Genomic platforms in breast cancer

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Disclosure

Dr. Martin has received speakers honoraria from Genomic Health, Nanostring, Agendia and Sividon and has participated in studies with Oncotype, Endopredict and Prosigna (PAM50). He is co-inventor in a PAM50-related patent.
Genomic platforms: definition

- **Genomics** platforms are multigene profiles, based on DNA or RNA expression, aimed at prognosticating the outcome and/or predicting the response to systemic therapies.
Genomic platforms: potential clinical applications in breast cancer

prognostication
Genomic platforms: potential clinical applications in breast cancer

prognostication

prediction of response to hormones
Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones
- Prediction of response to chemotherapy
Genomic platforms: potential clinical applications in breast cancer

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- Prediction of response to chemotherapy
- Prediction of response to single CT drugs
Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones
- Prediction of response to chemotherapy
- Prediction of response to single CT drugs
- Prediction of response to targeted therapies
Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones (ER+/HER2−)
- Prediction of response to chemotherapy
Most breast cancers are screen-detected today

The majority are small, node-negative and ER+/HER2-tumors at low risk of relapse, some are completely harmless (overdiagnosis)

The classical clinocopathological parameters are suboptimal for prognostication (risk of relapse)

The predictive value of classical pathological parameters varies:

• good (but not perfect) for hormonal efficacy
• inefficient for chemotherapy benefit
875 screen detected cancers [SDBCs] and 600 symptomatic cancers were treated in women aged 50–65 years.

Ten year survival was 92.1% for SDBC and 77.6% for symptomatic cancers (median FU 110 months).

Adjusting for baseline factors, SDBCs had a reduced mortality (RR = 0.42 (0.31–0.57), independent of grade, node status and tumour size.)
Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial.

**Overdiagnosis**

By the end of the 5-year screening period, there were 142 excess cases of breast cancer in the mammography group (666 vs 524). At 15 years after enrollment, the excess number of cancers in the mammography group became constant at 106 cancers. **The excess number represents 22% (106/484) of all screen-detected cancers.** Thus, there was one case of overdiagnosis of breast cancer for every 424 women screened by mammography during the trial.

*Miller et al. BMJ 2014;348:g366 doi: 10.1136/bmj.g366*
Overdiagnosis among women attending a population-based mammography screening program

Ragnhild Sørum Falk¹, Solveig Hofvind¹,², Per Skaane³ and Tor Haldorsen¹

¹ Department of Research, Cancer Registry of Norway, Norway
² Faculty of Health Sciences, Oslo and Akershus University College of Applied Science, Norway
³ Department of Radiology, Oslo University Hospital Ullevaal, University of Oslo, Norway

Increased incidence of ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC) after introduction of organized screening has prompted debate about overdiagnosis. The aim was to examine the excess in incidence of DCIS and IBC during the screening period and the deficit after women left the program, and thereby to estimate the proportion of overdiagnosis. Women invited to the Norwegian Breast Cancer Screening Program were analyzed for DCIS or IBC during the period 1995–2009. Incidence rate ratios (IRRs) were calculated for attended vs. never attended women. The IRRs were adjusted by Mantel-Haenszel (MH) method and applied to a set of reference rates and a reference population to estimate the proportion of overdiagnosis during the women's lifespan after the age of 50 years. A total of 702,131 women were invited to the program. An excess of DCIS and IBC was observed among women who attended screening during the screening period; prevalently invited women aged 50–51 years had a MH IRR of 1.86 (95% CI 1.65–2.09) and subsequently invited women aged 52–69 years had a MH IRR of 1.56 (95% CI 1.45–1.68). In women aged 70–79 years, a deficit of 30% (MH IRR 0.70, 95% CI 0.62–0.80) was observed 1–10 years after they left the screening program. The estimated proportion of overdiagnosis varied from 10 to 20% depending on outcome and whether the women were invited or actually screened. The results highlight the need for individual data with longitudinal screening history and long-term follow-up as a basis for estimating overdiagnosis.
Prognostication and prediction in early breast cancer: background (I)

- Most breast cancers are screen-detected

- The majority are small, node-negative and ER+/HER2—tumors at low risk of relapse, some are completely harmless (overdiagnosis)

