Gene expression profiling of breast cancer: past and future

Christos Sotiriou, MD, PhD
Jules Bordet Institute
Université Libre de Bruxelles (ULB)
Brussels, Belgium
Outline

• Prognosis/prediction of response

• IMPAKT meeting (Brussels 2012) guideline session

• Future directions
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• Future directions
Example of a clinical case

A 61-year-old postmenopausal woman with left breast cancer

**Surgery:**
Breast Conserving Surgery and Sentinel Node Biopsy

**Pathology:**
- Infiltrating ductal carcinoma
- Histological grade 2
- no vascular or lymphatic channel invasion
- tumor size **1.9 cm** with clear surgical margins
- ER 85% cells positive, PR 65% cells positive
- Ki-67 15%
- HER2 negative
- lymphadenectomy: all axillary nodes negative
Adjuvant! Online

For Breast Cancer (Version 8.0)

Patient Information
- Age: 61
- Comorbidity: Perfect Health
- ER Status: Positive
- Tumor Grade: Grade 2
- Tumor Size: 1.1 - 2.0 cm
- Positive Nodes: 0
- Calculate For: Mortality
- 10 Year Risk: 8

Adjuvant Therapy Effectiveness
- Horm: Aromatase Inhibitor for 5 yrs
- Chemo: 2nd Generation Regimens

No additional therapy:
- 86.4 alive in 10 years.
- 7.8 die of cancer.
- 5.8 die of other causes.

With hormonal therapy: Benefit = 2.3 alive.

With chemotherapy: Benefit = 1.9 alive.

With combined therapy: Benefit = 3.7 alive.

Ki67 15%
Next day... same pathologist regrade and Ki67:

- GRADE 1
- Ki67 10%
Another center

-Ki67 20%

-Grade 3
Prognosis - 10 years survival
Adjuvant! Online

Same patient -> 2 ≠ days ->2 ≠ pathologists...

Good

2.9%

≠ grading (Ki67%)

7.8%

12.7%

Worse

Chemotherapy question?
Gene prognostic signatures:

**Genomic Grade Index (GGI)**

- Population: Untreated
- Tissue: Fresh/Frozen

**MammaPrint**

- Sotiriou et al., J Natl Cancer Inst., 2005
- Van’t Veer et al., Nature, 2002

**H/I + MGI**

- Population: Tamoxifen-treated
- Tissue: FFPE

**Oncotype DX**

- Paik et al., NEJM, 2004

Add additional information to current clinico-pathological parameters for treatment decision making for **some** patients.
Recurrence score

Independent validation (TransATAC)

Postmenopausal
ER+, No chemo

TAM
Anastrazole
Anastrazole + TAM

96%!

**Key messages**

- Proliferation = driving force of 1st generation gene expression prognostic signatures
- Informative for ER+/HER2- BC
- Stage (T,N) still matters

Stage (T,N) still matters
Prognostic signatures don’t help!

High proliferative breast cancers benefit from chemotherapy...

CMF regimen
N-

CAF regimen
N+

Ki67, PAM50 and other proliferation-based signatures...

Paik et al, JCO 2006

Albain et al, Lancet Oncology 2009
Tumor microenvironment matters...

Several molecular processes and molecular pathways

Studies identified, N=18
Patients, n=1615

Studies non-eligible, N=10, n=610
- Non-eligible treatment*: N=3, n=104
- No publicly gene expression data available : N=8, n=473
- Custom-designed microarray with incomplete annotation N=1, n=100

Studies eligible, N=8
Patients, n=1005

Patients non-eligible, n=9
- Missing pCR : n=5
- Additional treatment** : n=4

(Univariate Analysis)
Studies eligible, N=8
Patients, n=996

 Patients non-eligible, n=151
Missing clinical variables:
- Age : n=36
- Clinical tumor size : n=8
- Clinical nodal status : n=13
- Histological grade : n=140

(Multivariate Analysis)
Studies eligible, N=8
Patients, n=845

? Response to chemotherapy

High immune signal = better chemo response (N= 845 pts)

Different processes/pathways are associated with pCR in different BC subtypes

**HER2+**

<table>
<thead>
<tr>
<th>Gene</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGI</td>
<td>0.86</td>
<td>0.25 to 2.72</td>
<td>8.0E-01</td>
<td>8.7E-01</td>
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<tr>
<td>Gene70</td>
<td>0.85</td>
<td>0.24 to 2.8</td>
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<tr>
<td>CIN70</td>
<td>0.76</td>
<td>0.22 to 2.41</td>
<td>6.4E-01</td>
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<tr>
<td>Stroma1</td>
<td>0.65</td>
<td>0.26 to 1.62</td>
<td>3.5E-01</td>
<td>7.5E-01</td>
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<tr>
<td>Stroma2</td>
<td>0.46</td>
<td>0.17 to 1.19</td>
<td>1.2E-01</td>
<td>4.0E-01</td>
</tr>
<tr>
<td>Immune1</td>
<td>7.13</td>
<td>2.38 to 25.51</td>
<td>1.0E-03</td>
<td>1.8E-02</td>
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<tr>
<td>Immune2</td>
<td>5.01</td>
<td>1.77 to 16.35</td>
<td>4.1E-03</td>
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<tr>
<td>RAS</td>
<td>0.34</td>
<td>0.09 to 1.12</td>
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<tr>
<td>MAPK</td>
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<td>0.37 to 2.84</td>
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<td>PTEN</td>
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<tr>
<td>AKTmTOR</td>
<td>0.39</td>
<td>0.14 to 0.99</td>
<td>5.4E-02</td>
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<tr>
<td>PIK3CA</td>
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<td>0.47 to 3.69</td>
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<tr>
<td>IGF1</td>
<td>0.79</td>
<td>0.3 to 1.94</td>
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<td>SRC</td>
<td>1.74</td>
<td>0.73 to 4.33</td>
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<td>MYC</td>
<td>0.77</td>
<td>0.31 to 1.82</td>
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<td>E2F3</td>
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<td>0.21 to 1.97</td>
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<td>BetaCat</td>
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<td>0.68 to 4.35</td>
<td>2.7E-01</td>
<td>6.5E-01</td>
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**ER+/HER2-**

