Genomics in Breast Cancer:
Learning Objectives

- Provide background on breast cancer, its staging and current adjuvant treatments
- Distinguish between role of Genomics and Genetics in clinical practice
- Understand the clinical utility of new genomic tests, such as the Onco
type DX® Breast Cancer Assay
- Explain the Onco
type DX Recurrence Score ® result and its association with risk of recurrence and prediction of chemotherapy benefit
- Identify the patients for whom the Onco
type DX assay has been clinically validated
- Describe the mechanism to obtain assistance regarding ordering and reimbursement of the Onco
type DX assay
Breast Cancer Figures

- **1 in 8** women in the United States will develop breast cancer, most occurring by age 70
- Incidence: **180,000** people in the United States will be diagnosed in 2007 with invasive breast cancer including 2,000 men
- **Over 40,000** women and men will die from the disease in 2007
- **Over 77%** of breast cancer cases are diagnosed in people **over the age of 50**

Source: American Cancer Society and National Cancer Institute
Breast Cancer Progress Report

- Breast Cancer mortality rates have decreased by 2.3% annually since 1990.

- The decline in mortality is primarily due to *early detection* and *new treatment* methods.

Source: *Breast Cancer Facts and Figures 2005-2006*
National Center for Health Statistics data as analyzed by NCI
Breast Cancer is diagnosed according to stages (stages 0 through IV) under the **TNM** classification.

Factors used in staging of Breast Cancer:

- **Tumor Size**  
  Size of primary tumor

- **Nodal status**  
  Indicates presence or absence of cancer cells in lymph nodes

- **Metastasis**  
  Indicates if cancer cells have spread from the affected breast to other areas of the body (i.e. skin, liver, lungs, bone)

Source: National Cancer Institute
Early Stage Breast Cancer

Stage 0
Ductal carcinoma in situ (DCIS) is very early breast cancer that has not spread beyond the duct.

Stage I
Tumor is < 2 cm and has not spread outside the breast.

Stage IIA
No tumor is found in the breast, but cancer is found in the axillary lymph nodes, or tumor is ≤ 2 cm and has spread to the axillary lymph nodes, or tumor is 2-5 cm but has not spread to the axillary lymph nodes.

Stage IIB
Tumor is 2-5 cm and has spread to the axillary lymph nodes or is > 5 cm but still confined to the breast.

Source: National Cancer Institute
Advanced Breast Cancer

Stage IIIA
The tumor in the breast is smaller than 5 centimeters and the cancer has spread to underarm lymph nodes that are attached to each other or to other structures, OR the tumor is more than 5 centimeters across and the cancer has spread to the underarm lymph nodes.

Stage IIIB
Tumor has spread to tissue near the breast (i.e. the skin or chest wall) and may have spread to lymph nodes within the breast area or under the arm.

Stage IIIC
Tumor has spread to the lymph nodes beneath the collarbone and near the neck, and may have spread to the lymph nodes within the breast area or under the arm and to the tissues near the breast.

Stage IV
Tumor has spread to other organs of the body (i.e. lungs, liver, or brain).

Source: National Cancer Institute
Genetics and Genomics
Genetics Help us Identify Patients at High Risk of Developing Breast Cancer

Genetics

- Genetics is the study of heredity
  - While genetics influence genomics, genetics is responsible for only 5-10% of breast cancer
  - Genetics focuses primarily on the likelihood of developing cancer
  - Genetic tests find mutations, not disease

Source: Understanding Cancer Series: Gene Testing, National Cancer Institute
Genomics Help us Look at the Patients Individual Tumor Biology

Genomics

- Genomics is the study of how genes interact and are expressed as a whole

• Genomics and gene expression profiling tools focus on the cancer itself and can help determine
  – How aggressive is the cancer (prognosis)
  – What is the likely benefit from treatment (prediction)
Examples of Genetic and Genomic Tests

Genetic Test

• BRCA1 and BRCA2
  • The genetic make up of patients is tested for BRCA1 and BRCA2 mutations. Patients with those mutations have higher chances of developing breast cancer.

Genomic Test

• Onco\text{type} DX® Breast Cancer Assay
  • The expression level of 21 genes is measured in tumor tissue from patients that have already been diagnosed with breast cancer. This assay evaluates if a patient is going to recur (prognostic) and predicts benefit from chemotherapy and hormonal therapy (predictive).
Adjuvant Treatment for Early Stage Breast Cancer Today
Hormonal Therapy

- Based on the Landmark NSABP B-14 Study using Tamoxifen

If 100 women with ER+, N- disease are treated with hormonal therapy how many will recur within 10 years?

