The Role of the Oncotype DX® Assay in the Treatment Selection for ER-positive, HER2-negative and Node-positive Breast Cancer
Does Every ER-positive, Node-positive Patient Need Adjuvant Chemotherapy?
The Onco\textit{type} DX\textsuperscript{®} Assay and Node-positive Breast Cancer

Case Study: Is Chemotherapy Always Necessary in Node-positive Disease

Node-positive Breast Cancer: Historical View vs Current View

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Patient CB (64 years old)
Medical history
- Infiltrating adenocarcinoma in right breast
  - Metastases found in 1 node
- Type 2 diabetes
  - Mild peripheral neuropathy
  - Mild peripheral vascular disease
  - No renal impairment
- Chronic atrial fibrillation
  - Takes digoxin and warfarin daily

Physical exam
- Irregular heart rate in the low 80s
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<td>Tumor grade</td>
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<td>Lymph nodes</td>
<td>1 of 15 nodes positive</td>
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<tr>
<td>ER/PR status</td>
<td>ER+/PR+</td>
</tr>
<tr>
<td>HER2 status</td>
<td>Negative</td>
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</tbody>
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• How can the Oncotype DX® Recurrence Score® result be used to inform the adjuvant treatment decision?
When Can Oncotype DX® Testing be Considered in Node-positive Early Stage Breast Cancer?

- Patients with micrometastases
- Patients with 1-3 positive nodes including:
  - Patients with or without comorbidities who are at risk of chemotherapy toxicity or want to avoid chemotherapy
  - Patients considering chemotherapy who want a reliable estimate of risk to help their decision
The **Onco\textit{type} DX\textsuperscript{®} Assay and Node-positive Breast Cancer**

- **Case Study: Is Chemotherapy Always Necessary in Node-positive Disease**
- **Node-positive Breast Cancer: Historical View vs Current View**
- **The Prognostic and Predictive Value of the Onco\textit{type} DX Assay in Node-positive Disease**
- **The Onco\textit{type} DX Assay Impacts the Decision to Use Chemotherapy in Node-positive Patients**
- **Case Study Follow-up: Is Chemotherapy Always Necessary in Node-positive Disease?**
Nodal Status Spans a Continuum from Node-negative to Node-positive Disease

Historical view: risk of recurrence can be discretely described based on nodal status

- **No positive nodes** → low risk
- **Positive nodes** → high risk

Emerging view: risk of recurrence is a continuous variable

- low
- moderate
- high

Because nodal status reflects a continuous biology of breast cancer

- Node negative
  - Micrometastases
  - 1-3 nodes
  - ≥ 4 nodes
Validity of the Onco
type DX® Assay Has Been Demonstrated in Multiple Studies and Guidelines Along a Continuum of Nodal Status

Information supporting the Onco
type DX assay along a continuum of nodal status

<table>
<thead>
<tr>
<th>Node negative</th>
<th>Node positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>NØ</td>
<td>Micrometastases</td>
</tr>
<tr>
<td>• NSABP B-14 and B-20 studies(^1,2)</td>
<td>• NCCN Guidelines(^3)</td>
</tr>
<tr>
<td>• NCCN(^\circledast) and ASCO(^\circledast) Guidelines(^3,4)</td>
<td>• NCCN Guidelines(^3)</td>
</tr>
<tr>
<td></td>
<td>• NCCN Guidelines(^3)</td>
</tr>
</tbody>
</table>

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HR(+), HER2(-) disease
pT1, pT2, or pT3; pN0 and pN1mi (≤ 2 mm axillary node metastasis)

Tumor > 0.5 cm
Consider Oncotype DX (Category 2A)

No test
Recurrence Score Result < 18
Recurrence Score Result 18-30
Recurrence Score Result ≥ 31

Adjuvant endocrine therapy ± adjuvant chemotherapy
Adjuvant endocrine therapy
Adjuvant endocrine therapy ± adjuvant chemotherapy
Adjuvant endocrine therapy + adjuvant chemotherapy

Adapted from NCCN Practice Guidelines in Oncology – v.3.2013.

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Case Study Resolution: Is Chemotherapy Always Necessary in Node-positive Disease?
The Oncotype DX® Assay Uses a Genomic Approach to Predict Recurrence Risk and Response to Adjuvant Therapy

16 INFORMATIVE CANCER GENES AND 5 REFERENCE GENES

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Proliferation</th>
<th>HER2</th>
<th>Invasion</th>
<th>Others</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>Ki-67</td>
<td>GRB7</td>
<td>Stromelysin 3</td>
<td>CD68</td>
<td>Beta-actin</td>
</tr>
<tr>
<td>PR</td>
<td>STK15</td>
<td>HER2</td>
<td>Cathepsin L2</td>
<td>GSTM1</td>
<td>GAPDH</td>
</tr>
<tr>
<td>Bcl2</td>
<td>Survivin</td>
<td></td>
<td></td>
<td></td>
<td>RPLPO</td>
</tr>
<tr>
<td>SCUBE2</td>
<td>Cyclin B1</td>
<td></td>
<td></td>
<td></td>
<td>GUS</td>
</tr>
<tr>
<td></td>
<td>MYBL2</td>
<td></td>
<td></td>
<td></td>
<td>TFRC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk category</th>
<th>The Recurrence Score® value (0-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 18</td>
</tr>
<tr>
<td>Intermediate</td>
<td>18-30</td>
</tr>
<tr>
<td>High</td>
<td>≥ 31</td>
</tr>
</tbody>
</table>