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<td>0.57 to 3.1</td>
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<td>Immune1</td>
<td>1.40</td>
<td>0.59 to 3.15</td>
<td>4.3E-01</td>
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<td>Immune2</td>
<td>1.71</td>
<td>0.7 to 4.17</td>
<td>2.4E-01</td>
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<td>RAS</td>
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<td>MAPK</td>
<td>0.86</td>
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<td>1.07</td>
<td>0.41 to 2.73</td>
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Clinical utility?

6 ≠ gene prognostic signatures including PAM50 ROR score?

Guidelines session in Brussels
Evaluation Process

Eligible articles for all 6 signatures were evaluated
(Q/C was performed by another reviewer)
Evaluation Methods

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

Genetics IN Medicine • Volume 11, Number 1, January 2009
According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing.
Clinical Validity

According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing.
According to EGAPP criteria, the panel grades **NONE** of the signatures as convincing.
Take home messages from the past...

✓ Level I evidence *is still awaited* (MINDACT, TAILORx, RxPONDER)

✓ May consider to use the genomic tests in:
  - ER+/HER2-/
  - Relatively high absolute risk with low comorbidity
  - Absolute benefit of chemotherapy (>1%)
  - *Patient’s preference!*
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Integration of genomic data with transcriptional data

Define and target the right phenotype
The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Integration of genomic and transcriptomic analysis of breast cancer

- Refine BC classification
- Define putative drivers
(1) Somatic and germline variants influence breast tumor expression architecture (39% 11,198/28609 probes)

- **Cis** = a variant at a locus has an impact on its own expression
- **Trans** = a variant at a locus is associated with genes at other sites in the genome
(2) Integrative clustering reveals 10 novel **IntClust** molecular subgroups beyond the intrinsic subtypes.
(3) **Trans**-acting associations reveal distinct modules

Strong “off-diagonal” patterns!

**Cis**  **Trans**
- -  +  +
These *trans* aberrations can be grouped into pathway modules (induction of adaptive immune response)
The **ENCODE** project provides information on the human genome far beyond that contained within the DNA sequence — it describes *the functional genomic elements that orchestrate the development and function of a human.*
Landscape of transcription in human cells

Sarah Djebali1*, Carrie A. Davis2*, Angelika Merkel1, Alex Dobin2, Timo Lassmann3, Ali Mortazavi4,5, Andrea Tanzer1, Julien Lagarde1, Wei Lin2, Felix Schlesinger2, Chenghai Xue2, Georgi K. Marinov4, Jainab Khatun6, Brian A. Williams4, Chris Zaleski2, Joel Rozowsky7,8, Maik Röder1, Felix Kokocinski9, Rehab F. Abdelhamid3, Tyler Alioto1,10, Igor Antoshechkin4, Michael T. Baer2, Nadav S. Bar11, Philippe Batut2, Kimberly Bell2, Ian Bell12, Sudipto Chakrabortty2, Xian Chen13, Jacqueline Chrust14, Joao Curado1, Thomas Derrien1, Jorg Drenkow2, Erica Dumais12, Jacqueline Dumais12, Radha Duttagupta12, Emilie Falconnet15, Meagan Fastuca2, Kata Fejes-Toth2, Pedro Ferreira1, Sylvain Foissac12, Melissa J. Fullwood16, Hui Gao12, David Gonzalez1, Assaf Gordon2, Harsha Gunawardena13, Cedric Howald14, Sonali Jha2, Rory Johnson1, Philipp Kapranov12,17, Brandon King4, Colin Kingswood1,10, Oscar J. Luo16, Eddie Park5, Kimberly Persaud2, Jonathan B. Preall2, Paolo Ribeca1,10, Brian Risk6, Daniel Robyr15, Michael Sammeth1,10, Lorian Schaffer4, Lei-Hoon See2, Atif Shahab16, Jorgen Skancke1,11, Ana Maria Suzuki3, Hazuki Takahashi3, Hagen Tilgner1†, Diane Trout4, Nathalie Walters14, Huaien Wang2, John Wrobel6, Yanbao Yu13, Xiaoxan Ruan16, Yoshihide Hayashizaki3, Jennifer Harrow9, Mark Gerstein7,8,18, Tim Hubbard9, Alexandre Reymond14, Stylianos E. Antonarakis15, Gregory Hannon2, Morgan C. Giddings6,13, Yijun Ruan16, Barbara Wold4, Piero Carninci3, Roderic Guigo1,19 & Thomas R. Gingeras2,12
“Here we report evidence that three-quarters of the human genome is capable of being transcribed, as well as observations about the range and levels of expression, localization, processing fates, regulatory regions and modifications of almost all currently annotated and thousands of previously un-annotated RNAs. These observations, taken together, prompt a redefinition of the concept of a gene”
The *huge challenge* is how to make sense out of all this...

“You’re the first patient ever to make sense of that chart. I’d say you’re dyslexic.”