Putting genomics into clinical practice in early breast cancer

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Breast Medical Oncology
Systems Biology

Vienna, Austria, 10, 2012
Outline

• The basics

• Available tests and supporting evidence

• Future applications of new technologies
The basics
Evolution of the concept of breast cancer

**Definition of Disease**

- Breast cancer = single disease with variable microscopic appearance
- Breast cancer = single disease, variable microscopic appearance and variable expression of estrogen/progesterone receptors
- Breast cancer = at least 4 molecularly different diseases of the breast
- Breast cancers = a collection of diseases with various combinations of deregulated molecular pathways

**Treatment strategy**

- Surgery (+/- chemotherapy)
  - Anti-estrogen therapy for estrogen receptor-positive cancers
  - Various combinations of treatments based on molecular type
  - Molecular pathway-directed therapies
Evaluation methods

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

Steven M. Teutsch, MD, MPH¹, Linda A. Bradley, PhD², Glenn E. Palomaki, BS³, James E. Haddow, MD³, Margaret Piper, PhD⁴, Ned Calonge, MD, MPH⁵, W. David Dotson, PhD²,⁶, Michael P. Douglas, MS²,⁶, and Alfred O. Berg, MD, MPH⁵, Chair, on behalf 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
Gene/protein prognostic signatures

Add additional information to current clinico-pathological parameters for decision making for SOME patients.
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

WHO CAN BE SPARED THERAPY?

WHICH THERAPY WILL WORK BEST?

Prognostic markers needed

Predictive markers needed

Modified from M. Piccart 2008
WHO CAN BE SPARED THERAPY?

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
Examples of prognosis

Oncotype DX RS

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<tr>
<th>Risk Level</th>
<th>No. at Risk</th>
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Mammostrat

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PAM50 ROR

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Paik et al N Engl J Med 2004
Parker et al J Clin Oncol 2009
Bartlett et al Breast Cancer Res 2010
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

Which therapy will work best?

Predictive markers needed

Identify tumors with **HIGH** chance to respond to a specific therapy

OR

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

Identify patients with a **HIGH** chance to respond to a specific therapy

OR

Identify patients with a **LOW** chance to respond to a specific therapy and find an alternative

PHARMACOGENOMICS

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

Identify patients with a **HIGH** chance to respond to an specific therapy

**OR**

Identify patients with a **LOW** chance to respond to an specific therapy and find an alternative

**PHARMACOGENOMICS**

**WHICH THERAPY WILL WORK BEST?**

Predictive markers needed

Modified from M. Piccart 2008
Examples of prediction of chemotherapy benefit

Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

SoominHyung Paik, Yong Tang, Steven Shih, Chungreae Kim, Joffe Baker, Wanseep Kim, Maureen Cronin, Frederick L. Bichner, Drew Watson, John Bryan, Joseph P. Carrianto, Charles E. Geyer Jr., D. Lawrence Wicksman, and Norman Wolmark


Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial


Albain et al. Lancet Oncol 2010
Available tests and supporting evidence
Gene-expression-based profiles used were the 70-gene good vs. poor outcome model (MammaPrint)

- FDA-approved for prognostication in node-negative <5cm tumors
- Fresh or frozen samples
- Poor/Good prognosis: 5-year recurrence
- Independent prognostic marker
- Provides prognostic information in node+ and HER2+
- Correlates with chemotherapy sensitivity (interaction?)

MINDACT

Breast cancer that is either node negative or involves ≤53 lymph nodes

MammaPrint prognostic signature
Adjuvant! Online

Good prognosis by MammaPrint and Adjuvant!

Discordant

Good prognosis by MammaPrint
Poor prognosis by Adjuvant!

Poor prognosis by MammaPrint
Good prognosis by Adjuvant!

