The Oncotype DX® Breast Cancer Assay helps you find an answer

Oncotype DX helps clarify one of the most difficult treatment questions by providing an individualized Recurrence Score® result that assesses the benefit of chemotherapy and the likelihood of breast cancer recurrence.1,2
Do all patients have the same magnitude of benefit from chemotherapy?

Landmark NSABP B-20 trial of 651 estrogen receptor–positive (ER-positive), node-negative breast cancer patients found¹:

- The addition of chemotherapy provided only a 4% absolute benefit, measured as the proportion of patients free of distant recurrence at 10 years

The Oncotype DX® Breast Cancer Assay is the only test that provides patients with an individual score validated to predict chemotherapy benefit and the likelihood of distant recurrence.¹ ³
Providing predictive and prognostic information for a broad range of patients

The OncoType DX® Breast Cancer Assay\textsuperscript{1,2}:  

- Analyzes the expression of 21 genes  
- Predicts chemotherapy benefit  
- Indicates the 10-year risk of distant recurrence

Eligible ER-positive breast cancer patients extend along a biologic continuum\textsuperscript{1,2,4-7}

<table>
<thead>
<tr>
<th>ER-positive, tamoxifen-treated, or AI-treated\textsuperscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAGE I</strong></td>
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<td></td>
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<tr>
<td><strong>STAGE II</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>STAGE III\textsuperscript{†}</strong></td>
</tr>
</tbody>
</table>

\textit{Al} = aromatase inhibitor; ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network. ASCO and NCCN do not endorse any product or therapy.  
\textsuperscript{*}T1b moderate/poorly differentiated or unfavorable features/1c/2/3, N1mi, M0; HER2-negative.  
\textsuperscript{†}Consider patients from a subset of stage IIIa as indicated; not all stage III patients.

The OncoType DX Breast Cancer Assay is the only multigene expression assay incorporated in both the ASCO\textsuperscript{®} and NCCN\textsuperscript{®} guidelines.\textsuperscript{5,6}
Accurate, precise, and reproducible

Why RT-PCR was chosen for the Oncotype DX® Breast Cancer Assay³:

- Precise, accurate, and highly reproducible over a wide dynamic range
- Minimizes variability that may result from:
  - Tissue preparation method, type of fixative, and fixation time
  - Tumor block age, storage, and variability in preparation
  - Sample heterogeneity
- Can be assayed using fixed tissue from core biopsy or surgical excision samples

Genomic Health’s® surgical pathologists take additional steps to ensure accuracy³

- Perform manual microdissection
- Clear sample contaminants
- Enrich for invasive tumor tissue

With a success rate >97% in generating an accurate result, you can feel confident in the Oncotype DX Breast Cancer Assay.³
21 genes identified through a rigorous selection process

- 447 patients with ER-positive and ER-negative, and node-positive and node-negative breast cancer were examined
- 250 breast cancer–associated genes were analyzed

21-gene panel used to develop the Recurrence Score® algorithm

<table>
<thead>
<tr>
<th>PROLIFERATION</th>
<th>INVASION</th>
<th>HER2</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67</td>
<td>Stromelysin 3</td>
<td>GRB7</td>
<td>Beta-actin</td>
</tr>
<tr>
<td>STK15</td>
<td>Cathepsin L2</td>
<td>HER2</td>
<td>GAPDH</td>
</tr>
<tr>
<td>Survivin</td>
<td></td>
<td></td>
<td>RPLPO</td>
</tr>
<tr>
<td>Cyclin B1</td>
<td></td>
<td></td>
<td>GUS</td>
</tr>
<tr>
<td>MYBL2</td>
<td></td>
<td></td>
<td>TFRC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESTROGEN</th>
<th>OTHER</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>GSTM1</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>CD68</td>
<td></td>
</tr>
<tr>
<td>Bcl-2</td>
<td>BAG1</td>
<td></td>
</tr>
<tr>
<td>SCUBE2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16 cancer genes
- Several identified with a consistent and strong statistical association to breast cancer recurrence
- Others with robust predictive power for chemotherapy benefit

5 reference genes
- Normalize gene expression
- Provide quality control

Gene expression levels determine the Recurrence Score (RS) result

\[
RS = +0.47 \times \text{HER2 group score} -0.34 \times \text{Estrogen group score} +1.04 \times \text{Proliferation group score} +0.10 \times \text{Invasion group score} +0.05 \times \text{CD68} -0.08 \times \text{GSTM1} -0.07 \times \text{BAG1}
\]
The proven prognostic utility of the Oncotype DX® Breast Cancer Assay

- Prospective analysis on archived tissue
- 668 patients treated with tamoxifen
- ER-positive, node-negative

10-year rate of distant recurrence was significantly lower for patients with low Recurrence Score values:

- Recurrence Score <18 (Low Risk): 6.8% (95% CI 4%-9.6%)
- Recurrence Score 18-30 (Intermediate Risk): 14.3% (95% CI 8.3%-20.3%)
- Recurrence Score ≥31 (High Risk): 30.5% (95% CI 23.6%-37.4%)

The majority of patients had low Recurrence Score values:

- RS <18: 51%
- RS 18-30: 22%
- RS ≥31: 27%

**Prognostic:** any measurement available at the time of diagnosis or surgery associated with clinical outcome in the absence of systemic adjuvant therapy or following the standard of care treatment.

