/08  
Rev. 8/08

Institutional pathology reports and other clinical reports cannot be entered in the OC-RDC application; therefore, a copy accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533) should be faxed to the CTSU Data Operations for tracking purposes. Please include the Patient ID and protocol number on all pages of the report and redact the patient's name. Submit along with a completed TAILORx CTSU Data Transmittal Form.

Sites experiencing technical problems (e.g., firewall issues) with RDC must contact the CTSU help desk (1-888-823-5923) to obtain permission for a waiver to submit hard-copy CRFs in lieu of using RDC.

### **SPECIAL MATERIALS OR SUBSTUDIES**

#### **Submission of Mandatory Tumor Block:**

Rev. 9/07  
Rev. 12/14

Mandatory submission of one tumor block for the determination of the *Oncotype* DX Recurrence Score is to be submitted to Genomic Health (see section [10](#) and [Appendix V](#)). Kits for tissue submission and *Oncotype* DX Recurrence Score assessments must be ordered within 24 hours following pre-registration. Samples are to be submitted within 3 days of pre-registration. Pathology report and the ECOG-ACRIN Generic Specimen Submission Form (#2981) must be completed and copies distributed to both Genomic Health (with the samples and requisition form) and the ECOG-ACRIN CBPF. If the Recurrence Score was previously determined by Genomic Health, tissue block **MUST** be submitted to the ECOG-ACRIN CBPF within 2 weeks following randomization.

Rev. 9/06  
Rev. 12/14

Rev. 9/07  
Rev. 9/06

All materials and reports must be labeled with the Patient ID and protocol number; patient names should be redacted from the pathology report. Specimens should not be submitted to the CTSU, although CTSU should be copied on **all** transmittal forms (*Oncotype* DX Requisition Form) and pathology reports. Starting June 2007, all specimens submitted for this study must be entered and tracked using the ECOG-ACRIN Sample Tracking System. Upon registering new patients to these studies, you can expect to receive an automatic email with instructions for logging into the system and shipping samples. You can also access the Tracking System from the CTSU Member Web Site. Go to the PACCT-1 protocol page and click on the link provided under the Case Report Forms header. See protocol Section [10](#) and [Appendix V](#) for further details on shipping details, sample collection and preparation.

*Special Notes for pre-selected Remote Data Capture (RDC) sites:*



Rev. 11/07

Institutional pathology reports and other clinical reports cannot be entered in the OC-RDC application; therefore hard copy should be submitted as described in the section above under the header “Submission of Mandatory Tumor Block” and accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533).

Rev. 9/06

Sites experiencing technical problems (e.g., firewall issues) with RDC must contact the CTSU help desk (1-888-823-5923) to obtain permission for a waiver to submit hard-copy CRFs in lieu of using RDC.

#### **Additional Studies/Banking:**

Rev. 9/07

Provided patient consent is obtained, primary tumor tissue is to be submitted within two weeks following registration/randomization for laboratory studies (defined in section [10](#)) and banking for future research. Peripheral blood and plasma samples, requested for banking for possible use in future studies, are to be collected after registration/randomization, prior to start of treatment.

Rev. 9/06,  
9/07, 2/13

Shipping and collection kits for the frozen tissue and blood samples are ordered by completing the *PACCT-1 Peripheral Blood Collection and Shipping Kit Order Form* ([Appendix VI](#)) and Faxing to Zemotak-International at 800-815-4675. For submissions pertaining to the EL112LAB Ancillary, guidelines for collection and submissions are outlined in [Appendix XII](#). For all other submissions, see Section [10](#), [Appendix V](#) and [Appendix VI](#) for details on sample collection, preparation, and shipping. All materials and reports must be labeled with the Patient ID and protocol number; patient names should be redacted from the pathology report. Specimens should not be submitted to the CTSU, although CTSU should be copied on all transmittal forms (Generic Material Submission Form (#2981) if STS is unavailable) and the pathology reports.

#### *Special Notes for pre-selected Remote Data Capture (RDC) sites:*

Rev. 9/06

All Specimen bank submission CRFs must also be entered in the CTSU RDC system. Institutional pathology reports and other clinical reports cannot be entered in the OC-RDC application; therefore, hard copy should be submitted as described in the section above under the header “Additional Studies/Banking” and accompanied by a completed TAILORx Source Document Tracking Coversheet (Form #2533).