Chemotherapy and Hormonal Therapy

Based on the Landmark NSABP B-20 Study using Tamoxifen + Chemotherapy

If all 100 women with ER+, N- disease are treated with chemotherapy and hormonal therapy, how many will benefit from the addition of chemotherapy?

Fisher et al. *J Natl Cancer Inst* 1997;89:1673-82
Your Patient Needs Better Tests to Assess Her Risk of Recurrence and Optimize Her Treatment

• Will her cancer spread?
• Does she need chemotherapy after surgery for her cancer type?
• What are the benefits and side effects of chemotherapy for her?
• Are there any new drugs for her cancer?
• Will she survive?
How Do We Assess Risk in Breast Cancer Patients?

Classic Pathological Criteria

- Lymph Node Status
- Age
- Tumor Grade
- Tumor Size
- ER/PR
- HER2
- Adjuvant!

New tools in the Genomic Era...

- Onco\textit{type} DX®

Computer-based model
With Genomic Tools We Can Now Analyze Cancer at the Molecular Level

1. Patient’s tumor
2. Oncotype DX® Assay
3. Analyze expression of tumor’s genes
4. Oncotype DX® Report
5. Shared Decision Making
Onco
type DX®: A Genomic Assay
Onco\textit{type} DX\textsuperscript{®} 21-Gene Recurrence Score\textsuperscript{®} (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

**PROLIFERATION**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**ESTROGEN**
- ER
- PR
- Bcl2
- SCUBE2

**INVATION**
- Stromelysin 3
- Cathepsin L2

**HER2**
- GRB7
- HER2

**REFERENCE**
- Beta-actin
- GAPDH
- RPLP0
- GUS
- TFRC

Onco\textit{type} DX\textsuperscript{®} 21-Gene Recurrence Score\textsuperscript{®} (RS) Assay

\textbf{Calculation of the Recurrence Score Result}

\textit{Coefficient} x \textit{Expression Level}

RS = + 0.47 x HER2 Group Score
     - 0.34 x ER Group Score
     + 1.04 x Proliferation Group Score
     + 0.10 x Invasion Group Score
     + 0.05 x CD68
     - 0.08 x GSTM1
     - 0.07 x BAG1

<table>
<thead>
<tr>
<th>Category</th>
<th>RS (0-100)</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>RS &lt;18</td>
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<tr>
<td>Int risk</td>
<td>RS (\geq) 18 and &lt;31</td>
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<tr>
<td>High risk</td>
<td>RS (\geq) 31</td>
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The Onco\textit{type} DX® Assay is for N-, ER+ Breast Cancer Patients
The Onco
type DX® Assay Has Been Extensively Studied in 3,300+ Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>No. Pts</th>
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<tr>
<td>Rush</td>
<td>Exploratory</td>
<td>78</td>
<td>Clin Cancer Res 2005; 11: 8623-31</td>
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<td>SABCS 2003; Abstract 16</td>
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<td>NSABP B-14</td>
<td>Prospective</td>
<td>668</td>
<td>NEJM 2004; 351:2817-26</td>
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<td>MD Anderson</td>
<td>Prospective</td>
<td>149</td>
<td>Clin Cancer Res 2005; 11: 3315-19</td>
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<td>Kaiser Permanente</td>
<td>Prospective</td>
<td>790</td>
<td>Breast Cancer Res 2006; 8: R25</td>
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<td>Case-Control</td>
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<td>Prospective</td>
<td>645</td>
<td>JCO 2005; 23 (16S): Abstract 510</td>
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<td></td>
<td>Placebo vs Tam</td>
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<td>Instituto Nazionale Tumori, Milan</td>
<td>Exploratory</td>
<td>89</td>
<td>JCO 2005; 23: 7265-77</td>
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<td>Pathologic CR</td>
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<tr>
<td>NSABP B-20</td>
<td>Prospective</td>
<td>651</td>
<td>JCO 2006; 24: 3726-34</td>
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<td></td>
<td>Tam vs Tam+Chemo</td>
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<td>ECOG 2197</td>
<td>Exploratory and Prospective</td>
<td>776</td>
<td>JCO 2007; 25 (18S): Abstract 526</td>
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39,000+ Commercial Assays as of September 30, 2007
NASBP B-14 Validation Trial for the Onco
type DX® Assay

• **Purpose:** To evaluate the Onco
type DX 21-gene panel and its Recurrence Score® (RS) result as predictors of the likelihood of distant recurrence

• **Population:** Tumor tissue from 668 N-, ER+, tamoxifen-treated patients enrolled in the NASBP B-14 study

