

PACCT-1 Trial: TAILORx

*A Clinical Trial Assigning Individualized
Options for Treatment (Rx)*

Oncotype DX Assay Fact Sheet

The TAILORx trial is designed to include a new test, Oncotype DX, into the decision making process for women with early stage breast cancer. The study is for women with early stage breast cancer whose tumors are estrogen receptor (ER) and/or progesterone receptor (PR) positive, Her2 negative and whose lymph nodes are negative. Each patient who enrolls in the study will have the Oncotype DX test. The test result is reported as a Recurrence Score™ (RS) that ranges from 0 to 100. The RS gives the patient information on the likelihood of her cancer recurring – the higher the RS, the higher the risk of recurrence.

Oncotype DX-What is it?

Oncotype DX is the first breast cancer test that provides an individual, quantitative assessment of the likelihood of disease recurrence. Oncotype DX results are provided in the form of a Recurrence Score™, a number between 0 and 100 which correlates to a specific likelihood of breast cancer recurrence within 10 years of initial diagnosis.

The risk of breast cancer recurrence may be estimated based upon clinical characteristics that may be evaluated in routine tests, such as tumor grade, tumor size, and other factors. However, some tumors that have favorable characteristics relapse, and many tumors that have unfavorable characteristics never relapse. Using genomic research that evaluated the relationship between hundreds of different genes and recurrence, researchers noticed key differences between relapsing and non-relapsing cancers in the expression of certain genes.

Further research showed that analyzing 21 genes in a breast cancer tumor could help predict recurrence within ten years of the initial diagnosis more accurately than could be predicted by existing methods. Oncotype DX uses the latest technology to analyze the “expression” or activity of the 21 genes. The results of the gene analysis are then put into a mathematical equation to convert those measures into the Recurrence Score.

At the time of surgery, pathologists routinely save the unused tumor specimen not required for diagnosis in paraffin (wax). The specimen is often referred to as a “paraffin block” and is usually retained by the local laboratory that initially analyzed the specimen. A pathologist can then cut very, very thin slices of the tumor block to be used in future testing. Oncotype DX uses a small amount of tissue removed during a patient’s original surgery (lumpectomy, mastectomy, or core biopsy) and stored in the paraffin block.

What do the results mean for me?

Oncotype DX assay has been tested for reliability and validity. Reliability means that if you use the test ten times on ten samples from the same tumor you will get the same result the tenth time as you got the first. Validity means that the test really measures a woman’s risk of recurrence.

Oncotype DX went through many tests and several clinical trials to determine its validity and reliability.



In addition to providing information about a possible recurrence of breast cancer, Oncotype DX provides information about how an individual patient may respond to treatment. Patients with a low Recurrence Score (Score of 1 to 17) respond well to hormonal treatment and seem to gain very little, if any, benefit from chemotherapy. Women with a high RS (31 or higher), on the other hand, gain a great benefit from chemotherapy being added to hormonal therapy. If the RS is between 18 and 30, it is unclear whether chemotherapy is necessary, and whether hormonal therapy alone may be sufficient. The TAILORx trial was designed to find out more information about each level of RS, particularly women with a mid-range RS.

What is different about the RS categories used in TAILORx?

Although researchers who developed the Oncotype DX test defined low, intermediate, and high RS as defined above (as shown in the table below), the test result is also predictive of recurrence across the risk groups. Since only women who meet current standard clinical criteria for chemotherapy would be included in TAILORx, researchers designed the trial to minimize the potential for under-treatment. In other words, minimize the chance that a patient who could potentially benefit from chemotherapy would be randomized not to receive it.

The definition of low, high, and mid-range RS was modified in TAILORx as shown in the table below.

- For the low RS group (called Secondary Study Group 1), the range was modified from 17 or less to 10 or less. This is because the risk of both distant and local recurrence for women in this group is very low. Chemotherapy is not recommended because of the low potential for the treatment being beneficial and the potential harms associated with chemotherapy.
- For the high RS group (called Secondary Study Group 2), the range was modified from 31 and above to 26 or above. This threshold was reduced in order to provide a greater level of assurance that patients who could potentially benefit from chemotherapy would receive it.
- For the mid-range group (called the Primary Study Group), a range of 11 to 25 was selected (rather than the 18 to 30 range for the intermediate group as defined below). This is because within this range, there is an elevated risk of recurrence in which chemotherapy would typically be recommended, but there is insufficient evidence demonstrating chemotherapy is beneficial.

For more information visit <http://www.genomichealth.com/oncotype/pathome.aspx>

Genomic Health, Inc.	Group	RS Low	RS Intermediate	RS High
	Recurrence Score	1 to 17	18 to 30	31+
TAILORx trial	Group	Secondary Study Group - 1	Primary Study Group	Secondary Study Group - 2
	Recurrence Score	1 to 10	11 to 25	26 +
	Treatment	Hormonal Therapy Alone	Randomized Group	Hormonal Therapy & Chemotherapy

References

The Oncotype DX assay was developed in a stepwise manner. First, scientists developed methods that allowed them to measure expression of genes in routinely processed, paraffin-embedded tumor tissue. This was a very significant technical accomplishment; previously, genes could be measured only in freshly processed or frozen tissue, making it impractical to use gene expression profiling for making clinical decisions.

Second, researchers identified specific genes that previous work indicated were prognostically important, and developed probes to measure these specific genes in tissue, resulting in a panel of about 250 individual genes that could be evaluated in tumor tissue.

Third, researchers correlated the expression of these 250 genes with relapse in a group of about 450 patients, and selected 16 of these genes for inclusion in the Oncotype DX assay because they were strongly linked to prognosis. The genes included several distinct groups, including genes related to the estrogen receptor, Her2/neu, invasion, proliferation, and other biological processes.