[Image of genomic approach diagram with gene list and risk category table]
### Clinical Validation of the Oncotype DX® Assay in Node-positive Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Total N</th>
<th>Nodal status</th>
<th>Prognostic</th>
<th>Predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>TransATAC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Prospective; tam vs Al</td>
<td>1231</td>
<td>Neg/Pos</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>ECOG 2197&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Prospective; hormonal + AC vs AT</td>
<td>465</td>
<td>Neg/Pos</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>NSABP B-28&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Prospective; tam + AC vs AC-P</td>
<td>1065</td>
<td>Pos</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>SWOG 8814&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Prospective; tam ± chemo</td>
<td>367</td>
<td>Pos</td>
<td>Yes</td>
<td>Yes Recurrence Score® result predicts chemotherapy benefit</td>
</tr>
</tbody>
</table>

TransATAC Study: Recurrence Score® Value is Prognostic in Node-positive Patients

Node+ (n = 306; both treatment arms)

Log-rank \( P < 0.001 \)

<table>
<thead>
<tr>
<th>The Recurrence Score group</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs Low</td>
<td>2.7 (1.5-5.1)</td>
</tr>
<tr>
<td>Int vs Low</td>
<td>1.8 (1.0-3.2)</td>
</tr>
</tbody>
</table>

Rate of Distant Recurrence Increases with the Number of Positive Nodes for all Recurrence Score® Values

Not all node-positive patients have the same risk of recurrence

ECOG 2197: The Recurrence Score® Result Predicts Risk of Recurrence Irrespective of Nodal Status

10-Year Recurrence Rates

There is little difference in recurrence rates for 1 and 0 positive nodes.

The Recurrence Score result was a highly significant predictor of recurrence in chemo-treated patients regardless of nodal status N- (p=0.003) or N+ (p=0.0007).

NSABP B-28: The Recurrence Score® Result is Prognostic in Chemo-treated Node-positive Patients by all Endpoints

**DFS**

- Proportion of Disease-Free Survival
- Time in years: 0, 2, 4, 6, 8, 10
- Proportion: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0
- RS Low, Intermediate, High

**DRFI**

- Proportion of Distant Recurrence-Free
- Time in years: 0, 2, 4, 6, 8, 10
- Proportion: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0
- RS Low, Intermediate, High

**OS**

- Proportion of Overall Survival
- Time in years: 0, 2, 4, 6, 8, 10
- Proportion: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0
- RS Low, Intermediate, High

**BCSS**

- Proportion of Alive w/o Disease
- Time in years: 0, 2, 4, 6, 8, 10
- Proportion: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0
- RS Low, Intermediate, High

**Table**

<table>
<thead>
<tr>
<th>RS Level</th>
<th>Events</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>102</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mamounas et al. ASCO Breast Cancer Symposium 2012.
NSABP B-28: The Recurrence Score® Result is Prognostic in Chemo-treated 1-3 or 4+ Node-positive Patients

**OS** (Overall Survival)

1 - 3
- RS Low: 93.3%, 79.2%, 70.7%
- RS Intermediate: 98.0%, 82.9%, 75.6%
- RS High: P < 0.001

4 +
- RS Low: 82.4%, 65.2%, 48.5%
- RS Intermediate: 88.1%, 70.3%, 54.0%
- RS High: P < 0.001

**BCSS** (Breast Cancer Survival)

1 - 3
- RS Low: 93.3%, 79.2%, 70.7%
- RS Intermediate: 98.0%, 82.9%, 75.6%
- RS High: P < 0.001

4 +
- RS Low: 82.4%, 65.2%, 48.5%
- RS Intermediate: 88.1%, 70.3%, 54.0%
- RS High: P < 0.001

**Events**

- RS Low: 268, 22; 118, 26
- RS Intermediate: 249, 60; 249, 60
- RS High: 205, 64; 205, 64

Mamounas et al. ASCO Breast Cancer Symposium 2012.
NSABP B-28: The Recurrence Score® Result is Prognostic in Chemo-treated Node-positive Patients Regardless of Age <50 or ≥ 50

**OS**

- **< 50**
  - RS Low: 91.9%
  - RS Intermediate: 74.7%
  - RS High: 68.9%
  - N: Events
    - RS Low: 158 / 10
    - RS Intermediate: 169 / 45
    - RS High: 184 / 61
  - P < 0.001

- **≥ 50**
  - RS Low: 88.6%
  - RS Intermediate: 74.8%
  - RS High: 54.7%
  - N: Events
    - RS Low: 227 / 33
    - RS Intermediate: 195 / 58
    - RS High: 131 / 60
  - P < 0.001

