Genomics in Breast Cancer

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Stage I ER+ HER-2 neu normal Breast Cancer

- Male 50 year old PH: well controlled multiple sclerosis and depression
- BRCA-2 deleterious mutation related
- ER+ 95%
- PR+ 2%
- Ki-67 30%
- HER-2 neu normal
- Histological grade
- 1.8 cm
- 1 SLN negative

- Options: Chemotherapy follow by Tamoxifen or Tamoxifen
# Genomic Assays Used in Oncology

- Genomic-based assays can assist in cancer treatment decisions based on the individual tumor biology

<table>
<thead>
<tr>
<th>Single Gene or Protein</th>
<th>Gene Expression Signatures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presence or absence of mutations (or overexpression) within genes</td>
<td>• Profiles based on expression levels of specific component genes</td>
</tr>
<tr>
<td>• For example, HER2 in breast cancer; EGFR in NSCLC; BRAF in melanoma</td>
<td>• For example, Oncotype DX, Mammaprint, PAM-50, etc...</td>
</tr>
</tbody>
</table>
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

WHO CAN BE SPARED THERAPY?
Prognostic markers needed

WHICH THERAPY WILL WORK BEST?
Predictive markers needed

Modified from M. Piccart 2008
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

Identify patients at **HIGH** risk of recurrence and treat

OR

Identify patients at **LOW** risk of recurrence and avoid the toxicity of adjuvant treatment

**Prognostic markers needed**

Modified from M. Piccart 2008
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

Identify tumors with **HIGH** chance to response to an specific therapy

OR

Identify tumors with **LOW** chance to response to an specific therapy and discover new effective targets to treat them under clinical trials

**Predictive markers needed**

**WHICH THERAPY WILL WORK BEST?**

Modified from M. Piccart 2008
Gene/protein prognostic signatures

Add additional information to current clinical and pathological parameters for decision making for SOME patients
Key Questions When Evaluating Invasive Breast Cancer Genomic Assays

- Prognostic?
- Predictive of chemo benefit?
- What is the level of evidence?
- Accurate and reliable?
- Incorporated in treatment guidelines?
What Makes a Clinically Useful Assay?

- **Guidelines**
  - Consensus on analytic and clinical validity and clinical and economic utility

- **Clinical Utility**
  - Affects treatment decision making

- **Clinical Validity**
  - Outcome endpoints (i.e. prognostic, predictive)

- **Analytic Validity**
  - Reproducible and reliable

MammaPrint

- FDA-approved for prognostication of patients with stage I, II node-negative breast cancer with tumors < 5cm.
  - Requires fresh or frozen samples (tumor cell content >30%)
  - New platform using paraffin
- Supervised analysis 25,000 genes ➔ identified 70 genes that could predict prognosis.
- Poor prognosis - Good prognosis defined based on 5-year recurrence.
- Independent prognostic marker that identifies good prognosis patients better than clinical guidelines.
  - Validated in retrospective studies in node- and node +.
Gene-expression–based profiles used were the 70-gene good-versus-poor outcome model.

MammaPrint

• Binary result
  – Low risk: 10% chance of recurrence without any additional therapy.
  – High risk: 29% chance of recurrence without any additional therapy.
Symphony Summary

For Patients

Patient: Jane Doe
DOB: 31-Oct-1963
Patient #: 024836267
Gender: Female

Specimen:
- Collection Date: 25-Mar-2012
- Date Received: 25-Mar-2012
- Report Date: 29-Mar-2012
- Specimen Type: Surgical

Physician:
- Ordering Physician: John Doe, MD
- Account: ABC Hospital
- Address: 123 Hospital Dr.
- City, St., Zip: New York, NY 10003