Sites experiencing technical problems (e.g., firewall issues) with RDC must contact the CTSU help desk (1-888-823-5923) to obtain permission for a waiver to submit hard-copy CRFs in lieu of using RDC.

### **ADVERSE EVENT (AE) REPORTING**

#### **Assessing and submitting expedited reports**

Rev. 9/11

**All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**

**The CTCAE version 4.0 is identified and located on the CTEP website at <http://ctep.cancer.gov>. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.** CTSU investigators should assess adverse events according to the instructions and tables in Section [5.3](#) of the protocol. All reporting should be conducted within the time frames specified in Section [5.3](#) of the protocol.

CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding submission of documentation of adverse events. Local IRBs must be informed of all reportable serious adverse events.

Expedited reports should be transmitted electronically using the CTEP CTEP-AERS application. A link to the CTEP-AERS application can be found on the CTSU member homepage.

Some adverse events require CTEP-AERS 24-hour notification to NCI and ECOG-ACRIN (refer to table 5.3.3). Select the 24 Hour Notification reporting track in the CTEP-AERS system. A full CTEP-AERS report is due within 5 calendar days.

Rev. 9/06

**NOTE:** Although most study data, from ECOG-ACRIN and non-ECOG-ACRIN institutions alike, is submitted to CTSU Data Operations, this does not include Expedited Adverse Event Reporting; data regarding expedited AEs must be submitted to ECOG-ACRIN and the NCI (not CTSU). Please follow instructions in protocol section [5.3](#) for submission of AE data.

#### **Secondary AML/MDS/ALL reporting:**

Rev. 9/06,  
9/07

Upon diagnosis of AML/MDS/ALL, please submit copies of the following to ECOG-ACRIN:

- NCI Secondary AML/MDS/ALL Report Form,

Rev. 9/06

- Pathology report confirming the AML/MDS/ALL
- Cytogenetics report (if available)

Rev. 9/07

[Deleted in Addendum #2]

#### **Reporting other secondary malignancies:**

Upon diagnosis of a secondary cancer, please submit copies of the following to the CTSU within 30 days of diagnosis:

- \* Second Primary Form (#1677)
- \* A copy of the pathology report (if available)
- \* Any additional supporting documentation

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[Deleted in Addendum #2]

#### **DRUG PROCUREMENT:**

CTSU investigators should refer to Section [8](#) for detailed instructions on drug procurement, formulation, storage, administration, and potential toxicities.

Commercial agents: Cyclophosphamide, Methotrexate, Fluorouracil (Infusional), Doxorubicin, Paclitaxel, Epirubicin, Docetaxel, Tamoxifen, Exemestane, Anastrozole, Letrozole

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#### **REGULATORY AND MONITORING**

##### Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment.

For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

#### Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the informed consent section of this protocol document; however, authorization for the release of Protected Health Information is considered separate and distinct from the Informed Consent process for participation in this clinical trial. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

#### Clinical Data System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.

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**Program for the Assessment of Clinical Cancer Tests (PACCT-1):  
Trial Assigning Individualized Options for Treatment:  
The TAILORx Trial**

**Appendix XII  
Ancillary Study EL112LAB**

**North American Breast Cancer Groups Biospecimen Bank for Determinants of  
Late Relapse in Operable Breast Cancer**

Study PI: Joseph Sparano, MD  
Study Statistician: Robert Gray, Ph.D.

Patients registered to treatment on E5103 or PACT1 who meet the criteria outlined in section [XII.6](#) are eligible to participate in this ancillary study. Patients must provide written signed consent, additional to that from participation in the treatment trial, to participate in this ancillary study.

Guidelines for enrollment and submission of data and specimens are outlined below in Section [XII.6](#). A model consent for this ancillary study is provided as a sub-appendix ([Appendix I-A](#)) to the model consent of the respective treatment trial.