RANDOMIZE

No chemotherapy
Chemotherapy based on Adjuvant prognosis
Chemotherapy based on MammaPrint prognosis
Chemotherapy
PAM 50 Risk of Relapse predictor

- “Intrinsic” subtypes alone and as part of a ROR predictor in:
  - Patients receiving no adjuvant systemic therapy
  - Patients undergoing (T/FAC) neoadjuvant chemotherapy

- ROR models being tested in ER+, node+ disease and as predictor of chemotherapy response

Parker et al. J Clin Oncol 2009
**Mammostrat risk predictor**

- Risk predictor in ER+, node- and node+, tamoxifen-treated

- **IHC:** P53, HTF9C, CEACAM5, IVFRGI, SLC7A5

- Significant association between patients outcome variables (RFI, DRFI, and BCSD)

- Chemo benefit in both high and low risk

- Test for interaction between chemo benefit and risk group ($P = 0.13$)

- **Mammostrat is not predictive of chemotherapy benefit**

21-gene Recurrence Score
Oncotype Dx

Level of Evidence
- Validated in tamoxifen treated patients with negative-nodes
- Experience in other populations
- NCCN/ ASCO guidelines

Clinical Utility
- Common disease type that is commonly overtreated
- Potential for result to influence treatment decisions

Practical Considerations
- CLIA approved, commercially available
- No special processing required
- Extensive post-marketing experience; precedent for reimbursement
Level I evidence for node+ disease is on the works!

Tissues will be used to validate other genomic signatures and compare them with the RS

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

(N= 600) RS already Available Physician and patients discuss

Refuse

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

PI: AM Gonzalez-Angulo
Effect of tumor size on the predictive value of Oncotype DX

Association with Time to Distant Recurrence:

RS: HR: 2.22 (P=0.001)
RSPC: HR: 2.43 (P=0.001)

Interaction with chemotherapy treatment:

RS: HR: 0.66 (P=0.037)
RSPC: HR: 0.65 (P=0.1)

Gong et al, J Clin Oncol 2011
Tumor burden may still matter

- Prognostic signatures may not help!

Dowsett et al. J Clin Oncol 2010
HR-positive and HER2-negative breast cancer

Surgery: Number of positive nodes?
  - Node-negative and tumor ≥2cm
  - 1-3 positive
  - ≥4 positive

Recurrence Score >25

Adjuvant Chemotherapy

Radiation therapy if indicated

Neoadjuvant chemotherapy: Residual disease?
  >4 positive lymph nodes

Randomization

Post-chemotherapy Everolimus or Placebo

Everolimus for 1 year + appropriate endocrine therapy for 5 years

Placebo for 1 year + appropriate endocrine therapy for 5 years

Stratification factors:
- Node negative
- 1-3 positive nodes Adjuvant
- >4 positive nodes Neoadjuvant

PI: M Chavez-MacGregor
UNIRAD trial

**Pre and postmenopausal women with HR⁺ HER2⁻ breast cancer (≥ 4⁺ nodes Or N+ post-neoadjuvant)**

Relapse-free after 2-3 yrs of adjuvant endocrine therapy

N= 2010

**Stratification:**
- Endocrine therapy (Tamoxifen vs AIs)
- Adjuvant chemotherapy

**Primary endpoint:**
DFS at 2 yr

**Secondary endpoints:**
OS, biomarkers, safety

**Everolimus 10 mg/d for 2 yrs + AI or Tamoxifen**

**Placebo for 2 yrs + AI or Tamoxifen**

**PI:** F. Andre
Examples of prediction of chemotherapy response

Ignatiadis et al J Clin Oncol 2012
Examples of prediction of chemotherapy response

**Different pathways are associated with pCR in different breast cancer subtypes**

Ignatiadis et al J Clin Oncol 2012
Level I evidence is on the works!

Choosing Neoadjuvant Chemotherapy versus Hormonal Therapy for Breast Cancer Based on Gene Expression Profile

HR+/Her-2 Neg. Breast Cancer Needing Neo Rx to Achieve BCT

Core Biopsy for Gene Expression Profile (RS)