1. Your Symphony Results

   MammaPrint Results
   - High Risk of Recurrence
   - Low Risk of Recurrence

   TargetPrint Results
   - ER Positive
   - PR Positive
   - HER2 Negative

   BluePrint Subtype when combined with MammaPrint
   - High Risk Luminal

2. Probability of Distant Recurrence Without Systemic Treatment

<table>
<thead>
<tr>
<th>Percentage</th>
<th>MammaPrint High Risk Within 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>100%</td>
<td>29%</td>
</tr>
</tbody>
</table>

   MammaPrint High Risk result means that a patient with early stage breast cancer has a higher risk for distant recurrence without subsequent systemic therapy. For High Risk patients, there is a 29% probability of distant recurrence within 10 years. See report for details. 1-2

3. Probability of Distant Recurrence With Systemic Treatment

<table>
<thead>
<tr>
<th>Percentage</th>
<th>MammaPrint High Risk With Chemo + Endocrine Therapy at 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>40%</td>
<td>50%</td>
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<tr>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>100%</td>
<td>12%</td>
</tr>
<tr>
<td>8.8%</td>
<td>MammaPrint High Risk at 5 Years RASTER (2004-2012)</td>
</tr>
</tbody>
</table>

   In the RASTER trial, MammaPrint High Risk patients had a 91.2% Distant Recurrence Free Interval at 5 years. 3-4 81% of the High Risk patients received chemotherapy and 91% of the ER+ patients received endocrine therapy.

Agenda Inc. | 22 Morgan | Irvine | CA | 92618 | Ph. 888.321.2732 | Fax 866.756.7548
customercare@agenda.com | www.agenda.com
Oncotype DX- Recurrence Score model

• Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) assay of 21 prospectively selected genes.
  – 16 cancer related and 5 reference genes
  – Calculate RS
• NSABP B-14 evaluated use of tamoxifen in ER+ and node- patients.
  – Archival samples used for validation (n=675
    • Low RS (<18) rate of distant recurrence: 6.8%
    • Intermediate (18-30) rate of distant recurrence: 14.3%
    • High (>31) rate of distant recurrence: 30.5%
NSABP B-14: Prognostic of Distant Recurrence in Tamoxifen-Treated Patients

*10-Year distant recurrence comparison between low- and high-risk groups: $P < 0.001$.

Oncotype DX

• NSABP-B20 randomized ER+, node- patients to receive tamoxifen vs CMF+tamoxifen
  – High risk patients experienced a significant benefit with chemotherapy and low risk patients had no benefit from chemotherapy.

• Predict benefit from adjuvant chemotherapy

• NCCN/ ASCO guidelines

Clinical Utility
• Potential for result to influence treatment decisions

Practical Considerations
• CLIA approved, commercially available
• No special processing required
• Extensive post-marketing experience; precedent for reimbursement
NSABP B-20: Validation to Predict Benefit From Chemotherapy

**PATIENT REPORT**

Patient: Doe, Jane  
Sex: Female  
DOB: 01/01/1950  
Medical Record/Patient #: 556677771  
Date of Surgery: 1/25/2008  
Specimen ID/Block ID: SURG-0001  
Requisition: R0003G  
Order Received: 2/13/2008  
Date Reported: 2/13/2008  
Client: Community Medical Center  
Treating Physician: Dr. Harry D Smith  
Submitting Pathologist: Dr. John P. Williams  
Additional Recipient: Dr. Sally J. Smith

**ASSAY DESCRIPTION**

Oncotype DX® Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score™ is calculated from the gene expression results. The Recurrence Score range is from 0-100.

**RESULTS**

Recurrence Score = 5

Test Results should be interpreted using the Clinical Experience information contained in this report which is derived from clinical studies involving patient populations with specific clinical features as noted in each section of the Clinical Experience. It is unknown whether the findings summarized in the Clinical Experience are applicable to patients with features different from those described.

**CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS**

The Clinical Validation study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 5 had an Average Rate of Distant Recurrence of 5% (95% CI: 2.7%-7.9%).

The following results are from a clinical validation study of 696 patients from the NSABP B-14 study. V. Engl J Med 2004; 351: 2811-26.

