

# Predicting Prognosis in Women with Early Breast Cancer



Tools that accurately predict the prognosis of women with early breast cancer are invaluable to both clinicians and patients when making decisions about adjuvant therapy. In women with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen, a 21-gene assay was recently found by the NSABP to predict the 10-year distant recurrence rate and the benefit associated with adjuvant chemotherapy. The Adjuvant! online computer program, developed by Dr Peter Ravdin, also allows for the prediction of outcomes in women with early breast cancer. In a presentation at ASCO 2004, the predictions from Adjuvant! were found to be very comparable to actual outcomes observed in patients from British Columbia. These and future tools that can predict outcomes should aid in the decision-making process about adjuvant therapies.

## MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE IN PATIENTS WITH ER-POSITIVE, NODE-NEGATIVE BREAST CANCER

Based on literature review and known prognostic factors in breast cancer, approximately 185 genes were selected for a multigene panel and tested in two data sets. Twenty-one genes appeared to predict for outcome, and they were then confirmed in a subset of patients from the NSABP-B-20 tamoxifen-only arm.

NSABP-B-14 tested this multigene panel prospectively in 668 patients with ER-positive, node-negative breast cancer biopsies, and the panel predicted recurrence risk far better than age, tumor size or tumor grade. This assay assigns patients a recurrence score from zero to 100 to assist in deciding on treatment alternatives.

— Melody A Cobleigh, MD

Previously, gene-expression profiling required frozen material; however, perhaps less than one percent of breast cancers biopsies are stored in that fashion. A breakthrough came when it was discovered that the RNA wasn't missing in paraffin blocks, it was just fragmented. As a result of this discovery and other new technologies, a multigene assay was developed that is predictive of breast cancer recurrence despite adjuvant tamoxifen therapy.

This assay was validated in NSABP-B-20 and B-14, and we now have a predictor that scores a woman's risk of relapse between one and 100. Apparently, it is as powerful as tumor grade in its predictive ability, but the assay is reproducible while tumor grade is not.

— Matthew J Ellis, MB, PhD

## THE 21-GENE ASSAY PREDICTS BENEFIT FROM ADJUVANT CHEMOTHERAPY AND TAMOXIFEN

We evaluated patients treated with adjuvant chemotherapy in NSABP-B-20 to determine if the 21-gene assay predicts for response to chemotherapy. The results were actually quite striking.

The absolute benefit from chemotherapy was zero in the patients at low and intermediate risk, but the absolute benefit in the 10-year distant recurrence rate was 28 percent and the relative risk reduction was 75 percent in the group of patients at high risk.

The women enrolled in NSABP-B-20 received tamoxifen at the same time as chemotherapy. Theoretically, the benefit from chemotherapy in the patients with an intermediate risk might have been reduced by tamoxifen.

In the women enrolled in the NSABP-B-14 trial, we can actually identify patients who don't gain any benefit from adjuvant tamoxifen — patients with low levels of estrogen receptor as determined by messenger RNA levels.

— Soonmyung Paik, MD

## PROGRAM FOR THE ASSESSMENT OF CLINICAL CANCER TESTS

Dr Soon Paik presented validation data from NSABP-B-14 demonstrating that a new multigene RT-PCR assay could identify gene expression profiles predictive of recurrence in patients with node-negative, ER-positive breast cancer who previously received adjuvant tamoxifen. On multivariate analysis, this assay was a significantly more powerful predictor than other conventional clinical features. On the other hand, Dr Esteva presented data from an MD Anderson trial in which the same assay did not fare so well. Esteva's data examined a more diverse group of patients who had not received any adjuvant therapy.

The Program for the Assessment of Clinical Cancer Tests is planning to study this new technology. The simplest way to validate it would be to study it prospectively, but that would take years to accomplish and by the time the study was completed, newer technology would be available. Another possibility is to prospectively study whether this or a similar assay can be used to select patients at low risk who can be spared chemotherapy, or patients at high risk who need intensive chemotherapy. Clearly, multiple approaches need to be considered, and the final trial design is still being developed.

— G Thomas Budd, MD

### ONCOTYPE DX 21-GENE RECURRENCE SCORE ASSAY

16 cancer and 5 reference genes from 3 studies

<b>Proliferation</b> Ki67 STK15 Survivin CCNB1 (cyclin B1) MYBL2	<b>HER2</b> GRB7 HER2	<b>Estrogen</b> ER PGR BCL2 SCUBE2
	<b>GSTM1</b>	
<b>Invasion</b> MMP11 (stromolysin 3) CTSL2 (cathepsin L2)	<b>CD68</b>	<b>Reference</b> ACTB (β-actin) GAPDH RPLPO GUS TFRC
	<b>BAG1</b>	

Recurrence Score =

$$\begin{aligned}
 &+0.47 \times \text{HER2 group score} \\
 &-0.34 \times \text{ER group score} \\
 &+1.04 \times \text{Proliferation group score} \\
 &+0.10 \times \text{Invasion group score} \\
 &+0.05 \times \text{CD68} \\
 &-0.08 \times \text{GSTM1} \\
 &-0.07 \times \text{BAG1}
 \end{aligned}$$

Category	Recurrence score (0 - 100)
Low risk of recurrence	<18
Intermediate risk of recurrence	≥18 and <31
High risk of recurrence	≥31

SOURCES: Paik S et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817-26.