- The classical clinicopathological parameters are suboptimal for prognostication (risk of relapse)

- The predictive value of classical pathological parameters varies:
  - good (but not perfect) for hormonal efficacy
  - inefficient for chemotherapy benefit
Pitfalls of immunohistochemistry techniques

- Different antibodies
- Non-automatized techniques
  - tissue sample fixation
  - deparaffinization
  - antigen retrieval
  - antibody staining
- Semiquantitative results
- Artificial cut-offs of positivity (i.e. ER, Ki67)
Validation of the 2001 St Gallen Risk Categories for Node-Negative Breast Cancer Using a Database From the Spanish Breast Cancer Research Group (GEICAM)

- 924 patients T1-2, N0, M0
- median follow-up 7.5 y
- low-risk 14%, high-risk 86%

High-risk criteria for N0 (St Gallen 2001):
- ER/PR negative
- and/or Tsize > 2cm
- and/or grade 2/3
- and/or age < 35y
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Fig 1. Disease-free survival curves by high-risk and low-risk category for patients with node-negative breast cancer.

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- The classical clinocopathological parameters are suboptimal for prognostication (risk of relapse)
- **The predictive** value of classical pathological parameters varies:
  - good (but not perfect) for hormonal efficacy
  - very poor for chemotherapy benefit
Early Breast Cancer Trialists' Collaborative Group

Approximately 5 years tamoxifen vs. Not
RECURRENT
ER-poor

- Control 34.8%
- 5 years tamoxifen 33.7%

15-year gain 1.1% (SE 1.5)
Logrank 2p = 0.45

Approximately 5 years tamoxifen vs. Not
RECURRENT
ER+

- Control 46.1%
- 5 years tamoxifen 33.0%

15-year gain 13.0% (SE 1.1)
Logrank 2p < 0.00001
Early Breast Cancer Trialists' Collaborative Group

http://www.ctsu.ox.ac.uk/~ebctcg/systemic2000/mmap.htm
Prognostication and prediction in early breast cancer: background

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An International Ki67 Reproducibility Study


Manuscript received April 2, 2013; revised September 3, 2013; accepted September 16, 2013.

Correspondence to: Torsten Nielsen, MD, PhD, FRCP, University of British Columbia Pathology and Laboratory Medicine, Anatomical Pathology, JP 1401, Vancouver Hospital & Health Sciences Centre, 855 W 12th Ave, Vancouver, BC V5Z 1M9, Canada (e-mail: torsten@mail.ubc.ca).

Background

In breast cancer, immunohistochemical assessment of proliferation using the marker Ki67 has potential use in both research and clinical management. However, lack of consistency across laboratories has limited Ki67's value. A working group was assembled to devise a strategy to harmonize Ki67 analysis and increase scoring concordance. Toward that goal, we conducted a Ki67 reproducibility study.

Methods

Eight laboratories received 100 breast cancer cases arranged into 1-mm core tissue microarrays—one set stained by the participating laboratory and one set stained by the central laboratory, both using antibody MIB-1. Each laboratory scored Ki67 as percentage of positively stained invasive tumor cells using its own method. Six laboratories repeated scoring of 50 locally stained cases on 3 different days. Sources of variation were analyzed using random effects models with log2-transformed measurements. Reproducibility was quantified by intraclass correlation coefficient (ICC), and the approximate two-sided 95% confidence intervals (CIs) for the true intraclass correlation coefficients in these experiments were provided.

Results

Intralaboratory reproducibility was high (ICC = 0.94; 95% CI = 0.93 to 0.97). Interlaboratory reproducibility was only moderate (central staining: ICC = 0.71, 95% CI = 0.47 to 0.78; local staining: ICC = 0.69, 95% CI = 0.37 to 0.68). Geometric mean of Ki67 values for each laboratory across the 100 cases ranged 7.1% to 23.9% with central staining and 6.1% to 30.1% with local staining. Factors contributing to interlaboratory discordance included tumor region selection, counting method, and subjective assessment of staining positivity. Formal counting methods gave more consistent results than visual estimation.

Conclusions

Substantial variability in Ki67 scoring was observed among some of the world’s most experienced laboratories. Ki67 values and cutoffs for clinical decision-making cannot be transferred between laboratories without standardizing scoring methodology because analytical validity is limited.

