

The Oncotype DX™ Test: Prediction of Recurrence

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The earliest gene-expression profile test marketed in the United States for early stage breast cancer is the Oncotype DX™. This fact sheet provides information about this test and the research behind its development. (See also, NBCCF's Fact Sheet on Gene-Expression Profile Testing).

Oncotype DX™;

Oncotype DX™ is a laboratory test that can be used on preserved (formalin-fixed, paraffin-embedded) stage I or II, estrogen receptor positive breast cancer tumor specimens from women whose tumors have not spread to their axillary nodes. Using a process known as reverse transcription-polymerase chain reaction (RT-PCR), it measures the level of expression of 21 specific genes to predict the probability of breast cancer recurrence. On the basis of those measurements, a "Recurrence Score" (RS) is assigned to the individual tumor.

Recurrence Score

The tumor sample is analyzed to determine how actively 21 specific genes are working to produce proteins in the cancer cells. Measurements of five of those 21 genes (Beta-actin, GAPDH, RPLPO, GUS, and TFRC) are used simply as "controls" - that is, to verify that the test has not been contaminated or run improperly. Activity in all samples should be about the same for these control genes. The other 16 genes, which produce their proteins at varying levels in different tumors, include:

- genes associated with cell proliferation (Ki-67, STK15, Survivin, Cyclin B1, and MYBL2);
- genes associated with cellular invasion (Stromolysin 3, and CathepsinL2);
- genes associated with HER2 activity (GRB7 and HER2);
- genes associated with estrogen activity (ER, PR, Bc12, and SCUBE2); and
- three other genes with distinctly different activity in cancer cells (GSTM1, BAG1, and CD68).

The RS is calculated by using a mathematical formula that includes the measured levels of these 16 genes to come up with a single RS between 1 and 100 for each individual tumor. The lower the score, the lower the predicted probability of disease recurrence.

Interpreting the Recurrence Score

The first published study on the validity of the RS was done on stage I or II, ER+, node negative tumors 1-4 cm in size, from women who took tamoxifen for five years, but who did not have chemotherapy.¹ The study was done by examining the preserved tumor tissue from women diagnosed ten or more years ago. Once the RS was calculated, it was compared with the women's later medical records to see whether it had accurately predicted what their health status would be ten years later.

In this research, the RS was shown to be a useful predictor of distant recurrence for up to 10 years after initial diagnosis. Tumors with low RS (scores below 18) recurred at a rate of 6.8% in the 10 years after diagnosis; tumors with moderate RS (between 18 and 30) recurred at a rate of 14.3%; and those with high RS (higher than 30) recurred at a rate of 30.5%. This means that with tamoxifen treatment but no chemotherapy, there was about a 93% chance that a woman with a low RS would survive for at least 10 years without a recurrence of breast cancer elsewhere in her body. On the other hand, the chance that a woman with a high RS would have this result was reduced to about 70%.

Other research on Oncotype DX™;

NBCCF has partnered with the Breast Cancer Intergroup on the first Phase III, randomized, prospective clinical trial seeking to determine whether women with early-stage breast cancer that is ER+ and HER2-, and who are at intermediate risk for breast cancer recurrence according to Oncotype Dx™, benefit from adding chemotherapy to standard treatment with hormonal therapy. The trial, known as TAILORx (Trial for Assigning Individualized Options for Treatment), also seeks to confirm that patients with a low recurrence score do not gain additional benefit from chemotherapy that precedes treatment with hormonal therapy. The results of the study will help patients and clinicians make more objective and informed decisions about adjuvant treatment, helping target these treatments to those who are more likely to benefit, and sparing those who are unlikely to benefit. (For more information on this trial, see NBCCF's TAILORx page. To find a trial site closest to you, visit ClinicalTrials.gov.)

