Which translational research is ready for prime time?

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Université Libre de Bruxelles
Breast International Group (BIG aisbl), Chair
ESMO President
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

WHO CAN BE SPARED THERAPY?

WHICH THERAPY WILL WORK BEST?

Prognostic tools

Predictive tools
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

WHO CAN BE SPARED THERAPY?

Prognostic tools
SENSITIVITY (WITH 95% CI) OF CLINICO-PATHOLOGICAL RISK ASSESSMENTS FOR BC DEATH WITHIN 10 YEARS

High sensitivity

= Low probability of falsely classifying a patient as LOW RISK among those who die from breast cancer

Good performance for identifying the "bad tumors"
SPECIFICITY (WITH 95% CI) OF CLINICO-PATHOLOGICAL RISK ASSESSMENTS FOR BC DEATH WITHIN 10 YEARS

**High specificity**

= Low probability of falsely classifying a patient as HIGH RISK among those who do not die from breast cancer

Poor performance of identifying the "good" tumors
# MULTIGENE “PROGNOSTIC” SIGNATURES

## Table: Multigene Prognostic Signatures

<table>
<thead>
<tr>
<th></th>
<th>Oncotype DX™</th>
<th>MammaPrint™</th>
<th>GGI</th>
<th>PAM50</th>
<th>Breast Cancer Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider</td>
<td>Genomic Health</td>
<td>Agenda</td>
<td>Ipsogen</td>
<td>–</td>
<td>Biotheranostics</td>
</tr>
<tr>
<td>Type of assay</td>
<td>21-Gene recurrence score</td>
<td>70-Gene assay</td>
<td>97-Gene assay</td>
<td>50-Gene assay</td>
<td>2-Gene ratio HOXB13 to IL17R and molecular grade index</td>
</tr>
<tr>
<td>Tissue sample</td>
<td>FFPE</td>
<td>Fresh or frozen</td>
<td>Fresh or frozen</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td>Technique</td>
<td>qRT–PCR</td>
<td>DNA microarray</td>
<td>DNA microarray</td>
<td>qRT–PCR</td>
<td>qRT–PCR</td>
</tr>
</tbody>
</table>

## A decade of translational research...!
Are those signatures « ready for prime time »?
Utility of prognostic genomic tests in breast cancer practice: The IMPAKT 2012 Working Group Consensus Statement†

H. A. Azim Jr¹, S. Michiels¹, F. Zagouri², S. Delaloge³, M. Filipits⁴, M. Namer⁵, P. Neven⁶, W. F. Symmans⁷, A. Thompson⁸, F. André³*, S. Loi¹* & C. Swanton⁹,¹⁰
Does the test add any independent information upon what the clinician already uses in clinical practice (Multivariate analysis / large data sets)?
<table>
<thead>
<tr>
<th></th>
<th>Oncotype</th>
<th>Mamma-Print</th>
<th>GGI</th>
<th>BCI</th>
<th>PAM50 (ROR-S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Unique patients</td>
<td>4,219</td>
<td>1,465</td>
<td>1,284</td>
<td>539</td>
<td>1,496</td>
</tr>
<tr>
<td>N. multivariate models</td>
<td>13 *</td>
<td>13 *</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Adjustment factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tumor size</td>
<td>92%</td>
<td>77%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>- Nodal status</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>- Histological grade</td>
<td>75%</td>
<td>77%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>- Age</td>
<td>75%</td>
<td>70%</td>
<td>75%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>- ER</td>
<td>100%</td>
<td>77%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>- PgR</td>
<td>16% ^</td>
<td>15%</td>
<td>75%</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>- HER2+</td>
<td>25% ^</td>
<td>23%</td>
<td>25%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>- Ki67</td>
<td>8% ^</td>
<td>0%</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>- Treatment</td>
<td>100%</td>
<td>70%</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* One study tested Oncotype in univariate model and was negative, One study tested MammaPrint in multivariate model and was negative
^ within the IHC4

Azim HA Jr et al., Ann Oncol 2013
**The Evaluation of Genomic Applications in Practice and Prevention initiative (EGAPP)**

**Analytic validity**

« *The test is robust and reproducible* »

**Clinical validity**

« *The test can reliably determine the patients’ prognosis* »

**Clinical utility**

« *Treatment decision based on the test results in improved clinical outcome* »

*Azim HA Jr et al., Ann Oncol 2013*
ANALYTICAL VALIDITY?