Ki67 for prediction of response to chemotherapy?
BIG & North American Breast Cancer Group

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Results
Intralaboratory reproducibility was high (ICC = 0.94; 95% CI = 0.93 to 0.97). Interlaboratory reproducibility was only moderate (central staining: ICC = 0.71, 95% CI = 0.47 to 0.78; local staining: ICC = 0.59, 95% CI = 0.37 to 0.68). Geometric mean of Ki67 values for each laboratory across the 100 cases ranged 71% to 23.9% with central staining and 6.1% to 30.1% with local staining. Factors contributing to interlaboratory discordance included tumor region selection, counting method, and subjective assessment of staining positivity. Formal counting methods gave more consistent results than visual estimation.

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### Absolute Benefit for Tamoxifen plus Chemotherapy vs Tamoxifen (5-year Recurrence Rate) in ER+ breast cancer*

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<tr>
<th>ER/N Status</th>
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<th>Comparison</th>
<th>Recurrence Endpoint</th>
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<tbody>
<tr>
<td>ER+ (88%) or unknown N+ 73%</td>
<td>50-69</td>
<td>TAM alone vs TAM + CT</td>
<td>28.9% vs 24%</td>
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<td>ER+ (87%) or unknown N+ 34%</td>
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*including HER2+ tumors

[http://www.ctsu.ox.ac.uk/~ebctcg/systemic2000/mmap.htm](http://www.ctsu.ox.ac.uk/~ebctcg/systemic2000/mmap.htm)
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NNT to avoid a relapse by adding CT to TAM

- no relapse due to chemotherapy (74%)
- relapse in spite of chemotherapy (20%)
- no relapse regardless of chemotherapy (6%)
Prognostication and prediction in early breast cancer: background (II)

- We need better tools for:

  - prognostication of risk of relapse
  - prediction of sensitivity to hormones
  - prediction of sensitivity to polychemotherapy regimens
  - prediction of sensitivity to single chemotherapy drugs

- Can genomic mRNA-based test help establishing a better therapeutic strategy in

  - prognostication?
  - prediction of response to treatments?
First/Second Generation Genomic Platforms

oncotye DX
Breast Cancer Assay

mammaprint

EndoPredict

prosigna
Breast cancer prognostic gene signature assay
Evaluation and aims of genomic platforms

- Analytical validity
- Clinical validity
- Clinical utility
Evaluation and aims of genomic platforms

- **Analytical validity**: test’s ability to accurately and reliably measure the genotype of interest.
- **Clinical validity**: test’s ability to accurately and reliably predict a survival end point 5–10 years.
- **Clinical utility**: improvement in measurable clinical outcomes and added value in clinical management and decision making compared with standard criteria.
Evaluation and aims of genomic platforms

**Analytical validity**
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**Clinical validity**
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The IMPAKT 2012 Working Group proposed the following recommendations:

- (i) a need to develop models that integrate clinicopathologic factors along with genomic tests
- (ii) the creation of registries for patients who are subjected to genomic testing in the daily practice
- (iii) demonstration of clinical utility should be made in the context of a prospective randomized trial
## Use of Archived Specimens in Evaluation of Prognostic and Predictive Biomarkers

Richard M. Simon, Soonmyung Paik, Daniel F. Hayes

### Table 1. Elements of tumor marker studies that constitute Levels of Evidence determination *

<table>
<thead>
<tr>
<th>Category Element</th>
<th>A Prospective</th>
<th>B Prospective using archived samples</th>
<th>C Prospective/observational</th>
<th>D Retrospective/observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>PCT designed to address tumor marker</td>
<td>Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility</td>
<td>Prospective observational registry, treatment and follow-up not dictated</td>
<td>No prospective aspect to study</td>
</tr>
<tr>
<td>Patients and patient data</td>
<td>Prospectively enrolled, treated, and followed in PCT</td>
<td>Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest</td>
<td>Prospectively enrolled in registry, but treatment and follow-up standard of care</td>
<td>No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review</td>
</tr>
<tr>
<td>Specimen collection, processing, and archival</td>
<td>Specimens collected, processed, and assayed for specific marker in real time</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion</td>
<td>Specimens collected, processed and archived with no prospective SOPs</td>
</tr>
<tr>
<td>Statistical design and analysis</td>
<td>Study powered to address tumor marker question</td>
<td>Study powered to address therapeutic question and underpowered to address tumor marker question</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study</td>
</tr>
<tr>
<td>Validation</td>
<td>Result unlikely to be play of chance</td>
<td>Result more likely to be play of chance that A but less likely than C</td>
<td>Result very likely to be play of chance</td>
<td>Result very likely to be play of chance</td>
</tr>
</tbody>
</table>

