Multigene Testing in NCCN Breast Cancer Treatment Guidelines, v1.2011

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Selection of Adjuvant Systemic Therapy in NCCN Breast Cancer Guidelines

• Biological stratification
  – Identifies biologically important subtypes or categories of breast cancer

• Histological/Anatomical stratification
  – Dominant factor for determining prognosis

• Multi-gene array stratification
  – Used in predicting benefit to chemotherapy
<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic</th>
<th>Predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological features</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anatomic features</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Multi-gene assays</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Version 1.2011
Invasive Breast Cancer
Clinical Practice Guidelines in Oncology – v.1.2011

SYSTEMIC ADJUVANT TREATMENT
HORMONE RECEPTOR POSITIVE - HER2 NEGATIVE DISEASE

Histology:
• Ductal
• Lobular
• Mixed
• Metaplastic

pT1, pT2, or pT3; and pN0
or pN1mi (≤ 2 mm axillary node metastasis)

Tumor > 0.5 cm
Consider 21-gene RT-PCR assay (category 2B)

Tumor ≤ 0.5 cm or
• Microinvasive

pN0
Adjuvant endocrine therapy

pN1mi
Adjuvant endocrine therapy (category 2B)

Not done
Adjuvant endocrine therapy ± adjuvant chemotherapy (category 1)

Low recurrence score (< 18)
Intermediate recurrence score (18-30)
High recurrence score (≥ 31)

Adjuvant endocrine therapy (category 2B)
Adjuvant endocrine therapy ± adjuvant chemotherapy (category 2B)
Adjuvant endocrine therapy + adjuvant chemotherapy (category 2B)

Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)
Adjuvant endocrine therapy + adjuvant chemotherapy (category 1)
Gene Profiling Technology:

FPET \[\rightarrow\] RNA extraction \[\rightarrow\] RNA \[\rightarrow\] Multigene RNA analysis \[\rightarrow\] Recurrence Score
Oncotype DX™ Technology: Algorithm and Recurrence Score (RS)

\[ RS = +0.47 \times \text{HER2 Group Score} \\
-0.34 \times \text{ER Group Score} \\
+1.04 \times \text{Proliferation Score} \\
+0.10 \times \text{Invasion Group Score} \\
+0.05 \times \text{CD68} \\
-0.08 \times \text{GSTM1} \\
-0.07 \times \text{BAG1} \]

<table>
<thead>
<tr>
<th>Recurrence Category</th>
<th>RS (0-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>18-30</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;31</td>
</tr>
</tbody>
</table>
RS as a predictive factor for benefit from tamoxifen: NSABP B-14

Breast cancer
Node negative
ER and/or PgR positive
(N=645) →
Placebo—(N=355)

Tam —(N=290)
21 Gene RT-PCR Assay Validation Study B-14

Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Percentage of Patients</th>
<th>Rate of Distant Recurrence at 10 Yr (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>51</td>
<td>6.8 (4.0–9.6) percent</td>
</tr>
<tr>
<td>Intermediate</td>
<td>22</td>
<td>14.3 (8.3–20.3) percent</td>
</tr>
<tr>
<td>High</td>
<td>27</td>
<td>30.5 (23.6–37.4) percent</td>
</tr>
</tbody>
</table>
RS as a predictive factor for benefit from adjuvant chemotherapy: NSABP B-20

Breast cancer
Node negative
ER and/or PgR positive

Tam + MF

Tam + CMF

Tam
RS and Breast Cancer Death in NSABP B-14 and B-20

NO SYSTEMIC RX

B14 No Tam

HORMONAL RX

B14 Tam

B20 Tam

HORM + CHEMO

B20 Tam + CT

10 Yr Absolute Risk BC Death (%) (95% CI)

Low Risk (RS < 18)
Intermediate Risk (RS 18 - 30)
High Risk (RS ≥ 31)

Largest Tamoxifen Benefit Observed in Low and Intermediate Recurrence Score Groups