Azim HA Jr et al., Ann Oncol 2013
CLINICAL VALIDITY?

Azim HA Jr et al., Ann Oncol 2013

YES

N. Panel Members
Oncotype
MammaPrint
Genomic Grade Index
Breast Cancer Index
PAM50 (ROR-S)
0
1
2
3
4
5
6
7
8
9
Convincing
Adequate
Inadequate

YES
CLINICAL UTILITY?

NO!
PROPOSALS TO MOVE FORWARD

• Results of ongoing MINDACT, TailorRx trials will help inform clinical utility

• Model that integrates clinicopathological data and genomic tests

• Registry to accumulate data for patients who are being profiled in daily practice out of trials
TAILORx (n=11,000 women) and MINDACT (n=6,600 women)  
Bringing molecular prognostic signatures to daily clinical practice

Node-negative B.C. population

- High risk 21-gene R.S.  
  OR
- High risk 70-gene signature + High risk adjuvant on line

- Medium risk 21-gene R.S.  
  OR
- Discordant risk group (mostly low risk 70-gene signature but high risk adjuvant on line)

- Low risk 21-gene R.S.  
  OR
- Low risk 70-gene signature + Low risk adjuvant on line

• RANDOMIZE CHEMO YES or NO (TailorX)
• RANDOMIZE FOR the decision-making tool (Mindact)

CHEMOTHERAPY

ENDOCRINE THERAPY

≈20-30%
≈30-45%
≈30-45%
Endopredict

Contribution of Genes

The EndoPredict Score combines the expression levels of proliferative genes and genes associated with ER-signaling / differentiation.

Two metagenes* were defined:

- **Proliferation:**
  - BIRC5, UBE2C and DHCR7

- **ER-Signaling / Differentiation:**
  - RBBP8, IL6ST, AZGP1, MGP and STC2

* Linear combination of dCt weighted with cox regression coefficients of the EP risk score

**Reference genes**

- CALM2
- OAZ1
- RPL37A

**Members**

- **Member 1**
  - BIRC5
  - RBBP8

- **Member 2**
  - UBE2C
  - IL6ST

- **Member 3**
  - AZGP1
  - DHCR7

- **Member 4**
  - MGP
  - STC2

*Courtesy P. Dubsky*
Background:
The EndoPredict (EP) signature

- Validated in two independent prospective-retrospective studies
- Evidence level: Ib (according to Simon et al., J Natl Cancer Inst, 2009)

Filipits et al., Clin Cancer Res. 2011
Dubsky et al., Ann Oncol. 2012
EndoPredict

High inter-lab correlation between the manufacturer (Sividon) and academic labs

Kronenwett R et al; BMC cancer 2012
Higher EP score correlates with higher risk of distant recurrences