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**Recurrence Score vs Distant Recurrence in NODE NEGATIVE, ER-Positive Breast Cancer**

![Graph showing recurrence score vs distant recurrence in node negative, ER-positive breast cancer.](image)

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**NODE NEGATIVE, ER-Positive Breast Cancer Chemotherapy Benefit**

![Graph showing the benefit of chemotherapy in node negative, ER-positive breast cancer.](image)

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**Laboratory Director:** Patrick Joseph, MD  
**CLA Number:** 05D/10/6272  
This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are not intended to be the ordering provider’s warranty.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE

- Tumor \( \leq 0.5 \text{ cm} \) or
- Microinvasive

\[ \text{pN0} \quad \begin{cases} \text{Consider adjuvant endocrine therapy (category 2B)} \\ \text{Adjuvant endocrine therapy}^\gamma \text{ (category 2B)} \pm \text{adjuvant chemotherapy (category 2B)} \end{cases} \]

\[ \text{pN1mi} \quad \begin{cases} \text{Not done} \\ \text{Low recurrence score (< 18)} \\ \text{Intermediate recurrence score (18-30)} \\ \text{High recurrence score (≥31)} \end{cases} \]

\[ \text{Consider 21-gene RT-PCR assay} \quad \begin{cases} \text{Adjuvant endocrine therapy}^\gamma \\ \text{Intermediate recurrence score (18-30)} \pm \text{adjuvant chemotherapy}^\nu \gamma \times \end{cases} \]

\[ \text{Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes)} \quad \text{Adjuvant endocrine therapy + adjuvant chemotherapy (category 1)} \]

See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)
The Oncotype DX® and the 70-gene Assays Are Not the Same

Poulet Study: Recurrence Score® Distribution Within MammaPrint® Categories

Nearly half of the 70-gene assay high-risk patients were classified as low-risk by Oncotype DX assay, indicating minimal if any chemotherapy benefit.
Oncotype and Mammaprint Classify Some Patients Differently

Of the patients classified as high risk by the 70-gene assay 33.3% of patients were classified as low risk by the Oncotype DX assay.

A wide range of Recurrence Score® results was observed within the 70-gene assay risk groups.

Of the patients classified as low risk by the 70-gene assay, 5.6% were classified as high risk by the Oncotype DX assay.
PAM 50

• Gene expression platform that measures 50 classifier genes and 5 control genes.

• Categorizes tumors according to the "intrinsic" subtypes (luminal A, luminal B, HER2-enriched, basal-like, and normal-like) alone and as part of a risk of relapse predictor.

• The risk of relapse models were compared with standard models using pathologic stage, grade, and routine biomarker status.
  • PAM50 provides independent information

• NCIC MA12 trial- PAM50 predictive of benefit of tamoxifen in premenopausal females.

• Several comparisons being made with Oncotype
PAM50 intrinsic subtype prognosis for relapse-free survival (RFS).
PAM50-Oncotype

- Compare risk assignments
- RNA extracted (n=151 patients)
- Good agreement for high and low risk, but PAM50 assigns more patients to low risk category.