• **Design:**
  – Multi-center study using a pre-defined panel of 21 genes with prospectively-defined endpoints, analysis plan and algorithm for calculation of the RS result
  – Blinded, triplicate analysis by RT-PCR of 10 μm fixed tumor block sections

The Recurrence Score® Result Stratifies Patients by their 10-Year Distant Recurrence-Free Survival

The Recurrence Score® Result Quantifies the Risk of Distant Recurrence (Prognosis)

The Recurrence Score® is a Continuous Predictor of the Risk of Distant Recurrence

Summary of the NASBP B-14 Trial

- Clinical validation study for the Onco\textit{type} DX\textsuperscript{®} assay showing that the Recurrence Score\textsuperscript{®} result quantifies the likelihood of distant recurrence in N- ER+, tamoxifen-treated breast cancer patients (prognosis)

- The Recurrence Score result identified a large subset of patients with low risk of recurrence

- The Recurrence Score result was a consistent predictor of distant recurrence independent of patient age, tumor size and tumor grade

NASBP B-20 Chemotherapy Benefit Trial for the Onco
type DX® Assay

- **Purpose:** To determine whether the Onco
type DX assay and its Recurrence Score® result could predict magnitude of chemotherapy benefit

- **Population:** Tumor tissue from 651 N-, ER+ patients from the NASBP B-20 study treated with either tamoxifen alone (n=227) or with tamoxifen plus CMF or MF chemotherapy (n=424)

- **Design:**
  - *Multi-center, randomized trial* using a pre-defined panel of 21 genes with prospectively-defined endpoints, analysis plan and algorithm for calculation of the RS result
  - Blinded, triplicate analysis by RT-PCR of 10 μm fixed tumor block sections

Paik et al. *J Clin Oncol.* 2006;24:3726-3734
The Onco\textsuperscript{type} DX\textsuperscript{®} Assay: Patients Do Not Benefit Equally from Chemotherapy

Paik et al. J Clin Oncol. 2006;24:3726-3734
Patients with High RS Derive Significant Benefit from Chemotherapy (Prediction)

Absolute Increase in Distant Recurrence Free Survival at 10 Yrs (mean ± SE)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low RS&lt;18</td>
<td>n = 353</td>
</tr>
<tr>
<td>Int RS18-30</td>
<td>n = 134</td>
</tr>
<tr>
<td>High RS ≥31</td>
<td>n = 164</td>
</tr>
</tbody>
</table>

Paik et al. *J Clin Oncol.* 2006;24:3726-3734
Summary of the NASBP B-20 Trial

• The Recurrence Score® (RS) result not only quantifies the risk of recurrence in women with N-, ER+ breast cancer, but also predicts the magnitude of chemotherapy benefit (predictive).

• Patients with a low RS have minimal, if any benefit, from chemotherapy while patients with a high RS have a significant benefit from chemotherapy.

Paik et al. J Clin Oncol. 2006;24:3726-3734
The Oncotype DX® Assay in Clinical Practice
The Onco\textit{type} DX\textsuperscript{®} Assay Recommended in ASCO Clinical Practice Guidelines

- The Onco\textit{type} DX assay is recommended on the ASCO Clinical Practice Guidelines for use in newly diagnosed patients with N-, ER+ breast cancer to:
  - \textit{Predict risk of recurrence}
  - Identify patients who are predicted to obtain the \textit{most therapeutic benefit from tamoxifen} and \textit{may not require chemotherapy}
  - Identify patients with high RS scores who appear to \textit{derive greater benefit from chemotherapy} (specifically CMF) than from tamoxifen

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

- The Onco\textit{type} DX assay is the only multi-parameter gene expression assay found to show clinical utility in breast cancer

Harris et al. \textit{J Clin Oncol.} 2007; published online ahead of print
The Onco
type DX® Assay Recommended for Consideration in NCCN Clinical Practice Guidelines
The Oncotype DX® Assay in Clinical Practice

• The Oncotype DX assay has been offered by Genomic Health, Inc., since January 2004
  • Genomic Health has a CLIA-certified and CAP-accredited reference lab
  • Send tumor block or 6 fixed, paraffin-embedded sections (10 μm each) to Genomic Health using the Oncotype® Specimen Kit
  • Turnaround time: 10-14 days
  • Customer Service: 1-866-ONCOTYPE
    1-866-662-6897
Reimbursement Support for Your Practice for the Oncotype DX® Assay

- Genomic Health helps your patient and practice by taking assignment of benefits and managing the billing and claims process.