Validated in NSABP B-14
Adding critical information to your treatment decision

Provides significant information about recurrence risk, independent of age and tumor size ($P<.001$)²

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HAZARD RATIO</th>
<th>95% CI</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery</td>
<td>0.71</td>
<td>(0.48, 1.05)</td>
<td>.08</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td>1.26</td>
<td>(0.86, 1.86)</td>
<td>.23</td>
</tr>
<tr>
<td>Recurrence Score®</td>
<td>3.21*</td>
<td>(2.23, 4.61)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*The hazard ratio for the Recurrence Score is calculated relative to an increment of 50 units.

May predict the magnitude of tamoxifen benefit, as shown in a follow-up study to NSABP B-14 (n=645)³†

*Results should not be used to indicate that tamoxifen should not be given to the high-risk group.³

- Patients with high ER scores (and low Recurrence Score values) saw the largest benefit from treatment with tamoxifen⁹
The proven predictive utility of the Oncotype DX® Breast Cancer Assay

- Prospective analysis on archived tissue
- 651 patients treated with tamoxifen or tamoxifen plus CMF/MF
- ER-positive, node-negative

**Low Recurrence Score® value (<18); little to no chemotherapy benefit**

- Proportion without distant recurrence
- $P=.61$
- **Tam + chemo** 218 8
- **Tam** 135 4
- $97\%$ vs $96\%$

**Intermediate Recurrence Score value (18-30); no substantial chemotherapy benefit**

- Proportion without distant recurrence
- $P=.39$
- **Tam + chemo** 89 9
- **Tam** 45 4
- $91\%$ vs $89\%$

*Clinically important benefit cannot be excluded.*
Helping you predict the benefit of chemotherapy in node-negative patients

**High Recurrence Score® value (≥31); large chemotherapy benefit**

- **Proportion without distant recurrence**
  - P<.001
  - n Events
  - Red: Tam + chemo 117 13
  - Black: Tam 47 18

- **Years**
  - 0 2 4 6 8 10 12

- **Absolute increase in proportion free of distant recurrence (mean ± SE)**

- **Recurrence Score Value <18**
  - (n=353)
  - 10%

- **Recurrence Score Value 18-30**
  - (n=134)
  - 20%

- **Recurrence Score Value ≥31**
  - (n=164)
  - 30%

**Predictive:** any measurement associated with benefit or lack of benefit from a particular therapy.³
Additional insight may help guide your treatment decision

- Younger patients can have low Recurrence Score values\(^1\)
- Older patients can have high Recurrence Score values\(^1\)

- Patients with larger tumors can have low Recurrence Score values\(^1\)
- Patients with smaller tumors can have high Recurrence Score values\(^1\)
Providing independent, significant data beyond traditional measures

- Significant proportions of high-grade tumors have low Recurrence Score values\(^1\)
- Even low-grade tumors can have high Recurrence Score values\(^1\)

Nearly 1 in 3 adjuvant treatment recommendations were changed based on the Recurrence Score results in a decision impact study.\(^{10}\)
Providing independent recurrence risk information across a biologic continuum

- Prospective analysis on archived tissue
- 1,231 postmenopausal patients treated with tamoxifen or AI
- 1,178 ER-positive, node-positive, and node-negative

Comparative risks were seen in node-negative patients and patients with 1 to 3 nodes who had low Recurrence Score values.

Oncotype DX® is the only multigene expression assay incorporated in the NCCN guidelines to help guide chemotherapy treatment decisions in patients with micrometastases.
Helping you predict the benefit of chemotherapy in node-positive patients

- Prospective analysis on archived tissue
- 367 postmenopausal patients treated with tamoxifen or tamoxifen plus CAF
- HR-positive, node-positive

Strong chemotherapy benefit seen only in the high Recurrence Score value group

- No substantial benefit in Breast Cancer Specific Survival from anthracycline based chemotherapy for node-positive patients with lower Recurrence Score values

**LOW RECURRENCE SCORE VALUE (<18)**

- 92% breast cancer-specific survival
- 87% breast cancer-specific survival
- 55 events for Tam only, 91 events for CAF-T

**INTERMEDIATE RECURRENCE SCORE VALUE (18-30)**

- 81% breast cancer-specific survival
- 70% breast cancer-specific survival
- 46 events for Tam only, 57 events for CAF-T