In order to adjust for differences in how much genetic material was in the individual specimen being analyzed, the expression of these 16 tumor related genes is normalized to the expression of five "housekeeping" genes found in both tumor tissue and normal tissue in equivalent amounts; in other words, variations in the five "housekeeping" genes from specimen to specimen reflected how much genetic material was being measured, but not the biology of the tumor. A mathematic model was developed that adjusted the gene expression patterns with its clinical importance, resulting in a number called the "Recurrence Score," and which some have called "the 21 gene profile."

After the Oncotype DX assay was developed and tested in the laboratory, the researchers needed to determine if the assay accurately correlated with the risk of recurrence. To do this, they needed access to tumor blocks from patients and to be able to match the tumor block to the patient outcomes. This was performed in several trials that are summarized in the table below, and which are described in greater detail.

Author (Trial)	No.	Patient Selection	Treatment Arms	Result
Paik et al. (B14)	668	ER-positive, node-negative	Tamoxifen	Recurrence Score correlates with prognosis
Paik et al. (B20)	651	ER-positive, node-negative	Tamoxifen vs. Tamoxifen plus Chemotherapy	Chemotherapy beneficial only if RS > 30
Habel et al.	790	ER-positive, node negative	Tamoxifen or No Therapy	Recurrence Score correlated with prognosis
Esteva et al.	149	Node-negative, ER -positive or negative	No Tamoxifen or Chemotherapy	Recurrence Score did not correlate with prognosis

*Tamoxifen: in NSABP trial B14 and B20, was given at a dose of 20 mg daily for five years; Chemotherapy – included either CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) or MF

To find enough tumor specimens associated with outcomes, scientists turned to the National Surgical Adjuvant Breast and Bowel Project (NSABP), which is a large group of researchers and clinicians who work together as a cooperative group to complete large clinical studies. The NSABP completed a study called B14 that compared women who had estrogen receptor-positive, lymph node-negative breast cancer treated only with adjuvant tamoxifen to women with the same type of breast cancer treated only with surgery. The Oncotype DX assay was done on 668 tumor specimens from the women treated with tamoxifen. After each patient's block was given a Recurrence Score™ (RS), the scores were compared to the actual outcome for each patient. The study found that a high RS (31 or higher) correctly identified women who were more likely to have a recurrence than those with a mid-range RS (18 to 30) or low RS (18 or lower) assuming they were treated with hormonal therapy.

Paik S, Shak S, Tang G, et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. *New England Journal of Medicine*. 2004;35 (27):2817-2826.

The NSABP conducted an additional study called B20 which looked at chemotherapy benefit. This study compared the outcomes of 651 patients with low, intermediate, and high RS who were treated with tamoxifen and chemotherapy to those of each RS group treated with adjuvant tamoxifen alone. This study showed that not all women benefited equally from chemotherapy. Women with low RS scores derived little benefit from chemotherapy and women with high Recurrence Scores had a large benefit from chemotherapy. For the women in the intermediate group, the benefit was more uncertain, which was the premise for the TAILORx study.

Paik S, Tang G, Shak S, et al. *Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor-Positive Breast Cancer*. JCO Early Release, published online ahead of print May 23 2006. <http://www.jco.org/cgi/content/abstract/JCO.2005.04.7985v1>

Another study was completed to determine if the Oncotype DX assay RS was associated with the risk of death from breast cancer when used in a different population of patients (patients who did not receive chemotherapy). Researchers identified 4964 patients who had been diagnosed between 1985 and 1994 who did not have chemotherapy, of whom tumor tissue was available for analysis in 220 patients who had died from breast cancer. They compared patients who died of breast cancer to those who of a matched group of 570 patients were alive at the time of the study. The Oncotype DX assay was used on archived tumor blocks to determine the RS. The findings were that for women with ER-positive, lymph node-negative breast cancer, the RS (low, intermediate, or high) was strongly associated with low, intermediate, or high risk of breast cancer death. At ten years, patients with a low RS treated with tamoxifen had a lower risk of breast cancer death (2.9%) than did patients with an intermediate RS (10.7%) or high RS (15.5%). This study, using different methods and a different population, supported the findings of the NSABP B14 study described above.

Habel L, Shak S, Jacobs M, et al. *A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients*. Breast Cancer Research 2006, 8:R25. <http://breast-cancer-research.com/content/8/3/R25>

All previous studies described evaluated the Oncotype DX assay in patients with estrogen receptor-positive, axillary lymph node-negative breast cancer treated with tamoxifen, tamoxifen plus chemotherapy, or no therapy. Researchers from MD Andersen Cancer Center evaluated a group of 149 patients with axillary lymph node-negative breast cancer treated over an 18-year period who had been selected not to receive chemotherapy or hormonal therapy, were followed for at least five years, and for whom tumor tissue was available for analysis. In this analysis, Recurrence Score did not correlate with relapse. This study points out the importance of performing the Oncotype DX test only if the tumor is estrogen receptor-positive.

Esteva FT, Sahin AA, Cristofanilli M, et al. Prognostic role of a multigene reverse transcriptase-PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. *Clin Cancer Res* 2005; 11: 3315-3319
<http://clincancerres.aacrjournals.org/cgi/content/full/11/9/3315>

Genomic Health, Inc. is the developer of the Oncotype DX assay. It also operates the laboratory where the RS is determined by the analysis of the patient's tumor block. Its Web site has a wealth of information for patients who wish to have more information about, for example, what is a recurrence, details of Oncotype DX's development, who is eligible for the assay, and how the assay is performed. The site also contains information on insurance coverage and a very useful question and answer section.

Genomic Health, Inc, Manufacturer's Web site with information about the Oncotype DX assay for patients and healthcare professionals: <http://www.genomichealth.com/oncotype/default.aspx>