- The Genomic Access Program (GAP) performs comprehensive benefits investigations and informs patients of their coverage and potential financial responsibility within 2 business days.
The Oncotype DX® Assay Is Widely Covered in the United States

– Oncotype DX is covered by several insurance plans representing 165+ million lives in the US¹
  • Plans include: Medicare², Aetna, United Healthcare, Kaiser Permanente, Cigna, WellPoint, Highmark BC, Harvard Pilgrim, BC/BS of Michigan, BC/BS FEP, CareFirst BC/BS, BC/BS of Minnesota, BC/BS of Alabama, BC/BS of New Jersey and others

– GAP also provides a generous financial assistance to qualifying patients

¹ As of September 2007
² Through a local coverage decision developed by the National Heritage Insurance Company which applies to all testing billed by Genomic Health’s California facility
Procedure for Ordering the Onco\textit{type} DX\textsuperscript{®} Assay

1. Patient Education and Reimbursement Information
   - Ensure that each patient that is considering the Onco\textit{type} DX assay has a copy “A Patient’s Guide to Onco\textit{type} DX”

2. Requisition Form
   - Fill out form completely, have an authorized Healthcare Provider sign form
   - If the authorized Healthcare Provider would like a Benefits Investigation done, complete the Benefits Investigation section by selecting service options and adding a Statement of Medical Necessity
   - Select Specimen Retrieval service option
   - FAX completed form to Genomic Health Customer Service (650-556-1073)

3. Acknowledgement of Referral Form
   - You will receive a FAX from GAP confirming the receipt of your Benefits Investigation

4. Benefits Summary
   - If you have selected a Benefits Investigation, within 2 business days you will receive a FAX entitled “Benefits Summary” and a GAP representative will call your patient to explain their laboratory benefits and any financial responsibility resulting from performing the assay
   - If you selected, “YES Investigate – Proceed pending patient confirmation”, Genomic Health Customer Service will be contacting you on how the test should proceed
Onco
type DX® Patient Report

• The patient report includes:
  – Recurrence Score® (RS)
  – Average 10-year distant recurrence rate for that RS
  – Graph of 10-year recurrence risk as a function of RS in tamoxifen-treated patients

• The report is sent to:
  – Treating physician
  – Submitting pathologist
How Can Nurses be Involved with the Onco
type DX® Assay?

• Identify appropriate patients
  – Stage I/II, lymph node negative, ER positive, who need to make decisions regarding adjuvant chemotherapy
    • Not for DCIS patients
    • Not for lymph node positive patients

• Educate patients on the Onco
type DX assay

• Help inform and assist with enrollment of eligible patients on the TAILORx trial
Onco\textsuperscript{type} DX\textsuperscript{®} Resources for Nurses

- Patient Education Brochure
  - English and Spanish

- \textit{My Breast Cancer Coach}
  - Interactive online program developed with the Breast Cancer Network of Strength. This program enables newly diagnosed women to personalize their online search for breast cancer information by answering a series of eight questions about their diagnosis, based on the information contained in their pathology reports.

- \texttt{www.MyTreatmentDecision.com}
  - Patient website providing an overview of invasive breast cancer and the tools used to determine recurrence risk and help make treatment decisions.
Genomic Health’s Commitment to Nursing

• Offer educational programs and activities on Genomics at both local and national levels
• Provide accurate medical and clinical information in a timely manner, including one on one assistance from our medical team
• Provide valuable assay results that are reliable, sensitive and reproducible
• Deliver actionable insights that can improve decision making for breast cancer patients
• Address reimbursement concerns
• Provide patient education and support
• Partner with advocacy groups to support breast cancer efforts
Patient 3: 39-year-old with 1.5 cm tumor

- Age: 39
- Tumor Type: Infiltrating Ductal Carcinoma (IDC)
- Tumor Size: 1.5 cm
- ER: 90% (Strong +)
- PR: 90% (Strong +)
- HER2/neu: Negative
- Grade: 2

The patient is a professional, recently engaged and concerned about fertility.

**General Health:** Perfect
**Lymph Nodes:** 0
Patient Cases

- Patient was identified as low risk by Onco
type DX® with a Recurrence Score® result of 4

- Patient received hormonal therapy since she was in a group in which chemotherapy does not provide benefit
Patient 4: 58-year-old with 1.3 cm tumor

- Age: 58
- Tumor Type: Infiltrating Ductal Carcinoma (IDC)
- Tumor Size: 1.3 cm
- ER: 100% 3+ IHC
- PR: Negative
- HER2/neu: Negative (FISH)
- Grade: 3 (Nottingham 8/9)

The patient is a 58-year-old postmenopausal woman, eager not to have chemotherapy for a newly diagnosed T1c N0 ER-positive IDC.

