Applying Genomics in the Management of Early-Stage Breast Cancer

Deborah Davison, DNP, CRNP
Genomic Health Medical Affairs
WHO Definitions: Genetics & Genomics

• GENETICS: The study of heredity
• GENOMICS: The study of genes and their functions

*Genetics* examines the function of a single gene (or chromosome) while *genomics* examines groups of genes and their relationships in order to identify their combined influence on an organism.
Clinical Utility of Genetics in Oncology

- Can be used to predict risk of disease development
  - BRCA1 & 2: Increased risk of breast, ovarian, and other tumors
  - APC (Adenomatous polyposis coli): Increased risk of familial adenomatous polyposis/colon CA
- Can be used to locate “targets” for intervention
- Generally involves mutations, variations
Clinical Utility of Genomics in Oncology

• Early and accurate diagnoses
• Greater individualization of treatment decisions
• Targeted therapy based on individual disease
• Greater likelihood of clinical trial success
• More rational drug discovery
• Faster drug development
  – Patient selection
  – Trial design

Normal gene expression and interaction
‘Given the swimming pools of booze I’d guzzled over the years – not to mention all the [drugs] – there’s really no plausible medical reason why I should be alive’

Ozzy Osborne
Ozzy’s DNA:

• **Well the results are in...**
• Researchers studying his DNA have determined that he is the descendant of a Neanderthal.
• Neanderthals were a human species that lived in parts of Europe and Asia until about 30,000 years ago, and were said to be stronger and more aggressive than Homo sapiens, from which modern man evolved.
• The study also determined that Ozzy is a distant relative of outlaw Jesse James, Russian tsar Nicholas II and England’s King George I. He also shares some genes with ancient Romans.
Evidence-Based Practice

• Enables clinicians to provide highest quality of care

• Five steps:
  – Ask the clinical question
  – Collect the most relevant and best evidence
  – Critically appraise the evidence
  – Integrate the evidence with the individual patient situation
  – Evaluate the practice decision

Melnyk B & Fineout-Overholt E, 2010
### Revised Criteria for Level of Evidence in Tumor Marker Studies

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study design</th>
<th>Validation studies available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prospective</td>
<td>None required</td>
</tr>
<tr>
<td>I</td>
<td>Prospective using archived samples</td>
<td>One or more with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>Prospective using archived samples</td>
<td>None, or inconsistent results</td>
</tr>
<tr>
<td>II</td>
<td>Prospective / observational</td>
<td>Two or more with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>Prospective / observational</td>
<td>None, or one with consistent results, or inconsistent results</td>
</tr>
<tr>
<td>IV-V</td>
<td>Retrospective / observational</td>
<td>Not applicable*</td>
</tr>
</tbody>
</table>

*Level of evidence IV and V studies will never be satisfactory for determination of medical utility

The Oncotype DX® assay fulfills the criteria for Level I evidence: more than one prospective validation study using archived samples with consistent results.

For genomic assays, my questions...

• Does the assay provide insight into the biology of the tumor?
  – What is the risk that my cancer will recur?
  – What treatment is best for me?
• Does the assay provide information that we didn’t already have?
• Is there clinical significance to the result?
• Can I be confident in the result?
The Recurrence Score® Result Uses Key Genes Linked to Critical Molecular Pathways

16 Breast Cancer Related Genes

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Proliferation</th>
<th>HER2</th>
<th>Invasion</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>Ki-67</td>
<td>GRB7</td>
<td>Stromelysin 3</td>
<td>CD68</td>
</tr>
<tr>
<td>PR</td>
<td>STK15</td>
<td>HER2</td>
<td>Cathepsin L2</td>
<td>GSTM1</td>
</tr>
<tr>
<td>Bcl2</td>
<td>Survivin</td>
<td></td>
<td></td>
<td>BAG1</td>
</tr>
<tr>
<td>SCUBE2</td>
<td>Cyclin B1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MYBL2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 Reference Genes

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

The Recurrence Score® Result Assesses Individual Tumor Biology for ER+ Breast Cancer

Distant recurrence at 10 years

CONTINUOUS BIOLOGY

LOW RECURRENCE SCORE DISEASE
Indolent
Hormone therapy-sensitive
Minimal, if any, chemotherapy benefit

HIGH RECURRENCE SCORE DISEASE
Aggressive
Less sensitive to hormone therapy
Large chemotherapy benefit

First Question: Prognosis

What is the risk that my cancer will recur?
Onco
type DX® Clinical Validation: NSABP B-14

- **Objective:** Prospectively validate the Recurrence Score® result as a predictor of distant recurrence in node-negative, ER+ patients

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

Onco
type DX® Clinical Validation:
B-14 Results – Distant Recurrence

Distant Recurrence Over Time – All 668 Patients

Proportion Without Distant Recurrence at 10 years = 85%

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

Distant Recurrence for the three distinct cohorts identified

First Question: Prediction

What treatment is appropriate for me?
Objective: Prospectively determine the relationship between Recurrence Score® result and chemotherapy benefit in node-negative, ER+ patients