**HIGH RECURRENCE SCORE VALUE (≥31)**

- 73% breast cancer-specific survival
- 54% breast cancer-specific survival
- 47 events for Tam only, 71 events for CAF-T

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Half of adjuvant treatment recommendations for node-positive patients were changed based on the Recurrence Score result in a decision impact survey

- For 33.3% of patients tested with Oncotype DX, their treatment was changed from chemotherapy plus hormonal therapy to hormonal therapy alone
- For 9.4% of patients tested with Oncotype DX, their treatment was changed from hormonal therapy alone to chemotherapy plus hormonal therapy
The Oncotype DX® Breast Cancer report

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
DOB: 01/01/1950
Medical Record/Patient #: 556877771
Date of Surgery: 9/25/2008
Specimen Type/ID: Breast/SURG-0001

Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008
Client: Community Medical Center
Ordering Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Submitting Pathologist: Dr. Sally M Jones

BREAST CANCER ASSAY DESCRIPTION

Oncotype DX Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score® is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

Breast Cancer Recurrence Score = 6

The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The Clinical Validation study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 6 had an Average Rate of Distant Recurrence of 5% (95% CI: 3%-7%).

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. * N Engl J Med 2004; 351: 2817-26.

Recurrence Score vs Distant Recurrence in Node Negative, ER-Positive Breast Cancer Prognosis

Laboratory Director: Patrick Joseph, MD

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This report also contains predictive information about chemotherapy benefit, validated in the NSABP B-20 study.

For node-positive patients, the report also includes both predictive and prognostic information, as validated in the SWOG 8814 study.

The first page of the report contains the individualized Recurrence Score® result between 0 and 100.

Estimate of the likelihood of distant recurrence at 10 years.
Helping to make a more informed decision with quantitative data

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
DOB: 01/01/1950
Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008

QUANTITATIVE SINGLE GENE REPORT

The OncoType DX assay uses RT-PCR to determine the RNA expression of the genes below. These results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.

The ER, PR, and HER2 Scores are also included in the calculation of the Recurrence Score.

ER Score = 10.0 Positive

The ER Score positive/negative cut-off of 6.5 units was validated from a study of 761 samples using the 1D5 antibody (immunohistochemistry) and 607 samples using the SP1 antibody (immunohistochemistry). The standard deviation for the ER Score is less than 0.5 units.

Clinical Experience:
For ER positive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5.

Please note: The Average Rate of Distant Recurrence reported on Page 1 based on the Recurrence Score was determined in patients who received 5 years of tamoxifen treatment and takes into account the magnitude of tamoxifen benefit indicated by the ER Score.

PR Score = 8.0 Positive

The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 samples using the PR636 antibody (immunohistochemistry) and another study of 607 samples using the PR636 antibody (immunohistochemistry). The standard deviation for the PR Score is less than 0.5 units.

HER2 Score = 9.5 Negative

The HER2 positive cut-off of ≥11.5 units, equivocal range from 10.7 to 11.4 units, and negative cut-off of <10.7 units were validated from concordance studies of 755 samples using the HercepTest™ assay (FISH) and another study of 568 samples using the PathVysion® assay (FISH). The standard deviation for the HER2 score is less than 0.5 units.

References:
1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative ERBB2 expression.
2. ASCO Breast Cancer Symposium 2007 Abstracts #47 by S.B. Badve et al., and #88 by F.L. Baehner et al.
3. ASCO Breast Cancer Symposium 2008 Abstract #510 by S. Paik et al.
4. ASCO Breast Cancer Symposium 2008 Abstract #13 by F.L. Baehner et al., and #41 by F.L. Baehner et al.

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are subjective to the ordering physician's workup.

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A personalized approach to breast cancer treatment

• Validated through an extensive suite of studies, across a continuum of more than 4,000 ER-positive patients in 13 clinical studies\textsuperscript{1,2,4-7}

• Only test incorporated in both the ASCO\textsuperscript{®} and NCCN\textsuperscript{®} guidelines to help guide chemotherapy treatment decisions\textsuperscript{5,6}

• Clinical utility in node-negative and certain node-positive, ER-positive breast cancer patients\textsuperscript{1,2,4-7}

• Changed adjuvant treatment recommendations for a significant proportion of both node-negative and node-positive patients\textsuperscript{10,11}

• Genomic Health\textsuperscript{®} is committed to making Oncotype DX available to your patients\textsuperscript{3}
  
  — Extensively reimbursed, with more than 95% of privately insured lives and Medicare beneficiaries covered for the test, as well as expanding coverage in node-positive patients

  — Provides numerous services to ease the reimbursement process for you, your staff, and your patients through the Genomic Access Program (GAP)

• Genomic Health is a CLIA-certified, CAP-accredited reference laboratory

Oncotype DX is now available for patients with stage II colon cancer, expanding Genomic Health’s technology to other cancer types.