**DCIS:** Nuclear grade 2, 5%

**Margins:** Negative

**Lymph Nodes:** 0/3 (negative)
Patient Cases

- Patient was identified as high risk by Oncotype DX® with a Recurrence Score® result of 34
- The Recurrence Score helped convince the patient on the likely benefits of taking chemotherapy given the biology of her disease
- Patient received chemotherapy and hormonal therapy
Patient Cases

Patient 7: 68-year-old with 2.3 cm tumor

- Age: 68
- Tumor Type: Infiltrating Ductal Carcinoma (IDC)
- Tumor Size: 2.3 cm
- ER: 30%
- PR: 50%
- HER2/neu: Negative
- Grade: 2

The patient is a 68-year-old, healthy, postmenopausal woman.

General Health: Perfect
Lymph Nodes: 0
Patient was identified as intermediate risk by Oncotype DX® with a Recurrence Score® result of 25

Is there benefit from chemotherapy for this patient? The TAILORx trial evaluates the utility of chemotherapy in the mid-range risk group.
Integration of New Tests in Clinical Decision-Making: TAILORx
**Trial Assigning Individualized Options for Treatment (Rx) (TAILORRx)**

- **Premise**
  - Integration of a new cancer test, the Onco\textit{type} DX\textsuperscript{®} assay, into the clinical decision-making process

- **Implications**
  - Reduce chemotherapy \textit{over-treatment} in those likely to be optimally treated with hormonal therapy alone
  - Reduce \textit{inadequate treatment} by identifying individuals who likely will derive great benefit from chemotherapy
  - Evaluate benefit of chemotherapy where uncertainty still exists about its utility

Trial sponsored by NCI. Participating cooperative groups include ECOG, SWOG, NCCTG, CALGB, NCIC, ACOSOG, and NSABP
Node N-, ER+ Breast Cancer

Register Specimen banking

Oncotype DX® Assay

RS ≤10 Hormone Therapy Registry

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

RS >25 Chemotherapy + Hormone Rx

Primary study group
Primary Objectives TAILORx

• To determine whether adjuvant hormonal therapy (i.e. experimental arm) is not inferior to adjuvant chemohormonal (standard arm) for patients in the “primary study group” (Oncotype DX® RS 11-25)

• To create a tissue and specimen bank for patients enrolled in this trial to learn more about breast cancer
TAILORx: Key Points

- **Participating groups**
  - Major North American cooperative groups, including ECOG, SWOG, NCCTG, CALGB, NCIC, ACOSOG, and NSABP

- **Adjuvant therapy**
  - Choice of hormonal and/or chemotherapy regimen is at discretion of treating physician
  - Permissible options are outlined in protocol, and are generally consistent with NCCN guidelines

- **Other trials**
  - May enroll on other CTSU or other cooperative group studies if treatment assignment on other trial is consistent with PACCT-assigned treatment

- **Cost**
  - Genomic Health will assist in securing reimbursement for patients who have health insurance
  - By agreement with NCI to avoid bias in enrollment in the trial, patients who are uninsured or who have co-payments or deductibles will not be responsible for the cost of the Oncotype DX® assay
Protocol and General Information
• Clinical Trials Support Unit
  – 1-888-823-5923
  – CTSUcontact@westat.com
  – www.ctsu.org

Eligibility Questions
• Eastern Cooperative Oncology Group
  – ecog.tailorx@jimmy.harvard.edu
  – www.ecog.org

TAILORx Patient Education Materials
• Eastern Cooperative Oncology Group
  – http://www.ecog.org/general/tailorx.html

Onco type DX® Information
• Genomic Health Customer Service
  – 1-866-ONCOTYPE (1-866-662-6897)
  – www.oncotypedx.com
Conclusions
Onco
type DX® is a Standardized and Quantitative Assay

Recurrence Score® in N-, ER+ patients

Lower RS’s
• Lower likelihood of recurrence
• Minimal, if any, chemotherapy benefit

Higher RS’s
• Greater likelihood of recurrence
• Clear chemotherapy benefit

3) Paik et al. JCO 2006, 4) Gianni et al. JCO 2005
The Onco\textit{type} DX Recurrence Score\textsuperscript{®} assay predicts \textit{likelihood of recurrence} (prognostic) and \textit{magnitude of adjuvant treatment benefit} for chemotherapy (predictive)

The Onco\textit{type} DX Recurrence Score assay shows \textit{consistent results} across multiple independent studies