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* PCT = prospective controlled trial; PRCT = prospective randomized controlled trial; SOPs = standard operating practices.
## Table 2. Revised determination of Levels of Evidence using elements of tumor marker studies*

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Category from Table 1</th>
<th>Validation studies available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>None required</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>One or more with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>B</td>
<td>None or inconsistent results</td>
</tr>
<tr>
<td>II</td>
<td>C</td>
<td>2 or more with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
<td>None or 1 with consistent results or inconsistent results</td>
</tr>
<tr>
<td>IV–V</td>
<td>D</td>
<td>NA†</td>
</tr>
</tbody>
</table>

* Levels of Evidence (LOEs) revised from those originally proposed by Hayes et al. (3).

† NA = not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility.
Prognostication
**Oncotype Dx: 21-gene recurrence score (ER+ tumors)**

16 Cancer and 5 Reference Genes

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

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

- **HER2**
  - GRB7
  - HER2

- **INVASION**
  - Stromolysin 3
  - Cathepsin L2

- **REFERENCE**
  - BAG1
  - GSTM1
  - CD68
  - Beta-actin
  - GAPDH
  - RPLPO
  - GUS
  - TFRC

- **Recurrence Score** =
  + 0.47 × HER2 Group Score
  − 0.34 × Estrogen Group Score
  + 1.04 × Proliferation Group Score
  + 0.10 × Invasion Group Score
  + 0.05 × CD68
  − 0.08 × GSTM1
  − 0.07 × BAG1

- Best RT-PCR performance and most robust predictions

*Paik S, et al: NEJM 2004*
The Oncotype Dx® recurrence score is a continuous predictor of recurrence risk.

What is the 10-year probability of distant recurrence for a patient with a Recurrence Score of 30?

RS 30 = 20% risk of distant recurrence at 10 years with tamoxifen.
The Oncotype Dx® recurrence score is a continuous predictor of recurrence risk.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Recurrence Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt; 18</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>18 - 30</td>
</tr>
<tr>
<td>High risk</td>
<td>≥ 31</td>
</tr>
</tbody>
</table>
OncoType DX® Clinical Validation: B-14 Results – Distant Recurrence

- 51% of population fell into the low-risk group
- 22% fell into the intermediate-risk group
- 27% fell into the high-risk group

Oncotype DX® Clinical Validation: B-14 Results – Distant Recurrence

78 breast tumors
Age < 55 years, Tumor size < 5 cm
Lymph node negative & No adjuvant therapy

Distant metastases within 5 years
No distant metastases for at least 5 years

Mammaprint

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Age < 55 years, Tumor size < 5 cm
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Mammaprint

Gene-Expression Profiling

CLASSIFICATION THRESHOLD

Low Risk Signature
High Risk Signature

Mammaprint: TRANSBIG Validation Results

![Graph showing probability of metastasis-free survival over time for different patient risk groups.](image)

- **Patients Risk group**: 111 MammaPrint Low Risk Signature, 191 MammaPrint High Risk Signature.

- **n=302**

- **p=0.001**

Mammaprint: TRANSBIG Validation Results

EndoPredict (Sividon Diagnostics)

- Decentralized test, currently, performed in 16 molecular labs in Germany, Switzerland and Austria
- 12 genes: 8 genes-of-interest, 3 normalization genes, 1 DNA control gene
- Two risk groups (low vs. high), no intermediate risk
- CE-IVD marks received as medical device
EndoPredict Report
Concise report showing relevant data

EP-Score
„molecular fingerprint“

Clinical-pathological parameters
tumor size + nodal status

= EPclin-Score
Scientific Validity of EndoPredict
Clinical validation trials

- Clinically validated in two independent cohorts from two randomized clinical trials in 1,702 samples (ER+, HER2 neg.)
- Level of evidence of Ib according to Simon et al. (JNCI 2009)
- Successful validation in one further cohort from a randomized chemotherapy trial in 555 samples (ER+, HER2 neg.)