**XII.1 Hypothesis and Specific Aims**

Late relapse (defined as occurring 5 or more years after diagnosis) accounts for up to one-half of all breast cancer recurrences, and is difficult to study because of the lack of adequate biospecimens linked to clinical data with sufficiently long follow-up. In addition, recurrence may be driven by dynamic rather than static host factors that may wax or wane with time. ***We propose that our current paradigm of assessing and counseling solely at diagnosis may need to be reconsidered to include a second evaluation point 5 or more years after diagnosis when patients continue to be at risk for recurrence, and needs to include an evaluation of both tumor and host-related factors in the context of competing risks. We hypothesize that tumor and host-related factors contributing to recurrence that may be identified and potentially modifiable via pharmacologic or nutritional or other lifestyle interventions.***

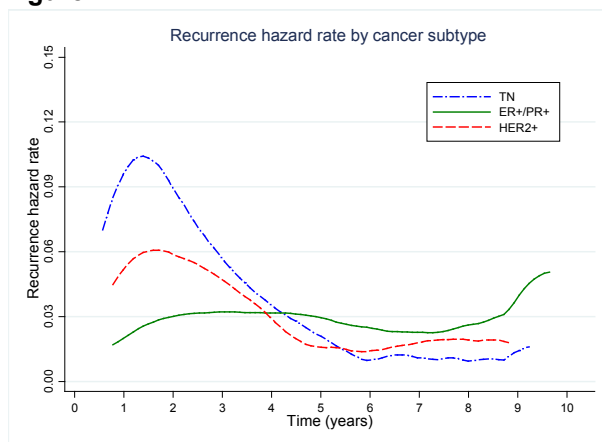
Our specific aims include:

1. To create a biospecimen repository including plasma, serum and CellSearch™ cassettes containing circulating tumor cells (CTC) for evaluating determinants of late relapse, including ***candidate biomarkers*** reflecting occult tumor burden (e.g., CTCs and plasma tumor DNA) and host factors (e.g., estrogen, insulin-IGF axis, inflammation, etc).
2. To create a biorepository of metastatic tumor samples in patients who have had a late relapse.
3. To determine body mass index (BMI) and comorbidity burden in patients with operable breast cancer five or more years after diagnosis.
4. To determine whether there is a relationship between late relapse and BMI at diagnosis and at 5 years after diagnosis, and whether BMI-associated inflammatory and/or metabolic biomarkers are associated with early and late recurrence.

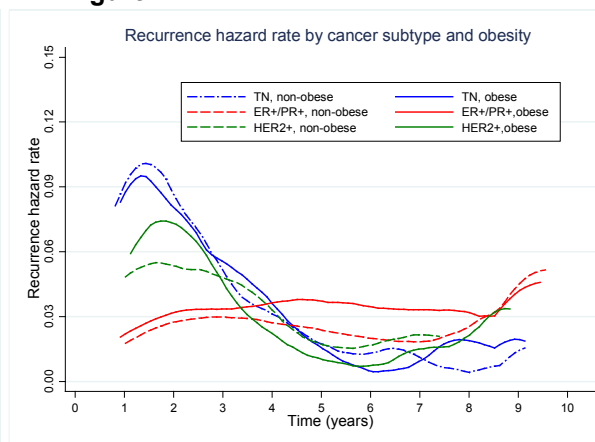
## XII.2 Background and Significance

Late relapse occurring after 5 years or more after a diagnosis of operable breast cancer is a major clinical problem accounting for up to one-half of all relapses in ER-positive disease, but also may occur unpredictably in other breast cancer subtypes.<sup>[1,2]</sup> For example, when evaluating patterns of recurrence in 4950 eligible patients enrolled in the E1199 trial who received adjuvant chemotherapy (plus endocrine therapy if ER-positive)<sup>[3]</sup>, the annual hazard rate (HR) of recurrence within the first 5 years of diagnosis was about 3-fold higher for patients with triple negative breast cancer (TNBC) and 2-fold higher for HER2/neu-positive (HER2+) breast cancer compared with ER- and/or PR positive, HER2-negative disease (ER+/PR+), but was higher for ER+/PR+ disease compared with other subtypes beyond 5 years and remained consistent over time (**Figure 1A, left**).<sup>[4]</sup> In addition, host factors such as body mass index (BMI) at diagnosis may contribute to late relapse, especially in ER+/PR+ disease (**Figure 1B, right**). Two prior reports have found a similar association.<sup>[5] [6]</sup>