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABCSG-6</th>
<th></th>
<th></th>
<th>ABCSG-8</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Unit HR (95% CI)</td>
<td>P</td>
<td>Unit HR (95% CI)</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.96–1.04)</td>
<td>0.864</td>
<td>1.02 (0.99–1.04)</td>
<td>0.194</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.09 (0.70–1.71)</td>
<td>0.704</td>
<td>1.57 (1.15–2.16)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
<td>2.47 (1.75–3.48)</td>
<td>&lt;0.001</td>
<td>2.32 (1.69–3.20)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>0.81 (0.48–1.37)</td>
<td>0.435</td>
<td>1.09 (0.60–1.99)</td>
<td>0.770</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER (IHC)</td>
<td>0.90 (0.58–1.40)</td>
<td>0.650</td>
<td>0.97 (0.70–1.34)</td>
<td>0.868</td>
<td></td>
<td></td>
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<tr>
<td>PR (IHC)</td>
<td>0.83 (0.63–1.10)</td>
<td>0.199</td>
<td>0.94 (0.77–1.15)</td>
<td>0.559</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki67</td>
<td>1.03 (1.00–1.06)</td>
<td>0.086</td>
<td>1.00 (0.98–1.02)</td>
<td>0.974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment arm</td>
<td>–</td>
<td>–</td>
<td>0.78 (0.51–1.19)</td>
<td>0.243</td>
<td></td>
<td></td>
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<tr>
<td>EP score</td>
<td>1.19 (1.04–1.36)</td>
<td>0.010</td>
<td>1.26 (1.15–1.38)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Highly prognostic even after adjusting for Ki67 (not tested by other genomic signatures!!)
EPclin CAN REFINE THE PROGNOSIS OF HIGH RISK CATEGORIES BY OTHER PROGNOSTIC CRITERIA

Adjuvant! Online

St Gallen intermediate / high risk

Dubsky P et al; Annals of Oncol 2013
EP CAN PREDICT LATE RELAPSES

**Table:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 – 5 years</th>
<th></th>
<th></th>
<th>&gt; 5 years</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Unit HR (95% CI)</td>
<td>P</td>
<td>Unit HR (95% CI)</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>1.20 (1.10–1.31)</td>
<td>&lt;0.001</td>
<td>1.28 (1.10-1.48)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.00-1.06)</td>
<td>0.032</td>
<td>0.97 (0.93-1.02)</td>
<td>0.263</td>
<td></td>
<td></td>
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<tr>
<td>Nodal status</td>
<td>2.15 (1.67-2.77)</td>
<td>&lt;0.001</td>
<td>2.45 (1.58-3.81)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Tumor size</td>
<td>1.26 (0.94-1.70)</td>
<td>0.121</td>
<td>1.11 (0.67-1.86)</td>
<td>0.678</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki67</td>
<td>1.01 (0.99-1.03)</td>
<td>0.171</td>
<td>1.01 (0.97-1.05)</td>
<td>0.760</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>1.21 (0.77-1.90)</td>
<td>0.414</td>
<td>0.64 (0.32-1.28)</td>
<td>0.209</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment arm</td>
<td>0.95 (0.61-1.48)</td>
<td>0.807</td>
<td>0.91 (0.40-2.09)</td>
<td>0.826</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dubsky P et al; SABCS 2012*
EPclin CAN IDENTIFY PATIENTS WITH DDFS >98% AT 10 YEARS!!

Dubsky P et al; SABCS 2012
## EP vs. Oncotype & MammaPrint

<table>
<thead>
<tr>
<th>Advantages of Endopredict (EP)</th>
<th>Oncotype Dx</th>
<th>MammaPrint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-lab validation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tested on samples prospectively collected in randomized phase III trials</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>RT-PCR on FFPE</td>
<td>Yes</td>
<td>Coming soon</td>
</tr>
<tr>
<td>Added prognostic value to ki-67</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Provides a risk score (EPclin) with key clinical prognostic factors (pT, pN))</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Can reliably determine long-term relapse</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Endopredict

Ready for primetime!
Acknowledgements

The IMPAKT task force

P. Dubsky

Medical Oncology

Task Force chair

Medical Oncology

Statistics

Medical Oncology

Pathology

Surgery

Laboratory

Gynecology/Surgery

Medical Oncology

Medical Oncology

Medical Oncology

Medical Oncology

Medical Oncology

Medical Oncology
BREAST CANCER CONFERENCE & EARLY CAREER TRAINING COURSE

Preliminary Program

Brussels, Belgium

2-4 MAY 2013

Important deadlines
9 January 2013, Abstract submission deadline
6 February 2013, Early registration and training course application
3 April 2013, Late registration and pre-registration closure