< 11

Neoadjuvant Hormonal Tx

11-25

Randomize

Neoadjuvant Hormonal Tx

< 11

Neoadjuvant Chemotherapy

11

> 25

Neoadjuvant Chemotherapy

> 25

SURGERY

Endpoints: Clinical Response, BCT, RCB, pCR

PI: H. Bear
# Key differences between assays relevant to whether to add chemotherapy for ER+ breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Oncotype DX®</th>
<th>MammaPrint®</th>
<th>PAM 50 ROR®</th>
<th>Mammostrat®</th>
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</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>NO</td>
<td>NO</td>
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<tr>
<td>Was the test externally validated in a suitable population?</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
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<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 (failure rate unpublished)</td>
<td>FFPE (failure rate unpublished)</td>
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<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>
<td>Surgical excisions</td>
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<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>Continuous; individualized risk assessment</td>
<td>Group risk assessment (low, intermediate, high)</td>
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<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>NOT YET</td>
<td>NO</td>
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<tr>
<td>What platform does the test use?</td>
<td>RT-PCR</td>
<td>Microarray</td>
<td>RT-PCR</td>
<td>IHC</td>
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<tr>
<td>What type of regulatory clearance does the test have?</td>
<td>CLIA</td>
<td>CLIA/FDA</td>
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<tr>
<td>Is the test incorporated in treatment guidelines of ASCO and NCCN?</td>
<td>YES</td>
<td>NO</td>
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Future applications of new technologies
Time-to-Treatment Failure
Comparison with Previous Systemic Therapy

Matched therapy
N=175, 1 aberration

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<th>Failed</th>
<th>Median</th>
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<td>Previous systemic</td>
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Paired analysis
p < .0001

Non-matched therapy
N=116, 1 aberration

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<td>Previous systemic</td>
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Paired analysis
p < .56

Courtesy of R. Kurzrock
Clearinghouse and BEAT-IT projects

CLIA - ACGS (Actionable Cancer Gene Scan)
Actionable mutation detected?

NO

Expanded ACGS
Actionable mutation detected?

T200
Actionable mutation detected?

YES

CLIA confirmation

NO

Whole Genome

Identify Drug/Clinical Trial available

MD Anderson Cancer Center
Making Cancer History®
# Sharing Research Data: Cancer Gene Mutation Browser

| Sample Id       | AKT1 | AKT2 | AKT3 | ALK  | BRAF | CDKN2A | CTNNB1 | EGFR | EPHA3 | FER | FGFR2 | FGFR3 | FOG2 | FOXL2 | FOXM1 | GIT1  | GNAQ | GNAS | HRAS | KIT  | KRAS | MET   | NRAS | P53  | FGFR1 | FGFR2 | FGFR3 | FGFR4 | FGF1  | PHLPZ | PKDCA | PKPT1 | PKRAG2 | PRCC | RET   | TNK2 |
|-----------------|------|------|------|------|------|--------|--------|------|-------|-----|-------|-------|------|-------|-------|-------|------|------|-------|------|------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 3496T_Plat172   |      |      |      |      |      |        |        |      |       |     |       |       |      |       |       |       |     |      |       |     |     |        |       |       |       |       |       |       |       |       |       |       |
| MKN18_1_1_F11172|      |      |      |      |      |        |        |      |       |     |       |       |      |       |       |       |     |      |       |     |     |        |       |       |       |       |       |       |       |       |       |       |

**Detected** | **Wild Type** | **Inconclusive** | **Not Available**

## FOXL2

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The MD Anderson Cancer Center logo is visible in the bottom right corner of the image.
Where are we now?

- Our medical practice is based on standards of care (EBM)
  - EBM: best approach for the average populations, not for specific individuals

- Application of systems biology to personalized cancer therapy—Breast cancer as a model
  - Molecular profiling technologies to tailor medical care

- Challenges:
  - Identifying and validating molecular markers
  - Molecular crosstalk and bypass mechanisms
  - High failure rate of molecular targeted therapeutics

- It is critically important to understand the pathways and networks to target as well as of the homeostatic loops induced by the interventions
It is much more complex
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 women 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

• Prospective validation trials are on-going in the neoadjuvant setting

• Until results of such studies are available the current guidelines still endorse the use of adjuvant chemotherapy among all women with node positive disease

• Contribute to clinical trials !!!
## Acknowledgements

### Mentorship
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- F. Meric-Bernstam

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- A. Trape

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