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

**B-20 Results**

**Tam vs Tam + Chemo – All 651 Patients**

- **Proportion without Distant Recurrence**
- **Years**
- **All Patients**
  - Tam + Chemo
  - Tam

*4.4% absolute benefit from tam + chemo at 10 years*

B-20 Results: Tam vs Tam + Chemo

28% absolute benefit from tam + chemo

Second Question

Does the assay provide information that I didn’t already have?
NSABP B-20: Many Small Tumors Have Intermediate to High Recurrence Score® Disease

NSABP B-20: Many Younger Patients Have Low Recurrence Score® Disease

NSABP B-20: Significant Proportion of High-Grade Tumors Have Low Recurrence Score® Disease

Third Question

Is there clinical significance to the result?
Does the Recurrence Score® Impact Treatment Decisions?

Is the Oncotype DX® Assay Cost-Saving and Cost-Effective?
## Meta-Analysis: The Recurrence Score® Result Changes Decisions Across 7 Independent Decision Impact Studies

<table>
<thead>
<tr>
<th>Before RS</th>
<th>CT + HT</th>
<th>HT</th>
<th>CT + HT</th>
<th>HT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>After RS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asad et al.</td>
<td>24</td>
<td>36</td>
<td>8</td>
<td>13</td>
<td>81</td>
</tr>
<tr>
<td>Henry et al.</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>Klang et al.</td>
<td>69</td>
<td>105</td>
<td>20</td>
<td>119</td>
<td>313</td>
</tr>
<tr>
<td>Liang et al.</td>
<td>125</td>
<td>85</td>
<td>3</td>
<td>47</td>
<td>260</td>
</tr>
<tr>
<td>Lo et al.</td>
<td>20</td>
<td>20</td>
<td>3</td>
<td>40</td>
<td>83</td>
</tr>
<tr>
<td>Oratz et al.</td>
<td>19</td>
<td>14</td>
<td>3</td>
<td>32</td>
<td>68</td>
</tr>
<tr>
<td>Thanasoulis et al.</td>
<td>8</td>
<td>30</td>
<td>2</td>
<td>38</td>
<td>78</td>
</tr>
</tbody>
</table>

Consistent, large impact of RS on treatment decisions in both directions:
- Half of patients initially recommended CT+HT are changed to HT only
- Some patients initially recommended HT alone have CT added upon being informed of “High RS Disease”

Overall, the RS led to a 37% change in treatment decisions
• 33% from CT + HT → HT
• 4% from HT → CT + HT

RS, Recurrence Score result
Clinical Utility of Genomics
36-year-old with 1.1-cm tumor

Menopausal Status: Premenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 1.1 cm
ER Status (IHC): Positive (80%, 3+)
PR Status (IHC): Positive (80%, 3+)
HER2/neu Status: Negative (FISH)
Histologic Grade: 6/9 with no LVI
Lymph Node Status: Negative

Submitted by:
Victor G. Vogel MD

39-year-old with 2.0-cm tumor

Menopausal Status: Premenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 2.0 cm
ER Status (IHC): Positive
PR Status (IHC): Negative
HER2/neu Status: Negative
Histologic Grade: 2
Lymph Node Status: Negative

Submitted by:
Ruth M. O’Regan MD
RESULTS:
Recurrence Score = 36

RESULTS:
Recurrence Score = 8
Fourth Question

Can I be confident in the results?
Refer to the Guidelines

OncoType DX

NCCN Guidelines™
Consider use in > 0.5 cm, HR+, HER2– disease
pT1, pT2, or pT3; pN0 and pN1mi
(≤ 2 mm axillary node metastasis)

ASCO Guidelines
Newly diagnosed patients with node-negative,
ER+ breast cancer who will receive tamoxifen

St. Gallen Consensus
OncoType DX has been shown to predict
chemotherapy benefit among patients with
HR+ disease

Adapted from NCCN Practice Guidelines in Oncology – v.2.2011.

ASCO is a trademark of the American Society of Clinical Oncology. NCCN and NCCN Guidelines are trademarks of the National Comprehensive Cancer Network. ASCO and NCCN do not endorse any therapy or product.
Background: Oncotype DX®

• The 21-gene Oncotype DX Recurrence Score® breast cancer assay is performed using an RT-PCR platform and provides a quantitative assessment of risk of recurrence and likelihood of chemotherapy benefit.

• The Oncotype DX assay has been validated in multiple clinical trials with consistent results as a prognosticator of breast cancer recurrence1-7 and as a predictor of the likelihood of benefit from chemotherapy in patients with ER-positive early stage invasive breast cancer.3,6

• The Oncotype DX assay is incorporated in major international guidelines, including NCCN®, ASCO®, St Gallen, and ESMO guidelines.8-11

References:

Background: MammaPrint®

- MammaPrint is a 70-gene assay performed on a microarray platform and characterizes breast cancer patients without systemic treatment as either high or low risk for distant recurrence.

- MammaPrint has been validated in a heterogeneous patient population that included ER-positive, ER-negative, triple negative, and HER2-positive patients.  