Kelly et al. The Oncologist 2012
<table>
<thead>
<tr>
<th><strong>Key Differences Between Genomic Assays</strong></th>
<th><strong>Oncotype DX® (Genomic Health)</strong></th>
<th><strong>MammaPrint® (Agenda)</strong></th>
<th><strong>PAM50</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the test strongly* predict recurrence risk, with low risk group sufficiently low risk?</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Was the test externally validated in a suitable population?</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>What type of tissue does the test use and what is the failure rate?</td>
<td>FFPE (failure &lt; 3%)</td>
<td>Fresh tissue (failure 27%)</td>
<td>FFPE</td>
</tr>
<tr>
<td>What types of samples does the test accept?</td>
<td>Surgical excisions, core biopsies</td>
<td>Surgical excisions, core biopsies</td>
<td>Surgical excisions, core biopsies</td>
</tr>
<tr>
<td>Does the test supply a result on a continuous scale or a risk category?</td>
<td>Continuous; individualized risk assessment</td>
<td>Group risk assessment (low, high)</td>
<td>Group risk assessment</td>
</tr>
<tr>
<td>Does the test predict chemotherapy benefit as defined by a significant test of treatment interaction?</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>What platform does the test use?</td>
<td>RT-PCR</td>
<td>Microarray</td>
<td>DNA-Microarray</td>
</tr>
<tr>
<td>What type of regulatory clearance does the test have?</td>
<td>CLIA</td>
<td>CLIA/FDA</td>
<td>FDA/European approvals pending</td>
</tr>
<tr>
<td>Is the test incorporated in published treatment guidelines of ASCO® and NCCN®?</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
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</table>
Level I evidence is coming...
EORTC 10041 BIG 3-04 trial MINDACT Trial Design
6,000 Node - & 1-3 N+ women
Trial Assigning Individualized Options for Treatment: The TAILORx

Node-Neg, ER-Pos Breast Cancer

Register Specimen banking

Oncotype DX™ Assay

RS 11-25
Randomize Hormone Rx vs Chemotherapy + Hormone Rx

RS <10
Hormone Therapy Registry

RS >25
Chemotherapy + Hormone Rx

Primary study group

http://www.clinicaltrials.gov
**RxPONDER(S1007) Trial of Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3+, ER+ HER2- BC**

Node-positive (1-3 nodes) HR-positive and HER2-negative breast cancer

(N= 8,800) Patients consent to study-sponsored RS testing, discussion of potential trials, tumor tissue submission and linkage to cancer registry data

**STEP 1 REGISTRATION** Tumor tissue submission for RS

(N= 3,800) Discuss alternative trials for high risk patients

RS > 25

(N= 5,600) Physician and patients discuss randomization knowing the RS

Accept

RS < 25

Refuse

N= 1,600 Record chosen therapy and followed for vital status through cancer registry

N= 4,000 Randomization stratified by

1. RS 0-13 vs. 14-25
2. Menopausal status
3. Axillary node dissection vs. Sentinel node biopsy

N= 2,000 Chemotherapy + appropriate endocrine therapy

N= 2,000 No Chemotherapy + appropriate endocrine therapy
Evaluation methods

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group

Analytical validity
A test’s ability to accurately and reliably measure genotype of interest

Clinical validity
A test’s ability to accurately and reliably identify or predict a relevant breast cancer survival endpoint

Clinical utility
The evidence that using a test to guide management in patients with early stage breast cancer will significantly improve health-related outcomes

Teutsch et al Genetics Med 2009
Modified from C. Sotiriou 2011
Analytical validity

According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing

Modified from C. Sotiriou 2011
Clinical validity

According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing

Modified from C. Sotiriou 2011
Clinical utility

May consider to use the genomic tests in:
• ER+/HER2-/Node-
• When it will help change a treatment decision
• Patient’s preference

Modified from C. Sotiriou 2011
Conclusions

• Prognostic and predictive signatures can help in treatment-decision for specific groups of patients.

• Some of these assays may be able to identify a group of patients with endocrine responsive disease that may not require chemotherapy thus avoiding the associated toxicities.

• Prospective validation trials are completed for node-negative disease and on-going for node-positive disease. We are awaiting the results.

• Use this platforms for the benefit of the patient, when it will help make a treatment decision.
Stage I ER+ HER-2 neu normal Breast Cancer

- Male 50 year old PH: well controlled multiple sclerosis and depression
- BRCA-2 deleterious mutation related
- ER+ 95%
- PR+ 2%
- Ki-67 30%
- HER-2 neu normal
- Histological grade
- 1.8 cm
- 1 SLN negative
- Oncotype-DX breast cancer recurrence score: 32
- Plan: Chemotherapy follow by Tamoxifen