Incorporating Genomics Into Early Stage Breast Cancer

Case Presentation

How should this patient be evaluated for treatment?
- 55y/o
- 1.2cm
- Grade 2
- ER/PR+
- HER2-negative

How is her risk of disease recurrence?

How likely is she to benefit from hormonal or chemotherapy?

Breast Cancer Treatment in the United States (2009)
- Approximately 110,000 women with ER+, lymph node-negative breast cancer are diagnosed annually in the United States
  - This represents ~50% of newly diagnosed patients today
  - Many women are offered chemotherapy, yet few benefit

Better identification of disease markers is needed to help make therapeutic decisions

Prognostic & Predictive Markers Utilized in Breast Cancer Management

Prognostic (recurrence risk)
- Axillary node status
- Histologic type/grade
- Tumor size
- Patient age
- Lymphatic/Vascular invasion
- ER/PR status
- HER2 neu status
- Oncotype DX

Predictive (treatment benefit)
- ER/PR status
- HER2 neu status
- Oncotype DX

These markers can be used to estimate the risk of disease recurrence

These markers can be used to predict treatment benefit

**Oncotype DX® Assay**

- Quantitatively predicts the likelihood of breast cancer recurrence in women with newly diagnosed, early stage invasive breast cancer
- Assesses the likely benefit from both hormonal therapy and chemotherapy
- Is the only multi-parameter gene expression assay to show clinical utility in breast cancer
- Is recommended by both ASCO and NCCN clinical practice guidelines


**Oncotype DX® Report Samples**

- Oncotype DX® provides valuable information on:
  - Clinical 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

**Oncotype DX® Technology Development Overview**

- Technical Feasibility (2001)
- Gene Discovery & Refinement (2002)
- Analytical Validation (2002)
- Clinical Validation (prognostic) (2004)
- Clinical Validation (predictive) (2005)
Onco
type DX® Gene Panel Was Developed from Clinical Trial Evidence

- 250 cancer-related genes were selected from a number of sources:
  - Scientific literature, microarray data, genomic databases, molecular biology
- Genes were analyzed for expression and relapse-free interval correlations across 3 independent studies of 447 breast cancer patients

<table>
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<th>Study Site</th>
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<td>B-</td>
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From these studies, 21 genes were selected

Onco
type DX® Recurrence Score Calculated from 21 Different Genes

16 CANCER RELATED GENES

- Estrogen: ER, PR
- Proliferation: Bcl2, SCUBE2
- HER2: Ki-67, STK15, Survivin, Cyclin B1, MYBL2
- Invasion: GRB7, Stromelysin 3, Cathespin L2
- Others: CD68, GSTM1, BAG1

5 REFERENCE GENES

- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

Onco
type DX® Recurrence Score Calculation and Risk Categories

Recurrence Score = + 0.47 x HER2 Group Score - 0.34 x Estrogen Group Score + 1.94 x Proliferation Group Score + 0.10 x Invasion Group Score + 0.05 x CD68 - 0.08 x GSTM1 - 0.07 x BAG1

Risk Group  Recurrence Score
Low risk  <18
Intermediate risk  18 - 30
High risk  ≥31

The Onco
type DX® Recurrence Score is a Continuous Predictor of Recurrence Risk

What is the 10-year probability of distant recurrence for a patient with a Recurrence Score of 30?

RS 30 = 20% risk of distant recurrence at 10 years

Dotted lines represent 95% CI.
**OncoType DX® Technology**

*Development Overview*

- Technical Feasibility
- Gene Discovery & Refinement
- Analytical Validation
- Clinical Validation (prognostic)
- Clinical Validation (predictive)

**Clinical Validation of OncoType DX® in Node Negative Disease**

**OncoType DX® Clinical Validation: NSABP B-14**

- **Objective**: Prospectively validate Recurrence Score as predictor of distant recurrence in N−, ER+ patients
- Multicenter study with pre-specified 21-gene assay, algorithm, endpoints, analysis plan