- MammaPrint is included as a prognosticator in the St Gallen and ESMO guidelines.

- There are no published data from randomized studies supporting that MammaPrint is predictive of chemotherapy benefit.

References:
Clinical Considerations Between MammaPrint® and the Oncotype DX® Assay

<table>
<thead>
<tr>
<th></th>
<th>MammaPrint</th>
<th>Oncotype DX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical validity</strong></td>
<td>• Validated for prognosis in a heterogeneous pooled population of both treated and untreated patients</td>
<td>• Validated in multiple homogeneous populations to predict risk of recurrence (prognosis) and treatment benefit (prediction) in node-negative and node-positive patients with ER+ breast cancer</td>
</tr>
<tr>
<td><strong>Clinical utility</strong></td>
<td>• No available data on impact of test on treatment decisions or patient satisfaction; risk may or may not be reduced in “high risk” patients by treatment; there is no data to indicate whether treatment should be hormonal treatment or chemotherapy treatment or both</td>
<td>• Numerous studies showing impact of test on treatment decisions and patient satisfaction</td>
</tr>
<tr>
<td><strong>Economic validity</strong></td>
<td>• Cost-neutral or cost-effective</td>
<td>• Overall cost-savings and cost-effective(^1,2)</td>
</tr>
</tbody>
</table>

These comparisons are not based upon findings from comparative studies.

Risk Classification of Early Stage Breast Cancer as Assessed by MammaPrint® and Oncotype DX® Genomic Assays

Poulet B,1 Jamshidian F,2 Butler S,2 Cherbavaz DB,2 Svedman C,2 Levy E1, Clough KB1

1L'Institut du Sein-Paris Breast Centre, Paris, Ile de France, France
2Genomic Health, Inc., Redwood City, CA.
Objectives

While the development and validation for Oncotype DX® and MammaPrint® are substantially different, the tests are frequently believed to provide equivalent information.

• Primary:
  • The study was designed to compare classifications by Oncotype DX and MammaPrint in the same patient specimens.
  • The study also evaluated the success of each test in generating results.

• Secondary:
  • To describe the distribution of the continuous Oncotype DX Recurrence Score® result within each MammaPrint risk category.
  • To describe the tumor characteristics of patients who were successfully tested.
  • To describe the tumor characteristics of the patients in subgroups based on the risk classification according to both assays.
In samples where both assays were successful, the following distribution was seen between the MammaPrint® risk groups and the Recurrence Score® risk groups:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Low Risk (%)</th>
<th>High Risk (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;18)</td>
<td>23 (66%)</td>
<td>10 (45%)</td>
<td>33</td>
</tr>
<tr>
<td>Int (18-30)</td>
<td>11 (31%)</td>
<td>11 (50%)</td>
<td>22</td>
</tr>
<tr>
<td>High (≥31)</td>
<td>1 (3%)</td>
<td>1 (5%)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>22</td>
<td>57</td>
</tr>
</tbody>
</table>

A high rate of discordance was observed.

Poulet et al. SABCS 2012.
A wide distribution of Recurrence Score results was observed within each MammaPrint risk category.
Why is measurement of ER important?

---

**PATIENT REPORT**

**Patient:** Doe, Jane  
**Sec:** Female  
**DOB:** 01/01/1960

**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**

The ER Score positive/negative cut-off of 0.5 units was validated from a study of 761 samples using the 120 antibody (immunohistochemistry) and 667 samples using the SPI 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 0.5 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**

The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 samples using the PR536 antibody (immunohistochemistry) and another study of 687 samples using the PR536 antibody (immunohistochemistry). The standard deviation for the PR Score is less than 0.5 units.

**HER2 Score = 9.5**

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 concordant studies of 766 samples using the HercepTest™ assay (immunohistochemistry) and another study of 688 samples using the PathVysion™ assay (ISH). The standard deviation for the HER2 score is less than 0.5 units.

**References:**

1. ER Score based on quantitative GSRI expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative IHC60 expression.
2. ASCO Breast Cancer Symposium 2007 Abstracts #7 by S.S. Bhatie et al. and #60 by F.L. Baehner et al.
3. ASCO Annual Meeting 2008 Abstract #164 by S. Fan et al.

**Laboratory Director:** Patrick Joseph, MD

**CLIA Number:** 0301018272

---
• There was a wide range of ER expression (assessed by RT-PCR) within both low and high MammaPrint® result risk groups.
• A number of the MammaPrint high risk patients had low Recurrence Score results (blue circles) and high ER expression and would be expected to have large benefits from hormonal therapy alone.

Poulet et al. SABCS 2012.
Closing Thoughts

- Importance of understanding and treating the **underlying individual tumor biology**
- Importance of standardizing emerging “next generation” technologies
- Genomic assays for clinical decision-making must be **“Fit for Purpose”**
  - Clinically validated in prospectively-designed studies of sufficient size and statistical power
  - Supported by evidence in target patient population, with demonstrated value beyond existing measures
  - Standardized and reproducible
  - Practical and clinically impactful
Thank You!