**Figure 1A**



**Figure 1B**



**Figure 1A (left):** Annual hazard rate (HR) for recurrence for patients with operable breast cancer treated with adjuvant sequential doxorubicin/cyclophosphamide-taxane therapy in trial E1199, including patients with ER- and/or PR-positive, HER2 negative disease (ER+PR+), triple negative disease (TN) and HER2/neu positive disease (since there was limited information beyond 8-9 years, the confidence intervals are wide at the tails of these curves)

**Figure 1B (right):** HR of recurrence in obese (BMI  $\geq 30$  kg/m<sup>2</sup>) vs. non-obese patients at diagnosis.

There are no clinical or pathologic features predictive of late relapse; gene expression assays predict earlier recurrences.<sup>[7] [8]</sup> Although extended adjuvant therapy with an aromatase inhibitor given for up to 5 years after 2-5 year course of tamoxifen therapy has been shown to reduce the risk of recurrence in ER-positive disease, the absolute benefits are low, resulting in many patients receiving unnecessary therapy.<sup>[9]</sup>

## XII.3 Candidate Biomarkers for Late Recurrence: Plasma Tumor DNA, Insulin/IGF Axis, and Inflammation

**Plasma Tumor DNA and Circulating Tumor Cells (CTCs).** Several assays are available that may detect occult tumor burden, but their clinical utility has not been established. Detection of circulating tumor DNA in the blood of cancer-free patients is one such assay, although the sensitivity, specificity, and positive/negative predictive value for predicting recurrence is currently unknown.<sup>[10]</sup> Enumeration of CTCs in the blood ( $\geq 1$  CTC in 7.5 ml blood) has also shown to be associated with recurrence when

detected in patients with operable breast cancer who have not yet had surgery<sup>[11]</sup>, but has not been evaluated as a predictor of recurrence in patients who are cancer free for at least 5 years after surgery. **Measurement of both plasma tumor DNA and CTC in the same patients at the same time offers an excellent opportunity to evaluate and directly compare these two technologies.** Although the CTC enumeration must be done in real time, the results will not be provided to the clinician or patient for clinical decision making. CellSearch™ cassettes containing the CTC will be dried and stored for future analysis. Plasma will be evaluated at a future date when the technology has been optimized, and when the sample collection has been completed and there is sufficient clinical follow-up and events to permit an analysis.

***Insulin-IGF Axis.*** As described above, obesity at diagnosis is associated with late relapse in ER+PR+ disease. Obesity is associated with hyperinsulinemia, and higher fasting insulin levels have been associated with increased breast cancer risk<sup>[12]</sup> and breast cancer recurrence.<sup>[13-15]</sup> The relation of obesity with insulin resistance, metabolic syndrome, and cardiovascular disease has been shown to vary. The concept of the “healthy obese” – a subset of patients who demonstrate few pernicious effects related to their obesity – has been described and increasingly studied.<sup>[16]</sup> This could apply as well to cancer risk in obese patients. Thus, risk stratification by relevant “pernicious biomarkers” could potentially be important in identifying which obese patients are at increased risk of recurrence and would therefore benefit from specific interventions. Insulin shares substantial amino acid sequence homology, downstream signaling pathways, and mitogenic/anti-apoptotic activity with insulin-like growth factor (IGF)-1, a peptide hormone that mediates many of the growth effects of growth hormone. Insulin receptors are expressed at high levels in breast cancer cell lines<sup>[17]</sup> and human breast cancer specimens.<sup>[18]</sup> Insulin decreases levels of sex hormone binding globulin (thereby increasing free estradiol)<sup>[19]</sup>, upregulates androgen secretion by the ovaries<sup>[20]</sup>, increases HR expression and binding capacity<sup>[21]</sup>, and induces proliferation in normal and dysplastic breast epithelial cells.<sup>[21,22]</sup> Moreover, higher expression of activated IGF-1/insulin receptors has been associated with higher risk of recurrence<sup>[23]</sup>, and IGF signaling has been associated with resistance to paclitaxel.<sup>[24]</sup> Elevated HOMA (homeostasis model assessment) scores and low levels of adiponectin (both associated with obesity) were associated with increased breast cancer mortality in women enrolled in the Health, Eating, Activity, and Lifestyle (HEAL) Study, a prospective cohort study of women with stage I-IIIa breast cancer.<sup>[25]</sup> The HOMA score is a method for assessing β-cell function and insulin resistance ( $[\text{insulin } \mu\text{mL} \times \text{glucose mmol/L}]/22.5$ ).<sup>[26]</sup> In addition, chronic hyperglycemia (reflected by an elevated Hemoglobin A1C level) has been associated with a higher risk of breast cancer recurrence and death.<sup>[27]</sup> Finally, a systematic review and meta-analysis examining the effect of pre-existing diabetes on breast cancer-related outcomes found that diabetics had a greater risk of death and present with more advanced stage disease.<sup>[28]</sup> The IGF-axis also includes and IGF-2, a related growth factor, and six IGF binding proteins (IGFBPs) which have both IGF-dependent and independent effects. In addition to their levels in circulation, IGF-axis proteins are produced locally in tissues with autocrine and paracrine activity. HR-positive breast cancers exhibit significantly higher gene expression of the IGF pathway.<sup>[29]</sup> Widespread gene expression alterations have been described in breast tumors from obese patients as compared to other tumors, which resulted in identification of a 662 gene signature; this signature correlated in publicly available datasets with a gene signature for IGF signaling, and in one cohort was associated with a shorter time to recurrence.<sup>[30]</sup>