**OncoType DX® Clinical Validation: NSABP B-14 – Distant Recurrence**

- **Distant Recurrence Over Time**
  - 10 year rate of recurrence = 6.8%*
  - 95% CI: 4.0%, 9.6%
  - Years
  - **10 year rate of recurrence = 14.3%**
  - 95% CI: 8.3%, 20.3%
  - **10 year rate of recurrence = 30.5%**
  - 95% CI: 23.6%, 37.4%

**Proportion Without Distant Recurrence**

- **RS <18, n = 338**
- **RS 18-30, n = 149**
- **RS ≥31, n = 181**
- **P<0.001**

*10-year Distant Recurrence comparison between low-and high-risk groups: P<0.001

**Oncotype DX® Clinical Validation: Conclusions – NSABP B-14**

- Oncotype DX® RS validated as predictor of recurrence in node-negative, ER+ patients
- Oncotype DX® RS performance exceeds standard measures (patient age, tumor size, and tumor grade)
- Oncotype DX® RS (based on tumor gene expression) more accurately quantifies the risk of distant recurrence than do the NCCN guidelines (based on patient age, tumor size, and tumor grade)

**Case Presentation**

- 55y/o
- 1.2cm
- Grade 2
- ER/PR+
- HER2-negative

How should this patient be evaluated for treatment?
What is her risk of disease recurrence?
How likely is she to benefit from hormonal or chemotherapy?
**Oncotype DX® Technology**

**Development Overview**

- Technical Feasibility
- Gene Discovery & Refinement
- Analytical Validation
- Clinical Validation (prognostic)
- Clinical Validation (predictive)

**Oncotype DX® Clinical Validation: NSABP B-20**

- Objective: To determine the relationship between RS and chemotherapy benefit in N-, ER+ patients

- Randomized
  - Tam + MF
  - Tam + CMF
  - Tam

- Multicenter study with pre-specified 21-gene assay, algorithm, endpoints, analysis plan

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**High RS Correlates with Greater Benefit from Chemotherapy (NSABP B-20)**

- **Patients with high RS**
  - 39% absolute benefit from tamoxifen + chemotherapy

**Recurrence Score Can Add Prognostic Discrimination Not Always Provided by Traditional Prognostic Factors**

- **Age**
  - 44% of patients ≤40 years old had low RS (i.e., there is a large fraction of younger patients for whom chemotherapy benefit may be minimal)

- **Tumor size**
  - 46% of patients with large tumors (>4 cm) had low RS
  - Some patients with small tumors (<1 cm) had intermediate or high RS

- **Tumor grade**
  - Assessment by local pathologists revealed that, even for poorly differentiated tumors, 36% of patients had low RS
  - Approximately 20% of poorly differentiated tumors still had a low RS
Onco
type DX® NSABP B-20: Many Younger Patients Have Low Recurrence Scores


Onco
type DX® NSABP B-20: Many Small Tumors Have Intermediate to High Recurrence Scores


Onco
type DX® NSABP B-20: Significant Proportion of High-Grade Tumors Have Low Recurrence Scores (NSABP B-20)

Grading by pathologist at local clinical trial site

Grading by pathologist at central lab

Case Presentation

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How should this patient be evaluated for treatment?
What is her risk of disease recurrence?
How likely is she to benefit from hormonal or chemotherapy?
ASCO Guidelines on the Use of Tumor Markers in Breast Cancer

- Oncotype DX® can be used to determine prognosis in newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer who will receive tamoxifen

- Conclusions may not be generalizable to hormonal therapies other than tamoxifen, or to other chemotherapy regimens

NCCN Clinical Practice Guidelines

Hormone Receptor Positive, HER2 Negative Disease

- Node Negative (pT1, pT2, or pT3 and pN0 or pN1m)
- No test

- Node Positive
  - RS ≤ 18
  - Consider Oncotype DX®
  - RS ≥ 31

Adapted from NCCN Practice Guidelines in Oncology – v.2.2008

Oncotype DX® Clinical Validation in Node-positive Patients (SWOG 8814 sub-analysis)

SWOG 8814

Sub Analysis

Patients with samples (n=666)
- RT-PCR obtained (n=601)
  - Tamoxifen alone (n=148)
  - CAF + T (n=243)
  - CAF alone (n=219)