Largest Chemotherapy Benefit Observed in High Risk Recurrence Score Group

NSABP B-20
Outcome by Recurrence Score

Overall
Low risk < 18

Int risk 18-30
High risk > 30

SWOG 8814: ER+ LN+, TAM ± CAF chemotherapy

Pattern of Expression of Genes Used to Determine the Prognosis and Clinical Characteristics of 295 Patients with Breast Cancer

Overall Survival among All Patients (Panels A, and B, Respectively), Patients with Lymph-Node-Negative Disease (Panels C and D, Respectively), and Patients with Lymph-Node-Positive Disease (Panels E and F, Respectively)

70-Gene (MammaPrint) Predictive Data

Knauer et al. Breast Cancer Res Treatment 2010;120:655
MammoPrint Predictive Value for Adjuvant Chemotherapy

• Pooled data from 1637 subjects
  – 7 trials
  – Non-phase III trials
  – Subjects retrospectively identified
  – Only 541 subjects with T1-3 disease, 0-3 + ALNs included
  – Multiple chemotherapies, non-random assignment
  – Median follow-up included subjects 7.1 yrs
    • Outcome censored at 5-years
<table>
<thead>
<tr>
<th>Variable</th>
<th>MammaPrint</th>
<th>Oncotype DX</th>
<th>Theros</th>
<th>MapQuant Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider</td>
<td>Agendia</td>
<td>Genomic Health</td>
<td>Biotheranostics</td>
<td>Ipsogen</td>
</tr>
<tr>
<td>Type of assay</td>
<td>70-Gene assay</td>
<td>21-Gene recurrence score</td>
<td>2-Gene ratio of HOXB13 to IL17R (H/I) and molecular grade index</td>
<td>Genomic grade</td>
</tr>
<tr>
<td>Type of tissue sample</td>
<td>Fresh or frozen</td>
<td>Formalin-fixed, paraffin-embedded</td>
<td>Formalin-fixed, paraffin-embedded</td>
<td>Fresh or frozen</td>
</tr>
<tr>
<td>Technique</td>
<td>DNA microarrays</td>
<td>Q-RT-PCR</td>
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<td>DNA microarrays</td>
</tr>
<tr>
<td>Centrally certified laboratory</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indication</td>
<td>To aid in prognostic prediction in patients &lt;61 yr of age with stage I or II, node-negative disease with a tumor size of ≤5 cm</td>
<td>To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy</td>
<td>To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy</td>
<td>To reclassify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors</td>
</tr>
<tr>
<td>Level of evidence (I–V)‡</td>
<td>III</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>FDA clearance</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Availability</td>
<td>Europe and United States</td>
<td>Europe and United States</td>
<td>United States</td>
<td>Europe</td>
</tr>
</tbody>
</table>

* ER denotes estrogen receptor, FDA Food and Drug Administration, and Q-RT-PCR quantitative reverse-transcriptase–polymerase chain reaction.
† Laboratories were certified according to the criteria of the Clinical Laboratory Improvement Amendments or by the International Organization for Standardization.
‡ Levels of evidence are measured on a scale ranging from I (strongest) to V (weakest).

Summary

• This review discusses the results of DNA microarray signatures in breast cancer.
• These signatures have been useful in the classification of breast cancers, and they have an association with clinical outcomes.
• Surprisingly, there is little overlap in the types of genes among several useful microarray signatures.
• The true value of these signatures will become apparent only when prospective trials, now in progress, have been completed.

Multiparameter Gene Expression Analysis for Breast Cancer

- **Onco**

\textit{type DX}™ can be used to determine prognosis in newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer who will receive tamoxifen.

- To predict risk of recurrence in patients considering tamoxifen
- To predicted therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy
- To predict therapeutic benefit from adjuvant chemotherapy (specifically CMF)

- The precise clinical utility and appropriate application for other multigene assays were insufficiently defined to recommend their use.
St Gallen 2009

“In an important change from the previous St Gallen conference and after a long debate, the Panel supported the use of a validated multigene-profiling assay, if readily available, as an adjunct to high-quality phenotyping of breast cancer in cases in which the indication for adjuvant chemotherapy remained uncertain.”

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