In addition, several studies looking at Oncotype Dx's predictive abilities have been published in peer-reviewed journals and/or presented at the 2004 and 2005 San Antonio Breast Cancer Symposiums:

- Predicting overall survival: RS was able to predict overall survival in ER+, node negative, tamoxifen-treated and

untreated women with breast cancer. For treated women whose tumors had a low RS, the probability of dying of breast cancer within 10 years was 2.8%. At intermediate RS levels the probability of dying of breast cancer was 10.7%, and at high RS levels, probability of breast cancer death was 15.5%. Among untreated women, the 10-year probabilities of dying from breast cancer were 6.2%, 17.8%, and 19.9% for low, intermediate, and high RS levels, respectively.²

- Predicting local and regional recurrences: RS predicted local and regional recurrences in women with ER+, node negative breast cancer who were treated with either tamoxifen alone, tamoxifen and chemotherapy, or placebo. Although significant findings were reported for all three groups, the most significant association between RS score and local and regional recurrences was found for patients treated with tamoxifen: the 10-year recurrence rates for low, intermediate, and high RS levels were 4.3%, 7.2%, and 15.8% respectively. This means that 96% of women with low risk scores survived for at least 10 years without a local or regional recurrence of breast cancer. On the other hand, 84% of women with a high risk score recurred. For a full brief of this study, see NBCC's Report on the 2005 SABCS .³

- Predicting response to chemotherapy: RS predicted response to chemotherapy in women with tumors that were ER+ and node negative, and who were treated with tamoxifen or with tamoxifen plus CMF (cytoxan methotrexate 5 fluorouracil) or MF (methotrexate 5 fluorouracil) chemotherapy. Ten years after diagnosis, women whose tumors had a low RS (< 18) had the same low levels of recurrence, whether they got chemotherapy or not. On the other hand, distant recurrence free survival was increased by 28% for women whose tumors had a high RS (>30) if they had chemotherapy, compared with those who didn't. ^{4, 5}

- Predicting response to tamoxifen: When combined with measurements of how many estrogen receptors are present in the tumor, RS predicted response to tamoxifen in women with tumors that were ER+ with no positive nodes, and who were treated with tamoxifen or with tamoxifen plus CMF or MF chemotherapy. The largest benefits of tamoxifen were found in women with high levels of ER and generally low RS. Smaller benefits were found in women with low levels of ER and generally high RS. ⁴

Comparing the Oncotype DX[®]; Recurrence Score to other information

In another study presented at the 2004 San Antonio Breast Cancer Symposium but not yet published in a peer reviewed journal, the 21-gene panel was shown to be a more accurate predictor of recurrence than age and tumor size, and more accurate than the more commonly used National Comprehensive Cancer Network (NCCN) or St. Gallen risk categories (which rely on age, tumor size, and tumor grade) in predicting the need for chemotherapy and 10 year distant recurrence free survival.⁶ Use of the RS instead of the NCCN or St. Gallen classifications for predicting risk of recurrence would result in many fewer women getting adjuvant chemotherapy (chemotherapy given shortly after initial surgery to remove their tumors).

All of these studies have been met with great interest, however, caution in interpreting them is warranted at this time. Until they have been published in peer-reviewed journals, and more prospective testing has been done, their clinical usefulness cannot be fully assessed by the scientific, medical, and advocacy communities. In addition, further research will be needed to determine whether the 21-gene panel provides better overall information about the likelihood of tumor recurrence under various treatment protocols than the collective results of currently applied clinical tests. As described above, it relies on measurements that include some of the same variables that are well-established correlates of cancer cell activity, such as estrogen receptor and HER2 activity.

About NBCCF

The National Breast Cancer Coalition Fund is a grassroots organization dedicated to ending breast cancer through the power of action and advocacy. The Coalition's main goals are to increase federal funding for breast cancer research and collaborate with the scientific community to implement new models of research; improve access to high quality health care and breast cancer clinical trials for all women; and expand the influence of breast cancer advocates in all aspects of the breast cancer decision making process.

Notes

A. Recurrence is a relapse of breast cancer during or after treatment. It can be local (in the breast), regional (in the area around the breast), or distant (in other areas of the body). To assess the effect of a treatment or intervention, researchers might measure the time to recurrence, or the interval of disease-free survival. In a clinical trial, this is the time from randomization until a patient experiences a recurrence, a new primary cancer, or death.

References

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