Sample for primary analysis
- 148 + 219 = 367
(60% of parent trial)

Superior Disease-Free Survival and Overall Survival over 10 Years

Recurrence Score is Prognostic for Node-Positive Patients (Tamoxifen Arm)

DFS by Risk Group (tamoxifen alone arm)

OS by Risk Group (tamoxifen alone arm)

10-year DFS: 60%, 49%, 43%
10-year OS: 77%, 68%, 51%

High Recurrence Score Predictive of Chemotherapy Benefit in Node-Positive Patients

DFS BY TREATMENT & RS GROUP

RS ≤18
RS 18-30
RS ≥31

DFS BY TREATMENT & RS GROUP

No benefit to CAF over time if low RS
Strong benefit if high RS

Albain, SABCS 2007, Abstract #10
**SWOG 8814: Breast cancer-specific survival of node-positive patients by treatment and Recurrence Score® group**

**BREAST CANCER-SPECIFIC SURVIVAL BY TREATMENT**

**10-yr BCSS**
- T: 92% vs CAF
- T: 87%

**RS < 18**
- 0 25 50 75 100
- Years since registration
- CAF
- T (n = 91, 10 events)
- Tamoxifen (n = 55, 4 events)
- Stratified log-rank P = 0.56 at 10 years

**RS 18-30**
- 0 25 50 75 100
- Years since registration
- CAF
- T (n = 46, 10 events)
- Tamoxifen (n = 57, 11 events)
- Stratified log-rank P = 0.89 at 10 years

**RS ≥ 31**
- 0 25 50 75 100
- Years since registration
- CAF
- T (n = 47, 18 events)
- Tamoxifen (n = 71, 20 events)
- Stratified log-rank P = 0.033 at 10 years

**Study Overview**

**ATAC Study Population (N=9366)**
- Tamoxifen
- Anastrozole
- Tamoxifen + Anastrozole (combination arm not examined)

**Primary Analysis:** To determine whether Oncotype DX® significantly adds to a proportional hazards model for time to distant recurrence (age, tumor size, grade, treatment) in N+, HR+, patients with no adjuvant chemotherapy

**Secondary analyses:**
- Determine whether the relationship between continuous RS and time to distant recurrence differs by nodal status or treatment arm
- Determine the relationship of predefined RS groups with time to distant recurrence by nodal status and treatment arm
- Evaluate whether RS adds to the Adjuvant! Online estimate of risk

**Risk of Distant Recurrence Using Oncotype DX® in Postmenopausal Primary Breast Cancer Patients Treated with Anastrozole or Tamoxifen: a TransATAC Study**

Dowsett M et al’ on behalf of the ATAC Trialists’ Group
Rate of Distant Recurrence Increases with the Number of Positive Nodes for all Recurrence Scores

ATAC Conclusions

- Confirms performance of Oncotype DX® Recurrence Score in postmenopausal HR+ patients treated with tamoxifen in a large contemporary population
- Demonstrates for the first time that the Oncotype DX® Recurrence Score is an independent predictor of distant recurrence in node negative and node positive HR+ patients treated with anastrozole
- The established relationship between Oncotype DX® Recurrence Score and distant recurrence for tamoxifen may be applied for anastrozole with adjustment for the lower risk of distant recurrence with the aromatase inhibitor

Reproducible Clinical Validation Essential in Changing Standard of Care
More than 4,500 Patients Studied in 12 Trials

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Prospective Multi-center Study of the Impact of Oncotype DX® on Medical Oncologist and Patient Adjuvant Breast Cancer Treatment Selection

Journal of Clinical Oncology
Jan 2010
Background

- This multicenter study was designed to prospectively examine whether RS affects physician and patient adjuvant treatment selection and satisfaction.

Methods

- 17 medical oncologists at 1 community and 3 academic practices participated. Each medical oncologist consecutively offered enrollment to eligible women with node-negative, ER-positive breast cancer.
- Each medical oncologist and consenting patient completed pre- and post- Oncotype DX® questionnaires.
- Medical oncologists stated their adjuvant treatment recommendation and confidence in it pre- and post- Oncotype DX® testing.
- Patients indicated treatment choice pre- and post- Oncotype DX® testing. In addition, patients completed measures for quality of life, anxiety, and decisional conflict pre- and post-assay.
- Oncotype DX® results were returned to the medical oncologist and shared with patients for routine clinical care.

