Translating Breast Cancer Genomics into Clinic

Prof. Miguel Martín
Instituto de Investigación Sanitaria
Hospital Gregorio Marañón
Universidad Complutense
Madrid
mmartin@geicam.org
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.
Genome 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

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

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- Prediction of response to single CT drugs
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- 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
- Prediction of response to chemotherapy

ER+/HER2-
Genomic platforms: potential clinical applications in breast cancer
Making Predictions Less of an Art, More of a Science

- Analysts for … more than a dozen US government organizations depend on their ability to forecast national and global events to help ward off various threats to the country

- Old-style approaches can produce flawed results

- The effects (of deliberation) have led analysts to predict events than didn’t occur, or miss events that did take place
Pitfalls of old prognostication tools in breast cancer

- **Overtreatment** (low accuracy in identifying patients that actually do not benefit from chemotherapy)

- **Undertreatment** (insufficient accuracy in identifying patients with apparent low risk that actually benefit from chemotherapy)
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)
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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*including HER2+ tumors

http://www.ctsu.ox.ac.uk/~ebctcg/systemic2000/mmap.htm
### Absolute Benefit for Tamoxifen plus Chemotherapy vs Tamoxifen (5-year Recurrence Rate) in ER+ Breast Cancer*

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*including HER2+ tumors

**No relapse due to chemotherapy**

**Relapse in spite of chemotherapy**

**No relapse regardless of chemotherapy**

http://www.ctsu.ox.ac.uk/~ebctcg/systemic2000/mmap.htm
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- no relapse due to chemotherapy
- relapse in spite of chemotherapy
- no relapse regardless of chemotherapy

NNT to avoid a relapse by adding CT to TAM
Prognostication in early breast cancer

- We need better tools for prognostication of the risk of relapse

- Can genomic mRNA-based test help establishing a better therapeutic strategy in prognostication?
First/Second Generation Genomic Platforms

- OncoType DX
- MammaPrint
- EndoPredict
- Prosigna
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 endpoint 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**
- 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 at 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**: 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 at 5–10 years.

- **Clinical utility**: Improvement in measurable clinical outcomes and added value in clinical management and decision making compared with standard criteria.
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 Prospектив</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>Accommodation of predictive marker requires PRCT</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>
<tr>
<td></td>
<td>Although preferred, validation not required</td>
<td>Requires one or more validation studies</td>
<td>Requires subsequent validation studies</td>
<td>Requires subsequent validation</td>
</tr>
</tbody>
</table>

*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.
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

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

**INVASION**
- Stromolysin 3
- Cathepsin L2

**CD68**

- GSTM1

• Best RT-PCR performance and most robust predictions

**Recurrence Score**

\[ \text{Recurrence Score} = + 0.47 \times \text{HER2 Group Score} - 0.34 \times \text{Estrogen Group Score} + 1.04 \times \text{Proliferation Group Score} + 0.10 \times \text{Invasion Group Score} + 0.05 \times \text{CD68} - 0.08 \times \text{GSTM1} - 0.07 \times \text{BAG1} \]

The Onco\textit{type} Dx\textsuperscript{®} recurrence score is a continuous predictor of recurrence risk.
Onco*type DX® Clinical Validation: B-14 Results – Distant Recurrence

Proportion without Distant Recurrence

RS <18 n = 338
RS 18-30 n = 149
RS ≥31 n = 181

- 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**

Proportion without Distant Recurrence

- **RS <18 n = 338**
- **RS 18-30 n = 149**
- **RS ≥31 n = 181**

### Survival Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 years</td>
<td>0.71</td>
<td>(0.48, 1.05)</td>
<td>0.084</td>
</tr>
<tr>
<td>Size &gt;2.0 cm</td>
<td>1.26</td>
<td>(0.86, 1.85)</td>
<td>0.231</td>
</tr>
<tr>
<td>Recurrence Score</td>
<td>3.21</td>
<td>(2.23, 4.61)</td>
<td>&lt;0.001</td>
</tr>
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</table>

Mammaprint: a 70-gene expression profile platform

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

Classification Threshold

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

Low Risk Signature

High Risk Signature

Mammaprint: a 70-gene expression profile platform

- 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

Classification Threshold

Low Risk Signature

High Risk Signature

Gene-Expression Profiling

- Probability of Remaining Metastasis-free
- Years
- Good signature
- Poor signature

Mammmaprint: 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

Tumor sample → RNA isolation → EndoPredict-Test → Test result

Turn-around-Time < 8 h
EndoPredict Report
Concise report showing relevant data

EP-Score
„molecular fingerprint“

Clinical-pathological parameters

\[ \text{tumor size} + \text{nodal status} \]

\[ = \]

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)
Clinical Validation
Validated for node positive and negative patients

Node negative

Node positive

Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2− breast cancer patients: results from the GEICAM 9906 trial