Filipits et al. 2011; Dubsky et al. 2012; Martin et al. (SABCS 2012)
EP Score is an independent predictor of distant recurrence

<table>
<thead>
<tr>
<th>Cox model</th>
<th>Variable</th>
<th>ABCSG-6</th>
<th>ABCSG-8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unit HR (95% CI)</td>
<td>Unit HR (95% CI)</td>
</tr>
<tr>
<td>Multivariate Cox model</td>
<td>Age</td>
<td>1.00 (0.96–1.04)</td>
<td>1.02 (0.99–1.04)</td>
</tr>
<tr>
<td></td>
<td>Tumor size</td>
<td>1.09 (0.70–1.71)</td>
<td>1.57 (1.15–2.16)</td>
</tr>
<tr>
<td></td>
<td>Nodal status</td>
<td>2.47 (1.75–3.48)</td>
<td>2.32 (1.69–3.20)</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
<td>0.81 (0.48–1.37)</td>
<td>1.09 (0.60–1.99)</td>
</tr>
<tr>
<td></td>
<td>ER (IHC)</td>
<td>0.90 (0.58–1.40)</td>
<td>0.97 (0.70–1.34)</td>
</tr>
<tr>
<td></td>
<td>PR (IHC)</td>
<td>0.83 (0.63–1.10)</td>
<td>0.94 (0.77–1.15)</td>
</tr>
<tr>
<td></td>
<td>Ki67</td>
<td>1.03 (1.00–1.06)</td>
<td>1.00 (0.98–1.02)</td>
</tr>
<tr>
<td></td>
<td>Treatment arm</td>
<td>–</td>
<td>0.78 (0.51–1.19)</td>
</tr>
<tr>
<td></td>
<td>EP score</td>
<td>1.19 (1.04–1.36)</td>
<td>1.26 (1.15–1.38)</td>
</tr>
<tr>
<td>Bivariate Cox model</td>
<td>Adjuvant! score</td>
<td>1.03 (1.02–1.04)</td>
<td>1.05 (1.04–1.07)</td>
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<td>EP score</td>
<td>1.19 (1.06–1.32)</td>
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Prosigna (PAM50/nCOUNTER)

- 50-gene platform designed to identify breast cancer subtypes (LumA, LumB, Basal-like, HER2-E)
- Provides a ROR score (and ROR-C score) and 3 categories of risk
- Designed to be performed in local laboratories (nCOUNTER)
PAM50/nCOUNTER (Prosigna)

**Analytical Validation**
- Reproducibility from tissue
  - Multiple pathologists review tissue
  - Multiple techs processing tissue
  - Multiple lots of RNA extraction kits
- Precision from RNA
  - Multiple sites and operators
  - Multiple instruments
  - Multiple reagent lots

*Analysis presented at USCAP March 2013*

**Clinical Validation**
- TransATAC
  - 1007 patients from the ATAC trial
  - 10yr median follow up
  - Includes direct comparison to Oncotype Dx
- ABCSG-8
  - 1478 patients from study 8 re-consented
  - Tissue shipped to testing lab

- Shown to provide more prognostic information than RS and to categorize fewer patients as intermediate risk than RS in the transATAC population
- Validated as predicting prognosis more accurately than and beyond clinicopathological factors in ABCSG-8
- Level of evidence of Ib according to Simon et al. (JNCI 2009)

*Parker et al, JCO 2009; Nielsen et al CCR 2010; Gnant et al, SABCS 2012; Cuzixk et al, ESMO 2012*
Prosigna

Patient Report:

Assay Description:
The Prosigna® breast cancer gene signature assay measures the expression of 50 different genes to identify subtype and rule out a Risk of Recurrence Score (RORS), which is used to assign patients to a predefined risk group. These results are derived from a proprietary algorithm based on the PAM50 gene signature, intrinsic subtypes, and clinical variables including tumor size and stage.