**BCSS**

- **< 50**
  - RS Low: 95.3%
  - RS Intermediate: 75.7%
  - RS High: 72.7%
  - N: Events
    - RS Low: 158 / 10
    - RS Intermediate: 169 / 45
    - RS High: 184 / 53
  - P < 0.001

- **≥ 50**
  - RS Low: 94.8%
  - RS Intermediate: 82.0%
  - RS High: 61.8%
  - N: Events
    - RS Low: 227 / 18
    - RS Intermediate: 195 / 42
    - RS High: 131 / 49
  - P < 0.001

Mamounas et al. ASCO Breast Cancer Symposium 2012.
SWOG 8814: Breast Cancer-Specific Survival of Node-positive Patients by Treatment and the Recurrence Score® Group

**Breast Cancer-Specific Survival by Treatment**

**Recurrence Score Result < 18**
- Stratified log-rank $P = 0.56$ at 10 years
- 10-yr BCSS:
  - T: 92% vs CAF $\rightarrow$ T: 87%

**Recurrence Score Result 18-30**
- Stratified log-rank $P = 0.89$ at 10 years
- 10-yr BCSS:
  - T: 70% vs CAF $\rightarrow$ T: 81%

**Recurrence Score Result ≥ 31**
- Stratified log-rank $P = 0.033$ at 10 years
- 10-yr BCSS:
  - T: 54% vs CAF $\rightarrow$ T: 73%

- No benefit to CAF over time for low Recurrence Score results
- Strong benefit to CAF over time for high Recurrence Score results

The OncoType DX® Report Provides Valuable Information Along a Continuum of ER+ Breast Cancer

• The OncoType DX report provides valuable information on:
  – Prognosis
  – Predicted chemotherapy benefit
  – Quantitative data on ER/PR/HER2

• Node-positive report contains an additional page with prognosis and predicted chemo benefit information specific to node-positive patients
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Case Study Follow-up: Is Chemotherapy Always Necessary in Node-positive Disease?
# The Oncotype DX® Assay Changes Treatment Decisions in Multiple Studies Worldwide

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Type</th>
<th>Patients (N)</th>
<th>Nodal status</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gligorov¹</td>
<td>France</td>
<td>Prospective</td>
<td>96</td>
<td>N0/N1mi</td>
<td>36</td>
</tr>
<tr>
<td>Holt²</td>
<td>England</td>
<td>Prospective</td>
<td>142</td>
<td>N0/N1mi</td>
<td>26.8</td>
</tr>
<tr>
<td>Blohmer³</td>
<td>Germany</td>
<td>Prospective</td>
<td>366</td>
<td>N0/N1</td>
<td>33.1</td>
</tr>
<tr>
<td>Bargallo⁴</td>
<td>Mexico</td>
<td>Prospective</td>
<td>96</td>
<td>N0/N1</td>
<td>32</td>
</tr>
<tr>
<td>De Boer⁵</td>
<td>Australia</td>
<td>Prospective</td>
<td>151</td>
<td>N0/N1</td>
<td>23.8</td>
</tr>
<tr>
<td>Oratz⁶</td>
<td>US</td>
<td>Retrospective</td>
<td>160</td>
<td>N1</td>
<td>51</td>
</tr>
</tbody>
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5. de Boer et al. SABCS 2011. Poster P4-09-18
Use of the Oncotype DX® Assay in the Node-positive Setting
Changes Treatment Decisions

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<td>Bargallo⁴</td>
<td>Mexico</td>
<td>34</td>
<td>N1</td>
<td>38%</td>
</tr>
<tr>
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<td>Australia</td>
<td>50</td>
<td>N1</td>
<td>26%</td>
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<td>Oratz⁶</td>
<td>US</td>
<td>138</td>
<td>N1</td>
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<tr>
<td>HER2 status</td>
<td>Negative</td>
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<tr>
<td>Oncotype DX® Recurrence Score®</td>
<td>8</td>
</tr>
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• How can the Oncotype DX Recurrence Score result be used to inform the adjuvant treatment decision?
Case Study: Prognosis and Predicted Chemotherapy Benefit

For node-positive patients, this page of the Oncotype DX® report should be used to discuss risk of recurrence and predicted chemotherapy benefit.
Case Study: The Recurrence Score® Result Provides Individualized Treatment Information

• CB considers the treatment options.

• You explain that her diabetes and heart problems could make chemotherapy a difficult course for her.

• Based on her Recurrence Score result, you and CB realize that she has a low risk of recurrence, despite nodal involvement.

• You both agree that CB should have hormonal therapy without chemotherapy.
The Onco
type DX® Breast Cancer Assay Adds Value to Treatment Decision-Making Across the Continuum of Nodal Status

• The Onco
type DX Recurrence Score® result allows for an individualized assessment of risk and likely response to adjuvant treatment, which can spare those who may not benefit from chemotherapy across the continuum of nodal status.

• NCCN Guidelines® include Onco
type DX testing in the adjuvant treatment decision pathway for patients with node-negative or micrometastatic disease.

• The risk of distant recurrence increases with increasing number of positive nodes.

• A low Recurrence Score result suggests a low risk of distant recurrence for patients with 1-3 positive nodes.