Medical Oncologist Treatment Recommendations Changed 31.5% of the Time

<table>
<thead>
<tr>
<th>Medical Oncologist Treatment Recommendation Pre to Post Oncotype DX®</th>
<th>Number of Cases (%)</th>
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<tbody>
<tr>
<td>CHT → HT</td>
<td>20 (22.5%)</td>
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<tr>
<td>HT → CHT</td>
<td>3 (3.4%)</td>
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<tr>
<td>CHT or HT → Equivalents</td>
<td>5 (5.5%)</td>
</tr>
<tr>
<td>Treatment plan did not change</td>
<td>01 (11.5%)</td>
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<tr>
<td>Total</td>
<td>86 (100%)</td>
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</table>

- Treatment recommendation changed for 28 (31.5%) cases after results of the Oncotype DX® assay were known.
- The most common change was recommendation from CHT to HT (22.5% of cases).

Discussion

- Patients reported significantly lower conflict about the decision for adjuvant treatment post-RS and had significantly decreased situational anxiety immediately after learning the results of the RS assay, which remained stable at 12 months. Perceived risk of recurrence was an important factor in women’s choice of treatment.
- In our sample, women’s quality of life remained stable over the year of diagnosis and treatment, a time when it can be expected to decline for some women.
- Our findings are consistent with past research that demonstrated that women with breast cancer want to participate in treatment decision making. Stable quality of life found in our study also lends support to a report in which women actively involved in decision making for breast cancer treatment do not have a decline in quality of life 3 years later, as compared with women who took a less active role.
Clinical Summary
Oncotype DX® Assay

- **Onco

  type DX provides:**
  - An individualized prediction of 10-year distant recurrence risk for patients who receive 5 years of tamoxifen
  - An individualized prediction of tamoxifen benefit
  - An individualized prediction of chemotherapy benefit to inform adjuvant treatment decisions in women with early stage breast cancer

- Quantitative RT-PCR for ER/PR/HER2 is highly concordant with both IHC and FISH (using ASCO/CAP guidelines for determination of concordance)
  - 93-96% concordant with IHC for ER
  - 90% concordant with IHC for PR
  - 95% and 97% concordant with IHC and FISH for HER2, respectively

- Oncotype DX is the only proven, multi-gene expression assay recommended by ASCO and NCCN clinical practice guidelines

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More than 4,000 Patients Studied in 12 Trials

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<td>ASCO</td>
<td>Prospective Matched to Test</td>
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Case Study Revisited

- **A 55-year old post-menopausal woman presents with an infiltrating ductal carcinoma**
  - Tumor size 1.4 cm
  - ER/PR IHC positive
  - HER2 IHC negative
  - Grade 2
  - Sentinel lymph node negative
  - Excellent overall health

**How should this patient be evaluated for treatment?**
**What is her risk of disease recurrence?**
**How likely is she to benefit from hormonal or chemotherapy?**

RESULTS
Recurrence Score = **11**

CLINICAL EXPERIENCE
Patients with a Recurrence Score of **11** in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 7.5-10% (95% CI: 5.9-10.1%)
OncoType DX 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.

1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor).

Clinical Experience: For ER+ breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5. Note that the Average Rate of Distant Recurrence based on the Recurrence Score assumes 5 years of tamoxifen treatment and takes into account the magnitude of tamoxifen benefit indicated by the ER Score.

The ER Score positive/negative cut-off of 6.5 units, PR Score positive/negative cut-off of 5.5 units, and HER2 positive cut-off of ≥11.5 units were validated from multiple studies. The standard deviation for each of these scores is less than 0.5 units.

Key Elements to Assess Genomic Tests

- Does the test provide insight into the prognosis of the disease?
- Does the test provide information on the benefit of a therapy?
- Does the test provide “clinical utility”?
- Has the test been evaluated by ASCO or NCCN?