Risk of Recurrence:
- Low risk
- Intermediate risk
- High risk

Probability of Distant Recurrence:
In the clinical validation studies, patients who were node-negative, luminal B subtype, with an RORS of 52 were in the intermediate-risk group. This group averaged an 11% probability of distant recurrence at 10 years.

Clinical Validation Studies:

Type of Disease:
- Luminal A (55%)
- Luminal B (95%)
- HER2-enriched
- Basal-like

Subtype and Prognosis:
Intrinsic subtype is related to prognosis in the clinical patient population. The most common subtype of breast cancer is luminal subtype A and luminal B. In the combined analysis of 2 clinical validation studies of hormone receptor-positive patients, 53% of the stage I and II patient population was found to be luminal A, and 27% was luminal B. The gene expression pattern of these subtypes resembles the luminal subtype component of the breast phenotype. These subtypes have characteristics of high expression of stem cell markers (TRA1), progesterone receptor (PR), and HER2 status associated with luminal A subtype.

TransATAC clinical validation study:

ABCSD-8 clinical validation study:

References:

NanosString Technologies, Inc.
530 Fawcett Avenue N., Suite 300
Seattle, Washington 98109
1-206-778-4026
nanosstring.com

© 2014 Nanosstring Technologies, Inc.
For more information, visit PROSIGNA.com or e-mail dcsupport@nanosstring.com.
PAM50/Prosigna

- CE mark received in Sept, 2012
- FDA clearance received in Dec 2013
- Available in EU and other countries recognizing the CE mark
- Decision impact studies in Germany (ongoing) and Spain (GEICAM, just finished)
Recurrence Score® result and Adjuvant! correlate weakly (correlation coefficient of 0.10 and 0.19 for local and central grade, respectively)

Recurrence Score and Adjuvant! independently predict relapse

<table>
<thead>
<tr>
<th></th>
<th>P value (central grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence Score</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjuvant!*</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The Onco

ype DX® Assay and Adjuvant! independently predict time to distant recurrence: E2197

ROR Defined Risk Groups have statistically significant different outcomes at 10 years.

**ABC哲G-8 trial**

- **Low**: 96.7% (94.6-98.0)
- **Intermediate**: 91.3% (88.1-93.8)
- **High**: 79.9% (75.7-83.4)

Probability of distant recurrence-free survival (%) vs. Follow-up time (years).
Late Relapse ROR Defined Risk Groups have significant different outcomes in the 2nd Quinquennium

ABCSG-8 trial

10-yr DRFS (95% CI)
- low: 98.7 (96.9 - 99.5)
- intermediate: 95.2 (92.3 - 97.0)
- high: 91.5 (87.8 - 94.1)

15-yr DRFS (95% CI)
- low: 97.6 (94.7 - 98.9)
- intermediate: 90.9 (85.9 - 94.2)
- high: 82.5 (74.8 - 88.1)

Patients at risk
- low: 460, 447, 439, 412, 331, 250, 188, 125, 81, 50, 25
- high: 370, 347, 330, 301, 238, 198, 153, 119, 82, 43, 24
# Comparison of PAM50 Risk of Recurrence Score With Oncotype DX and IHC4 for Predicting Risk of Distant Recurrence After Endocrine Therapy

## Table 1. Comparisons of Added Prognostic Information

<table>
<thead>
<tr>
<th>ROR (including tumor size)</th>
<th>No. of Patients</th>
<th>No. of DRs</th>
<th>CTS (1 df)</th>
<th>ROR (1 df)</th>
<th>RS (1 df)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR $- \Delta \chi^2$</td>
<td>P</td>
<td>LR $- \chi^2$</td>
<td>P</td>
<td>LR $- \chi^2$</td>
</tr>
<tr>
<td>All patients</td>
<td>1,007</td>
<td>160</td>
<td>144.9 &lt; .001</td>
<td>99.9 &lt; .001</td>
<td>38.2 &lt; .001</td>
</tr>
<tr>
<td>Node-negative patients</td>
<td>739</td>
<td>79</td>
<td>45.1 &lt; .001</td>
<td>60.9 &lt; .001</td>
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<tr>
<td>HER2-negative/node-negative patients</td>
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<td>683</td>
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<td>615</td>
<td>59</td>
<td>13.6 &lt; .001</td>
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Abbreviations: CTS, clinical treatment score; DR, distant recurrence; HER2, human epidermal growth factor receptor 2; LR, likelihood ratio; ROR, risk of recurrence; RS, recurrence score.