Paik S. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14. Presentation, San Antonio Breast Cancer Symposium, 2003;Abstract 16.

### NSABP-B-20 CHEMO BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE

ARM 1	Tamoxifen + MF
ARM 2	Tamoxifen + CMF
ARM 3	Tamoxifen

Objective: Determine the magnitude of the chemotherapy benefit as a function of 21-gene recurrence score assay.

### B-20 EVALUATION PATIENTS (N=651) SIMILAR TO ALL PATIENTS (N=2,299)

	Number of eligible patients			
	Tam	Tam+MF	Tam+CMF	Total
All B20	770	763	766	2299
GHI-B20	227 (29.5%)	203 (26.6%)	221 (28.9%)	651 (28.3%)

Tam = tamoxifen

GHI-B20 study subjects were similar to all B-20 patients. Loss of cases due principally to blocks never collected.

### TEN-YEAR DISTANT RECURRENCE-FREE SURVIVAL ACCORDING TO A 21-GENE RECURRENCE SCORE

Risk group	Tamoxifen (n=227)	Tamoxifen + chemotherapy (n=424)	p-value
Low (RS < 18)	95%	96%	0.76
Intermediate (RS = 18-30)	89%	90%	0.71
High (RS ≥ 31)	60%	88%	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCES: Paik S. Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20. Presentation, San Antonio Breast Cancer Symposium, 2004;Abstract 24.

Paik S et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817-26.

Paik S. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14. Presentation, San Antonio Breast Cancer Symposium, 2003;Abstract 16. Available at www.sabcs.org; accessed December 22, 2004

### NSABP-B-14 TAM BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE

ARM 1	Placebo - Eligible
ARM 2	Tamoxifen - Eligible

Objective: Determine whether the 21 gene recurrence score assay captures: prognosis, response to tamoxifen, or both.

### KAPLAN-MEIER ESTIMATES OF THE 10-YEAR DISTANT RECURRENCE RATE ACCORDING TO A 21-GENE RECURRENCE SCORE (N=668)

Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low (RS < 18)	51	6.8%	4.0-9.6
Intermediate (RS = 18-30)	22	14.3%	8.3-20.3
High (RS ≥ 31)	27	30.5%	23.6-37.4

RS = recurrence score  
p < 0.001 for comparison between high- and low-risk groups

SOURCES: Paik S et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817-26.

### COMPARISON OF OUTCOMES PREDICTED BY ADJUVANT! AND ACTUAL OUTCOMES OBSERVED BY THE BREAST CANCER OUTCOMES UNIT (BCOU) IN BRITISH COLUMBIA (N=4,083)

Risk group	Adjuvant!-predicted	BCOU-observed	Difference between predicted and observed
10-year OS	71.7%	72.0%	-0.3%*
10-year BCSS			
Overall	83.2%	82.5%	+0.7%*
No therapy	89.1%	90.1%	-1.0%*
T	81.2%	79.4%	+1.8%*
C	74.6%	73.7%	+0.9%*
T + C	75.2%	70.6%	+4.6%†
10-year EFS	71.0%	70.1%	+0.9%*

OS = overall survival; BCSS = breast cancer-specific survival; T = tamoxifen; C = chemotherapy; . = event-free survival

\* p-values are nonsignificant; † p < 0.05

SOURCES: Olivetto IA et al. An independent population-based validation of the adjuvant decision-aid for stage I-II breast cancer. *J Clin Oncol* 2004;22(14 Suppl):Abstract 522.

### SELECT PUBLICATIONS

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Paik S. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14. Presentation, San Antonio Breast Cancer Symposium, 2003;Abstract 16. Available at www.sabcs.org; accessed December 22, 2004.

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Paik S et al. Risk classification of breast cancer patients by the Recurrence Score assay: Comparison to guidelines based on patient age, tumor size, and tumor grade. *Breast Cancer Res Treat* 2004;88(1 Suppl 1):118;Abstract 104.

Piccatt MJ et al. Multi-center external validation study of the Amsterdam 70-gene prognostic signature in node negative untreated breast cancer: Are the results still outperforming the clinical-pathological criteria? San Antonio Breast Cancer Symposium, 2004;Late Abstract 38.

Ravdin PM et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 2001;19(4):980-91.

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