Evaluating Genomic Assays in Oncology: Reference to Oncotype DX as a Case Study

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Definitions: Analytic & Clinical Validity

• Analytic validity – ability to accurately and reliably measure genomic expression of interest
• Clinical Validity – ability of a test to predict a clinical outcome (e.g., risk of recurrence, response to treatment, etc.) for a specific patient population

Burke. NEJM 2002; 347(23): 1867

Definition: Clinical Utility

• Clinical usefulness of test considering balance of associated risks and benefits if introduced into clinical practice
  – “Requires that the test is ‘actionable,’ that the clinical context and medical indication for use of the test is clear, and that the magnitude of outcomes or treatment effects associated with different results of the test are sufficiently great as to influence treatment decisions.”


Roadmap for Developing Genomic Classifiers (Simon Criteria)

Key Steps in Development & Validation
1. Analytical Validation:
   - Internal validation to assess accuracy
   - Demonstrate reproducibility
2. Clinical Validation:
   - Sufficiently homogeneous study population receiving uniform treatment
   - Independent validation on a prospectively planned study
3. Clinical Utility:
   - Address a specific important therapeutic decision
   - Demonstrate impact on physician decisions in practice
   - Platform useful for broad clinical application


Analytical Validation: Controlling All Sources of Variability for Accuracy and Reproducibility

• Sensitive
• Specific
• Wide dynamic range
• Reproducible
• Reliable, quantifiable gene expressions from 10µ fixed paraffin embedded sections

Clark-Langone, BMC Genomics. 2007; 8:279.

RT-PCR for RNA Quantification from Fixed Paraffin-Embedded Tumor Tissue

• Sensitive
• Specific
• Wide dynamic range
• Reproducible
• Reliable, quantifiable gene expressions from 10µ fixed paraffin embedded sections

Onco<sub>type</sub> DX<sup>®</sup> is Analytically Validated
Assessment of assay performance characteristics and optimal conditions for accuracy, precision and reproducibility

**Assay Finalization in Preparation for Validation**
- Heterogeneity assessment
- PCR amplification efficiency
- Finalization of algorithm and cut points
- Standard Operating Procedures
- Final Assay Format
- Calibration and qualification of instruments and reagents

**Analytic Validation**
- Analytical sensitivity (limits of detection and quantitation)
- Assay precision and linear dynamic range
- Analytical reproducibility

Clinical Validation: Evaluating the Strength of Evidence

Onco<sub>type</sub> DX<sup>®</sup> Extensively Studied in >4000 Breast Cancer Pts

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>No. Pts</th>
<th>Nodal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providence</td>
<td>Exploratory</td>
<td>136</td>
<td>Neg</td>
</tr>
<tr>
<td>Rush&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Exploratory</td>
<td>78</td>
<td>Pos</td>
</tr>
<tr>
<td>NSABP B-20</td>
<td>Exploratory</td>
<td>233</td>
<td>Neg</td>
</tr>
<tr>
<td>NSABP B-14&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Prospective</td>
<td>668</td>
<td>Neg</td>
</tr>
<tr>
<td>MD Anderson&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Prospective</td>
<td>140</td>
<td>Neg</td>
</tr>
<tr>
<td>Kaiser Permanente&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Prospective</td>
<td>700</td>
<td>Cases/Controls</td>
</tr>
<tr>
<td>NSABP B-14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Prospective-Placebo vs Tam</td>
<td>640</td>
<td>Neg</td>
</tr>
<tr>
<td>Milan&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Exploratory</td>
<td>72</td>
<td>Neg/Pos</td>
</tr>
<tr>
<td>NSABP B-20&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Prospective-Tam vs Tam+Chemo</td>
<td>651</td>
<td>Neg</td>
</tr>
<tr>
<td>ECOG 2198&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Exploratory and Prospective</td>
<td>776</td>
<td>Neg/Pos</td>
</tr>
<tr>
<td>SWOG 8814&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Exploratory and Prospective</td>
<td>621</td>
<td>Neg</td>
</tr>
<tr>
<td>ATAC&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Prospective-Japanese Pts</td>
<td>200</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Onco<sub>type</sub> DX<sup>®</sup> – Confirmatory Study in Japan

**Oncotype DX Recurrence Score<sup>®</sup> as a Prognostic Factor in Early Stage Breast Cancer in the Japanese Population (JBCRG-TR 003)**

- **Primary objective:**
  - Demonstrate that distant recurrence risk for patients with a low RS is significantly lower than that for patients with a high RS
- **Inclusion criteria:**
  - ER+ patients who received tamoxifen between 1993-1998
  - Have FPET sample available
  - Clinically eligible with follow-up data
- **Exclusion criteria:**
  - Insufficient tumor or RNA for RT-PCR

Toi et al, Cancer 2010; 116 (13): 3112-3118

**JBCRG-TR 003: Low RS Patients Had a Significantly Lower Risk of Distant Recurrence than High RS**

- **Primary Endpoint:** DRFI for Low RS vs. High RS (Node-negative patients)
- **Proportion Event-Free**
  - Low RS<sup>†</sup> (<dollar>18</dollar>)
  - High RS<sup>†</sup> (<dollar>31</dollar>)
- **10 Year Event-Free Rate**
  - Low RS<sup>†</sup> (<dollar>96.7</dollar>)
  - High RS<sup>†</sup> (<dollar>90.0, 98.9</dollar>)