_Dowset et al, JCO 31:2783, 2013_
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Dowset et al, JCO 31:2783, 2013

PAM50 vs Oncotype
Ten-year Risk Group Classification: ROR Score vs. RS in node negative patients (with Clinical Treatment Score)

<table>
<thead>
<tr>
<th>Score</th>
<th>H+L Groups</th>
<th>Score</th>
<th>H/L Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROR</td>
<td>572 (77%)</td>
<td>ROR</td>
<td>7.16 [4.07 – 12.61]</td>
</tr>
<tr>
<td>RS</td>
<td>538 (73%)</td>
<td>RS</td>
<td>6.2 [3.3 – 11.5]</td>
</tr>
</tbody>
</table>

Dowset et al, JCO 31:2783, 2013, SABCS 2011
Conclusion
ROR provides more prognostic information in endocrine-treated patients with ER-positive, node-negative disease than RS, with better differentiation of intermediate- and higher-risk groups.
Evaluation and aims of genomic platforms

- Analytical validity
- Clinical validity
- Clinical utility

Improved therapeutic strategy
Evaluation and aims of genomic platforms

- Analytical validity
- Clinical validity
- Clinical utility

- Improved therapeutic strategy
  - Added prognostic value
  - Better selection of patients for hormones, CT
  - Added Predictive value
Evaluation and aims of genomic platforms

- Analytical validity
- Clinical validity
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- Improved therapeutic strategy
  - Added prognostic value
  - Better selection of patients for hormones, CT
    - Added Predictive value
    - Increased survival
      - Similar survival, less exposure to CT
Evaluation and aims of genomic platforms

- Analytical validity
- Clinical validity
- Clinical utility

- Improved therapeutic strategy
- Added prognostic value
- Better selection of patients for hormones, CT
- Added Predictive value
- Increased survival
- Similar survival, less exposure to CT
Genomic Platforms as Predictors
Are prognostication and prediction linked?

- Genomic platforms were designed for prognostication of risk of relapse
- Does risk of relapse according to genomic tests correlated with sensitivity to hormones, chemotherapy?
- Genomic tests are mainly based on ER-related and proliferation-related genes
RS identifies patients in the B-14 study most likely to benefit from tamoxifen.

DISTANT RECURRENCE FREE INTERVAL

RS < 18

p = 0.039

Placebo 171
Tamoxifen 142

RS 18-30

p = 0.02

Placebo 85
Tamoxifen 69

RS ≥31*

p = 0.82

Placebo 99
Tamoxifen 79

Interaction P = 0.06

*Results should not be used to indicate that tamoxifen should not be given to the high-risk group

High Recurrence Score® result correlates with greater benefit from chemotherapy (NSABP B-20)

Overall, 4.4% absolute benefit from tamoxifen + chemotherapy
High Recurrence Score® result correlates with greater benefit from chemotherapy (NSABP B-20)

Overall, 4.4% absolute benefit from tamoxifen + chemotherapy

LOW RS GROUP
Recurrence Score <18

INTERMEDIATE RS GROUP
Recurrence Score 18-30

HIGH RS (>30)

28% absolute benefit

Number of Patients Needed to Treat (NNT) to Avoid a Distant Recurrence with tamoxifen + CT vs tamoxifen alone (NSABP B-20)

<table>
<thead>
<tr>
<th>Population</th>
<th>Distant Recurrence Rate with tamoxifen</th>
<th>Distant Recurrence Rate with tamoxifen + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>High RS</td>
<td>40%</td>
<td>12%</td>
</tr>
</tbody>
</table>
## Potential Pros and Cons of Genomic Platforms