**Inflammation.** There is also compelling evidence that obesity produces a systemic inflammatory state<sup>[31]</sup>, which in some settings may promote neoplastic transformation or growth.<sup>[32]</sup> In both dietary and mouse genetic models of obesity, necrotic adipocytes surrounded by macrophages form crown-like structures (CLS) in the mammary glands and visceral fat, and are associated with activation of NF-kappaB, proinflammatory mediators, and elevated levels of aromatase.<sup>[33]</sup> Indeed, it has been shown that the relative benefit of the aromatase inhibitor (AI) anastrozole versus tamoxifen tends to be better in leaner women compared to overweight women in the ATAC trial.<sup>[34]</sup> It is conceivable therefore, that CLS may serve as biomarker for AI resistance, and such patients may require tamoxifen or higher than conventional AI dosing in order to adequately suppress the estrogen signaling.

***Given the important role that each of these factors described above, a late relapse biospecimen bank will facilitate evaluation of tumor and host factors that may contribute to recurrence. Potential candidate biomarkers therefore include biomarkers reflecting occult tumor burden (plasma tumor DNA and CTCs) and host factor (possibly including but not limited to estrogens and their metabolites, inflammatory markers, and multiple components of the insulin/IGF-axis ligand and receptor levels in circulation and in tissues).*** Moreover, an ongoing NCI-sponsored clinical trial (MA32) is evaluating the role of metformin to prevent early recurrence within 5 years, and will attempt to identify predictive biomarkers of benefit (similar to those being evaluated in this proposal). Should that trial prove to be positive, this will provide a foundation whether metformin or other strategies may be useful in preventing late relapse.

#### **XII.4 Comorbidities and Competing Risks in Operable Breast Cancer**

From 2004-2008, the median age at diagnosis for cancer of the breast was 61 years of age, and approximately 16% were 70 years of age or older (including 15.5% between 75 and 84 and 5.6% 85+ years of age)

(<http://seer.cancer.gov/statfacts/html/breast.html#references>). Comorbidities are common in the elderly and pose a competing risk that attenuates the potential benefit of adjuvant therapy. For women with early stage ER-positive breast cancer, the risk of death enrolled in the ATAC trial from causes other than breast cancer at 10 years ranges from 20-60%.<sup>[35]</sup> ***Given our focus on factors contributing to late relapse, it will be critical to evaluate competing risks in this patient population who will be on average at least 5 years older than at presentation.***

#### **XII.5 Research Plan**

We propose to evaluate patients enrolled on two ECOG-ACRIN-coordinated adjuvant trials, including: (1) **E5103:** This trial accrued 4994 patients with node-positive (or high risk node-negative), HER2/neu negative operable breast cancer between 11/2/07 and 2/28/11. All patients received sequential doxorubicin/cyclophosphamide-paclitaxel chemotherapy alone or in combination with bevacizumab, plus endocrine therapy for patients with ER-positive disease (2) **TAILORx:** This trial enrolled 10,273 patients with ER-positive, HER2/neu negative, node negative breast cancer between 4/7/06 and 10/6/10, of whom 1629 with a Recurrence Score (RS) < 11 were assigned to endocrine therapy alone, 1737 with an RS > 25 were assigned to chemotherapy plus endocrine therapy, and 6907 were randomized to endocrine therapy vs. chemoendocrine therapy. Consenting trial participants in both trials had banking of tumor, germ-line DNA, and serum/plasma at baseline. ***This proposal will be accomplished by amending the current protocols. Sites will be notified about potentially eligible subjects by the ECOG-ACRIN Operations Office – Boston.***