Toi et al, Cancer 2010; 116 (13): 3112-3118

**JBCRG-TR 003: Covariate-adjusted Analysis of RS 200 Node-Negative Patients**

- **Model without RS**
  - HR: 0.72 (0.29, 1.76)  P: 0.469
- **Model with RS**
  - Age (<dollar>50</dollar> vs. <dollar>75</dollar>): 1.65 (0.65, 4.19)  P: 0.285
  - Tumor size (<dollar>2</dollar> vs. <dollar>2</dollar>): 1.38 (0.54, 3.53)  P: 0.490

Toi et al, Cancer 2010; 116 (13): 3112-3118

<sup>†</sup>Tumor grade not included in model due to the limited number of samples with this information
Clinical Utility: Assessing Impact on Clinical Practice

- Value provided beyond available measures
- Comparison to existing paradigms of practice
- Assessing impact on clinical practices

Onco
type DX® and Adjuvant! Online Independently Predict Risk of Distant Recurrence – NSABP B-14

Correlation of Recurrence Score Values between Oncotype DX and Adjuvant!

<table>
<thead>
<tr>
<th>Value</th>
<th>Oncotype DX</th>
<th>Adjuvant!</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>0.004</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Recurrence Score values and Adjuvant! correlate weakly

Comparative Effectiveness: Relationship of NCCN vs. RS Directed Classification

- RT-PCR Assay Reclassification
  - Low Risk
  - Intermediate Risk
  - High Risk

NCCN Classification

- Low Risk
- Intermediate Risk
- High Risk

Role of Standard Clinical Factors and Genomic Information in Adjuvant Chemotherapy Decision-making

Objective

- Determine how MDs integrate RS and standard clinical/pathologic data in adjuvant chemotherapy decisions

Data

- Medical Records: All women tested by Oncotype DX

Study Cohort:

- Newly diagnosed ER+, Node-
  neg, HER2 neg breast cancer
- Oncotype DX ordered
  (n=269)

Results—Rates of Chemotherapy by Recurrence Score

<table>
<thead>
<tr>
<th>Oncotype DX RS</th>
<th>No. Pts</th>
<th>% chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>9/135</td>
<td>7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45/207</td>
<td>43%</td>
</tr>
<tr>
<td>High</td>
<td>11/22</td>
<td>49%</td>
</tr>
<tr>
<td>Total</td>
<td>75/264</td>
<td>27.7%</td>
</tr>
</tbody>
</table>

Gold et al., ASCO 2009, #72.
### Results—Multivariate Predictors of Chemotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥60 vs. &lt;60)</td>
<td>0.6</td>
<td>0.4-1.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Grade (II vs. I)</td>
<td>5.0</td>
<td>1.2-20.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Grade (III vs. II)</td>
<td>9.6</td>
<td>1.9-48.0</td>
<td>0.01</td>
</tr>
<tr>
<td>PR (Neg vs. Pos/low)</td>
<td>1.5</td>
<td>0.4-6.6</td>
<td>0.57</td>
</tr>
<tr>
<td>LV (Y vs. N)</td>
<td>2.4</td>
<td>1.0-6.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Multifocality (Y vs. N)</td>
<td>1.0</td>
<td>0.4-2.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Size (≥8 vs. &lt;8)</td>
<td>2.8</td>
<td>1.6-4.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>RS (≥10 vs. &lt;10)</td>
<td>15.7</td>
<td>7.1-34.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Gold et al., ASCO 2009, #572

### ASCO Guidelines on the Use of Tumor Markers in Breast Cancer

- **Oncomt 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 treatment with tamoxifen.

To identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy.

Patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than 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**

- **pT1, pT2, or pT3 and pN0 or pN1m**
  - Tumor ≤0.5 cm or
  - MicroInvasive or
  - Tumor 0.6-1.0 cm, well differentiated, no unfavorable features

- **Node Positive (micromets: >0.2mm to ≤2mm)** or **pT3 and pN0 or pN1m**
  - Tumor >1cm

- Consider Onco type DX®
  - pT1, pT2, or pT3 and pN0 or pN1m
  - No test

- RS <18 
  - Adjuvant endocrine therapy
  - RS 18-30 
  - Adjuvant endocrine therapy ± adjuvant chemotherapy
  - RS ≥31
  - Adjuvant endocrine therapy ± adjuvant chemotherapy

Adapted from NCCN Practice Guidelines in Oncology – v.2.2008

### Technology Assessment: How Genomic Assays should be Evaluated

**Onco type DX®**

- **Analytic Validity**
  - Yes
- **Clinical Validity**
  - Yes
- **Clinical Utility**
  - Yes
- **Economic Utility**
  - Yes
- **Professional Organization Recommendations**
  - ASCO
  - NCCN
  - BCBS Tech Assessments


### US Adjuvant Chemotherapy vs Oncotype DX Utilization Rates in Node Neg ESBC

- ODx Penetration Rate (Data on file Q1. 2009)
  - 55%
  - 60%
  - 65%
- % of Patients Chemo (OncoReport T1 2009)
  - 20%
  - 25%
  - 30%
  - 35%
  - 40%
  - 45%
  - 50%


OncotypeDX Technology Assessment:  How Genomic Assays should be Evaluated

OncoReport Medical Technology 2009