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can help identify very low-risk, harmless tumors (?)</td>
<td>↓survival (?)</td>
</tr>
<tr>
<td>Can help identify tumors highly sensitive to hormones</td>
<td>High cost (cost-effectiveness?)</td>
</tr>
<tr>
<td>Can help identify high-risk tumors that apparently have good-risk features by conventional parameters</td>
<td>No level IA evidence of clinical utility so far (?)</td>
</tr>
<tr>
<td>Reduction on the use of adjuvant chemotherapy (reduction in overtreatment)</td>
<td></td>
</tr>
<tr>
<td>Can help identify patients at high risk of relapse after 5 years of endocrine therapy</td>
<td></td>
</tr>
</tbody>
</table>
MINDACT: Optimizing decision-making for adjuvant chemotherapy

Assess clinical and genomic risk

Clinical and genomic BOTH HIGH RISK

Clinical and genomic BOTH LOW RISK

DISCORDANT clinical and genomic risks

RANDOMIZE decision-making

Use clinical risk

High risk

Chemotherapy

Use genomic risk

Low risk

No chemotherapy

High risk
Registries
PREGECAM
(Programa de Predicción Genómica en Cáncer de Mama de la Comunidad de Madrid)

Population: 6,300,000 inh.
New breast cancers per year: 2,800

ER+/HER2-
N0 o Nmic, T > 1cm or
T<1 and G2-3 or Ki67 >13%
or lymphovascular invasion

May 2012-Dec 2013

Prospective data collection including cost-efficacy analysis

<table>
<thead>
<tr>
<th>TEST</th>
<th>Nº. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype Dx®</td>
<td>185</td>
</tr>
<tr>
<td>Mammaprint</td>
<td>239</td>
</tr>
<tr>
<td>All</td>
<td>424</td>
</tr>
</tbody>
</table>
## PREGECAM (Madrid County, Spain)

<table>
<thead>
<tr>
<th></th>
<th>No. of tests</th>
<th>Result</th>
<th>No result (technical problems)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncotype</strong></td>
<td>185</td>
<td>181</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td><strong>Mammaprint</strong></td>
<td>239</td>
<td>218</td>
<td>21 (8.8%)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>424</td>
<td>399</td>
<td>25 (5.9%)</td>
</tr>
</tbody>
</table>
PREGECAM (Madrid County, Spain)

switch in therapy (n=176)

- CT+HT → HT: 32.4%
- HT → CT+HT: 11.5%
PREGECAM (Madrid County, Spain)

44% change in treatment decisions, 20% reduction in the use of chemotherapy

Switch in therapy (n=176)

32.4%

11.5%
Meta-analysis: overall impact of RS (Oncotype Dx) on treatment decisions

Overall, the RS led to a 37% change in treatment decisions

Conclusions

- Genomic platforms are contributing to an individualized therapeutic strategy in early breast cancer
- Genomic tests provide relevant prognostic information for ER+/HER2- early breast cancer patients
- Clear correlation between genomic prognostication and prediction of response to TAM/chemotherapy in ER+/HER2- tumors
- Debate about the need for prospective validation of clinical utility
- Registries necessary to check the performance of the tests in the real life
Back-up slides
Ongoing Trials
TAILORx Schema

**Trial Assigning Individualized Options for Treatment**

Patients with node-negative, hormone receptor-positive, HER2-negative breast cancer

**Oncotype DX® Assay**

- **Recurrence Score <11**
  - **ARM A** Hormone therapy registry

- **Recurrence Score 11-25**
  - Randomize to:
    - ARM B hormone therapy or
    - ARM C chemo+hormone therapy

- **Recurrence Score >25**
  - **ARM D** Chemotherapy + hormone therapy

**Accrual goal n = 11,248**

Initiated April 2006, recruitment completed October 2010

- **Primary endpoint**: disease free survival
- **Sample size**: n=4,390 for primary study group corresponding to a total accrual of n=11,248
- **Non-Inferiority design**: decrease in 5-year DFS rate from 90% (with chemo) to 87% (without chemo) defined as unacceptable (one-sided type one error of 10% and 5% type II error)

**PACCT-1 Intergroup Study**: ECOG, SWOG, NCCTG, CALGB, NCIC, ACOSOG, and NSABP + study groups from Australia, Canada, Ireland, Peru; Sponsor: NCI
Schema and Patient Flow

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

(N=600)
RS already Available

RS ≤ 25 ?

RS > 25

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

RS ≤ 25

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

Accept

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

Refuse

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

N=2,000
No Chemotherapy; appropriate endocrine therapy

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