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We will identify patients who meet the following criteria: (1) alive and disease-free between 4.5-7.5 years after registration in the parent trial, (2) willingness to sign informed consent and donate blood specimens annually x 5 years after registration. ***In addition to being followed for recurrence, second primary cancer, and survival in accordance with the parent protocol, patients will also be evaluated at 6 time points (in E5103) as described in the table below, including 1 CTC measurement at baseline.*** Patients who have a recurrence will be asked to provide a blood specimen and specimen from the metastatic tumor (when feasible).

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Serum/plasma samples will be forwarded to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF). CTC samples will be sent to and analyzed within 96 hours of collection in the laboratory of Dr. Katherine Alpaugh at the Fox Chase Cancer Center using CellSave tubes and the Veridex CellSearch™ platform, which allows detection of as few as 1 CTC/9 ml blood. The Alpaugh lab has considerable expertise in CTC measurement in both research and clinical settings. [36-39] The CTC portion of the laboratory is CLIA certified to perform the FDA-approved clinical diagnostic testing for metastatic breast, prostate and colon cancer and has a CTC research division exploring alternative CTC separation methods to obtain single CTC for mutational gene analysis. The laboratory has supported two previous ECOG studies (E1104 and E1105) and four GOG studies for which samples were shipped for analysis.

## **XII.6 Patient Participation Requirements for Ancillary Study EL112LAB**

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The ECOG-ACRIN Operations Office – Boston will provide sites a list of patients who have been identified as potential candidates for EL112LAB. The information provided will include the date range for which the patients would be eligible to participate which is dependent on the date of randomization to treatment. Routine notifiers will also be utilized to serve as reminders to sites regarding the timeline of a patient's potential eligibility.

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The list of **potentially eligible** patients at your site will be provided via a password protected WebPortal. The location and access information to the WebPortal:

web link: <https://webapps.ecog.org/LabStudyEligible/>

web name: EL112LAB Potential Eligible Patient List

You access the WebPortal using your CTSU login and password. Access to the listing will be based on your site association assignment in RSS, thus it is important that the sites' contacts are up to date with CTEP.

The listing of eligible patient will be rolling, being updated as new patients enter the eligibility window. The list is based on time of registration to treatment on the respective parent trial, are alive and recurrence free, and have not withdrawn participation from follow-up on the respective trial as reported to ECOG-ACRIN or the CTSU on the relevant study forms. Full eligibility requirements are outlined below. Actual patient eligibility is to be verified by the site prior to registration to EL112LAB and collection of the EL112LAB blood specimens.

### **XII.6.1 Patient Eligibility**

Patients must meet the following criteria:

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1. Patient was registered to treatment on ECOG trials E5103 or PACT1/ TAILORx, at least 4.5 years (54 months) and no more than 7.5 years (90 months) prior to registration to step 3. It is preferable for patients to be registered to step 3 at 5 years (60 months +/- 6 months) after registration



to treatment on the relevant clinical trial. Patient must be willing to contribute the required information and specimens,

2. Patient is disease free, with no prior recurrence, at time of registration to EL112LAB.
3. Patient must be willing to contribute the required information and specimens.
4. Previous submission of tumor tissue or blood specimens:
  - a. E5103 patients – If primary tumor specimens had not been submitted after patient registered to treatment per E5103 Section [10](#), tumor tissue must be available for submission within 4 weeks following registration to Step 3
  - b. PACT1/TAILORx - The primary tumor tissue and peripheral blood samples were previously submitted for research studies just prior to or following registration to treatment as outlined in PACT1/TAILORx Section [10](#).
5. Patient must provide written signed consent to participate in the Ancillary Substudy EL112LAB: *North American Breast Cancer Groups Biospecimen Bank for Determinants of Late Relapse in Operable Breast Cancer*. The model consent for the substudy is provided as [Appendix I-A](#) of the relevant parent clinical trial.