Figure 1: Kaplan-Meier metastasis-free survival curves for ER+/HER2− breast cancers. (A) Curves representing EndoPredict (EP) test results indicating estimated high and low risk of metastasis-free survival (MFS). The cutoff point was prespecified at 5. (B) Curves representing EPclin results indicating estimated high and low risk of MFS. The cutoff point was prespecified at 3.3. Numbers in parentheses indicate the 95% confidence intervals of the hazard ratios. ARR: Absolute risk reduction estimated at 10 years; ER+/HER2−: Estrogen receptor–positive/human epidermal growth factor receptor 2–negative. The MFS in the EP score–based low-risk category was 93% vs 70% in the EP score–based high-risk group. The MFS in the EPclin-based low-risk category was 100% vs 72% in the EPclin score–based high-risk group.
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; Cuzik 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 report a Risk of Recurrence Score (ROR), which is used to assign patients to a predefined risk group. These results are derived from a proprietary algorithm based on the Prosigna gene signature, luminal subtype, and clinical variables including tumor size and menopause.

Risk of Recurrence:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>52%</td>
<td>90%</td>
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</table>

*The ROR ranges from 0 through 100 and correlates with the probability of distant recurrence (DR) in the breast cancer population. The risk classification is provided to guide the management of the ROR among patients with breast cancer.

Probability of Distant Recurrence:

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

Clinical Validation Studies:

Subtypes and Prognosis:

Tumors are classified as luminal A (95% of cases) or luminal B. The combined analysis of 2 clinical validation studies of hormone receptor-positive patients, 59% of the test population population was found to be luminal A and 27% was luminal B. The gene expression pattern of these subtypes resembles the luminal epithelial component of the breast. These lumins are characterized by high expression of estrogen receptor (ER), progesterone receptor (PR), and the genes associated with ER activation. Luminal A breast cancers exhibit low expression of genes associated with cell cycle arrest and generally have a better prognosis than luminal B.

TransATAC clinical validation study:

The TransATAC study analyzed RNA from a prospective, non-selected cohort of patients, including patients with luminal A and B subtypes. The study found that the TransATAC score was significantly associated with distant recurrence and overall survival. The TransATAC score was calculated by assessing the expression of 50 different genes in the tumor sample. The score was then used to predict the risk of recurrence and overall survival.

REFERENCES:

For more information, visit PROSIGNA.com or e-mail customer.service@nanosting.com.
Clinical Validation of the PAM50 Risk of Recurrence (ROR) score in ABCSG-8
ROR Defined Risk Groups have statistically significant different outcomes at 10 years.

ABC哲-8 trial

Probability of distant recurrence-free survival (%)

Follow-up time (years)
Late Relapse ROR Defined Risk Groups have significant different outcomes in the 2nd Quinquennium

ABCAG-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
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**
  - Improved therapeutic strategy
  - Added prognostic value

- **Clinical validity**
  - Better selection of patients for hormones, CT
  - Added predictive value

- **Clinical utility**
  - 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

- Increased survival
- Similar survival, less exposure to CT
- Added Predictive value
Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones
- Prediction of response to chemotherapy
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
Prognostication and prediction are linked in ER+/HER2- breast cancer
RS identifies patients in the B-14 study most likely to benefit from tamoxifen.

DISTANT RECURRENCE FREE INTERVAL

RS <18

RS 18-30

RS ≥31*

$p = 0.039$

$p = 0.02$

$p = 0.82$

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

<table>
<thead>
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<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>
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Ongoing Trials
MINDACT: Optimizing decision-making for adjuvant chemotherapy

Assess clinical and genomic risk

- Clinical and genomic BOTH HIGH RISK
- DISCORDANT clinical and genomic risks
- Clinical and genomic BOTH LOW RISK

Randomize decision-making

- Use clinical risk
  - High risk → Chemotherapy
  - High risk → Use genomic risk
    - Low risk → No chemotherapy

Use genomic risk
  - Low risk → No chemotherapy
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

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

(N= 8,800)

RS ≤ 25 ?

RS > 25

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

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

RS ≤ 25

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

N= 2,000
No Chemotherapy; appropriate endocrine therapy

RS > 25

Refuse

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

SWOG, and study group from Spain (GEICAM); Sponsor: NCI
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
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

Prospective data collection including cost-efficacy analysis

May 2012-April 2014

<table>
<thead>
<tr>
<th>TEST</th>
<th>Nº. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype Dx®</td>
<td>255</td>
</tr>
<tr>
<td>Mammaprint</td>
<td>370</td>
</tr>
<tr>
<td>All</td>
<td>625</td>
</tr>
</tbody>
</table>
switch in therapy (n=275)

CT+HT → HT: 33.6%
HT → CT+HT: 10.4%

PREGECAM (Madrid County, Spain)
PREGECAM (Madrid County, Spain)

Switch in therapy (n=275)

44% change in treatment decisions, 22% reduction in the use of chemotherapy

33.6% 10.4%

CT+HT → HT HT → CT+HT
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
- 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 evaluate the performance of the tests in the real life