#### XII.6.2 Registration to the Ancillary Study EL112LAB

Patients are registered to Step 3 as outlined in Section [4](#) of the parent protocol (E5103, section 4.11; PACCT-1/TAILORx section [4.4](#)).

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#### **Regarding timing of Registration to EL112LAB, blood collection and sample submission:**

It is understood that blood collection may immediately follow obtaining the patient's consent to participate in EL112LAB, thus registration to EL112LAB may follow the blood collection. If this occurs, register the patient to step 3 within 48 hours following the blood collection. Step 3 registration is required to update the consent permission for the specimen collection and use. Note that STS will allow logging the samples prior to registration to step 3 and report the actual date of blood collection.

If the blood collection is delayed more than 1 week following time of consent, registration to EL112LAB (step 3 registration) is to be delayed until just prior to the blood draw. Expectancy timepoints are tagged from date of registration, not time of actual collection. A long time frame between registration to EL112LAB and the initial EL112LAB blood draw will result in expectancy tracking problems for the site and the lab.

#### XII.6.3 Data and Specimen Submissions

**NOTE:** Requirements for EL112LAB do NOT impact or change the requirements of the parent protocol.

##### A. Comorbidity, BMI and Menstrual History

EL112LAB Comorbidity Form is to be completed at time of registration to EL112LAB.

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The EL112LAB Menstrual History Form is to be completed at the following time points:

- Registration to EL112LAB
- Years 1,2,3,4,5 from time of registration to EL112LAB

Please refer to the Forms Packet of the relevant parent clinical trial for copies of the forms. The E5103 or PACT1/TAILORx Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (<http://www.ecog.org>) or from the CTSU website. Forms must be submitted to the ECOG-ACRIN Operations Office – Boston (ATTN: DATA) at FSTRF, 900 Commonwealth Avenue, Boston, MA 02215.

B. Specimen Submissions

To order the blood collection/submission kits, complete the EL112LAB Collection and Shipping **Kit Order Form** and Fax to Zemotak-International at (800) 815-4675. This form may be located in E5103 Appendix XIV or PACT1/TAILORx [Appendix- VI](#).

It is strongly encouraged that **blood collections be FASTING blood draws** and occur at the time the patient attends the clinic for their standard or follow-up appointments to monitor their health. Trips to the clinic specifically for collection of these research samples are not required. If draw is not a fasting draw, report the date and time of last caloric intake in STS.

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All sample submissions must be logged and tracked using the **ECOG-ACRIN Sample Tracking System (STS)**. The STS generated shipping manifest is to be included with all shipments. If STS is unavailable at time of sample submission, follow the instructions in section [10.4](#) of E5103 or PACT1/TAILORx.

**Access to the shipping account for specimen shipments** for this project can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org)

Specimen collection and submission requirements are summarized in Table 2. Collection tubes are listed in order of recommended draw order, however follow your institutional draw order requirements.

All specimens submitted must be labeled with the parent protocol number, the ECOG-ACRIN protocol specific patient ID, patient initials, date of collection and sample type (e.g. PST, RST, PPT, CTAD, Immunex).

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**Table XII.1** Specimen Submission Summary

Specimen Type	Collection type	Protocol: Time points	Submit to:
Plasma <sup>1,2</sup> + residual cells (WBC+RBC)	CTAD (sodium citrate, theophylline, adenosine, dipyridamole; light blue top)	<u>E5103</u> <ul style="list-style-type: none"> <li>Registration to EL112LAB</li> <li>Years 1,2,3,4,5</li> <li>Recurrence</li> </ul> <u>PACT1/TAILORx</u> <ul style="list-style-type: none"> <li>Registration to EL112LAB</li> <li>Recurrence</li> </ul>	ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)
Serum <sup>1,2</sup>	Rapid Serum Tube (RST – no anticoagulant, orange top)		
Plasma <sup>1,2</sup>	Plasma Separator Tube (PST – lithium heparin, green top),		
Plasma <sup>1,2</sup>	Plasma Preparation Tube (PPT - EDTA, pearl white top)		
Peripheral Blood <sup>1</sup>	CellSave <sup>®</sup>	<u>E5103</u> <ul style="list-style-type: none"> <li>Registration to EL112LAB</li> </ul>	Fox Chase Cancer Center Clinical Protocol Support Lab, P2011
Tumor Tissue Block	Primary Tumor	<u>E5103</u> Required if not previously submitted	ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)
	Recurrence, diagnostic biopsy	All patients	

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1. FASTING DRAWS STRONGLY ENCOURAGED. Date and time of specimen collection and last caloric intake is to be provided, via STS, with submission of the blood specimens.

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2. If a kit is not available at time of sample collection, institutional supplies may be utilized. If the equivalent tube types cannot be obtained, the following standard tubes may be substituted: RST = SST or red top, PST = heparin (green top) tube, PPT = EDTA (purple top) tube, CTAD = citrate (light blue top). For E5103 patients, there are no substitutions for the CellSave<sup>®</sup> vacutainers.

**I. Submission to the FCCC Clinical Protocol Support Laboratory (LAB015)**

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Peripheral Blood (Veridex CellSave Tubes): Draw 9 mL of blood into each tube. Sample must be shipped *day of collection* at ambient temperature. DO NOT REFRIGERATE SAMPLE

FASTING DRAWS STRONGLY ENCOURAGED. Provide date and time of last caloric intake in STS.

Samples must be sent by overnight courier at ambient temperature on the *day of collection* to address below. Questions may be directed to Kathy Alpaugh at (215) 214-1634 or email ([rk\\_alpaugh@fccc.edu](mailto:rk_alpaugh@fccc.edu)). Samples must be sent to arrive Monday through Friday. The laboratory is CLOSED on Saturdays, Sundays and holidays. IF DRAWN ON A FRIDAY mark the waybill "FOR MONDAY DELIVERY". If to be drawn on a DAY BEFORE A HOLIDAY, telephone the Fox Chase Laboratory to receive alternative shipping instructions.

Ship Veridex tubes *only* to:

Fox Chase Cancer Center  
Clinical Protocol Support Lab, P2011  
Attn: Kathy Alpaugh  
333 Cottman Avenue  
Philadelphia, PA 19111-2497

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## II. **Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)**

Questions are to be directed to the ECOG-ACRIN CBPF at [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org) or call 844-744-2420.

### a. **Plasma and Serum Samples**

- FASTING DRAWS STRONGLY ENCOURAGED. Provide date and time of last caloric intake in STS.
- Peripheral blood should be collected into each vacutainer.
- Immediately invert tube several times: CTAD, 3-4 times; RST, 5-6 times; PPT and PST, 8-10 times.
- For the RST tube, allow to clot for at least 5 minutes. If an SST or standard red top tube is used, allow to clot for 30 minutes.
- Centrifuge, within two hours of draw, at room temperature at 1100g – 1300g for 10 minutes in a swing bucket or 15 minutes for a fixed angle centrifuge

Plasma & Serum → • Aliquot serum and plasma into 2 cryovials for each vacutainer collected. CLEARLY LABEL CRYOTUBES WITH RST, PPT, PST or CTAD or institutional tube types utilized.

CTAD RBC+WBC → • For the CTAD vacutainer – DO NOT DISCARD RESIDUAL CELLS. Restore the cap to the plastic vacutainer tube and store with the plasma and serum samples. If the vacutainer is glass, transfer cells to a vryovial prior to freezing.

- Freeze cryovials at –70°C. Batch ship overnight on dry ice.

### b. **Tumor tissue specimens**

The required representative tumor blocks (see table XII.1) are to be submitted within 4 weeks of registration to EL112LAB (primary tumor) or collection (recurrence.) If a block is not available, contact the ECOG-ACRIN CBPF at 844-744-2420 to discuss possible alternative submission guidelines.

The following forms are to be submitted with the tumor tissue:

- ECOG-ACRIN Generic Specimen Submission Form (#2981). Please identify the clinical status of the submitted material.
- Copy of the Pathology Report

Samples are to be shipped Monday through Thursday only. Pathology materials are to be submitted at ambient within one month of collection.

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Plasma and serum samples are to be shipped on dry ice quarterly. Multiple patient samples may be batched shipped together, however each plastic bag must contain samples from a single patient only.

Ship with the relevant documentation to:

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 (713-745-4440 Local or International Sites)  
Fax: 713-563-6506  
Email: [eacbpf@mdanderson.org](mailto:eacbpf@mdanderson.org)

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## XII.7 References

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