Relevancia práctica de la clasificación de subtipos intrínsecos en cáncer de mama

Miguel Martín
Instituto de Investigación Sanitaria Gregorio Marañón
Universidad Complutense
Madrid
The new technologies have changed our understanding of breast cancer.

**XIX century**
- morphology/histology

**1980s**
- HE

**1990s**
- IHC
- single genes

**XXI century**
- FISH
- DNA/RNA arrays
- SNP analysis
- Multiplex PCR
- NGS TECHNOLOGY
- multiple genes
Molecular portraits of human breast tumors

The intrinsic subtype classification

Comprehensive molecular portraits of human breast tumors
The Cancer Genome Atlas Network

825 patients
↓
463 patients
  • Gene Expression
  • DNA Copy Number
  • miRNA Expression
  • DNA Methylation
  • Exome Sequencing
↓
348 patients
  • Reverse Phase Protein Arrays

Integration of information across 5 platforms confirmed the existence of 4 main breast cancer classes

<table>
<thead>
<tr>
<th>Gen</th>
<th>Mutado</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>187 (37%)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>180 (36%)</td>
</tr>
<tr>
<td>GATA3</td>
<td>54 (11%)</td>
</tr>
<tr>
<td>MAP3K1</td>
<td>39 (8%)</td>
</tr>
<tr>
<td>MLL3</td>
<td>37 (7%)</td>
</tr>
<tr>
<td>CDH1</td>
<td>33 (6.5%)</td>
</tr>
<tr>
<td>MAP2K4</td>
<td>21 (4%)</td>
</tr>
<tr>
<td>RUNX1</td>
<td>18 (3.5%)</td>
</tr>
<tr>
<td>PTEN</td>
<td>17 (3.4%)</td>
</tr>
<tr>
<td>TBX3</td>
<td>13 (2.5%)</td>
</tr>
</tbody>
</table>

doi:10.1038/nature11412
Defining Breast Cancer Intrinsic Subtypes by Quantitative Receptor Expression

MAGGIE C.U. CHEANG, a,c MIGUEL MARTIN, d TORSTEN O. NIELSEN, e ALEIX PRAT, f DAVID VODUC, g ALVARO RODRIGUEZ-LESCURE, h AMPARO RUIZ, i STEPHEN CHIA, g LOIS SHEPHERD, j MANUEL RUIZ-BORREGO, k LOURDES CALVO, i EMILIO ALBA, m EVA CARRASCO, n ROSALIA CABALLERO, n DONGSHENG TU, j KATHLEEN I. PRITCHARD, o MARK N. LEVINE, p VIVIEN H. BRAMWELL, q JOEL PARKER, a,b PHILIP S. BERNARD, r MATTHEW J. ELLIS, s CHARLES M. PEROU, a,b ANGELO DI LEO, t LISA A. CAREY a

Figure 1. REMARK diagram, including intrinsic subtype frequencies for each trial. Abbreviations: BLBC, basal-like subtype; HER2-E, HER2-enriched subtype; LUMA, luminal A subtype; LUMB, luminal B subtype.
Conclusion
Significant discordance remains between clinical assay-defined subsets and intrinsic subtype.
Distribution of PAM50 intrinsic subtype across IHC-based biomarkers (N=1396, Both Centrally Determined)

Data from: TAMseries (CCR 2010), GEICAM 9906 (JCO 2013) and GEICAM 2012-09 (CMRO 2015)

**Ki-67**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>0-10% N</th>
<th>11-20% N</th>
<th>21-30% N</th>
<th>&gt;30% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>LumA</td>
<td>620</td>
<td>112</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>LumB</td>
<td>265</td>
<td>219</td>
<td>112</td>
<td>36</td>
</tr>
</tbody>
</table>

**PR**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>0-10% N</th>
<th>11-90% N</th>
<th>91-100% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>LumA</td>
<td>243</td>
<td>347</td>
<td>160</td>
</tr>
<tr>
<td>LumB</td>
<td>334</td>
<td>249</td>
<td>59</td>
</tr>
</tbody>
</table>

**ER**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>0-10% N</th>
<th>11-90% N</th>
<th>91-100% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>LumA</td>
<td>93</td>
<td>378</td>
<td>267</td>
</tr>
<tr>
<td>LumB</td>
<td>100</td>
<td>333</td>
<td>196</td>
</tr>
</tbody>
</table>

**Cortesy: A. Prat**
Figure 2. Distribution of the intrinsic molecular and pathology-based subtypes within triple-negative and basal-like tumors.

Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.
Conclusions
The standard immunohistochemical panel for breast cancer (ER, PR, and HER2) does not adequately identify the PAM50 gene expression subtypes.

Bastien et al. BMC Medical Genomics 2012, 5:44
Plataformas Genómicas en Cáncer de Mama

- Oncotype Dx (Genomic Health, 21 genes)
- Mammaprint (Agendia, 70 genes)
- Prosigna™ (Nanostring, 50 genes-PAM50)
- EndoPredict (Sividon, 12 genes)
- Map-Quant Dx (Ipsogen, 97 genes)
- Breast Cancer Index/Theros (Biotheranostics, 2 genes)
Genomic platforms: potential clinical applications in breast cancer

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

prognostication
**OncoType DX®: B-14 Results – Distant Recurrence**

- **Bajo riesgo (6.8%)**
- **Riesgo intermedio (14.3%)**
- **Alto riesgo (30.5%)**

Mammaprint

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

Good signature

Poor signature

\[ \uparrow 43\% \]

Years

Mammaprint: TRANSBIG Validation Results

Prognostic ability of EndoPredict compared to research-based versions of the PAM50 risk of recurrence (ROR) scores in node-positive, estrogen receptor-positive, and HER2-negative breast cancer. A GEICAM/9906 sub-study

Miguel Martin1 · Jan C. Brase2 · Amparo Ruiz6 · Aleix Prat7 · Ralf Kronenwett2 · Lourdes Calvo8 · Christoph Petry2 · Philip S. Bernard9 · Manuel Ruiz-Borrego10 · Karsten E. Weber2 · César A. Rodriguez11 · Isabel M. Alvarez12 · Miguel A. Segui13 · Charles M. Perou3,4,5 · Maribel Casas14 · Eva Carrasco14 · Rosalía Caballero14 · Alvaro Rodriguez-Lescure15

**Figure 1:** Kaplan-Meier plot of metastasis-free survival (MFS) by EP risk groups (N=555).

**Figure 2:** Kaplan-Meier plot of metastasis-free survival (MFS) by EPclin risk groups (N=555).
Late Relapse ROR Defined Risk Groups have significant different outcomes in the 2nd Quinquennium

ABCSDG-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
Genomic platforms: potential clinical applications in breast cancer

**prognostication**

**prediction of response to hormones**
Objective: Determine whether the 21-gene RS assay provides predictive information for patients who were treated with tamoxifen (likelihood of recurrence)

B-14 Benefit of Tamoxifen
By Recurrence Score Risk Category

Low Risk (RS<18)
- Placebo: 171
- Tamoxifen: 142

Int Risk (RS 18-30)
- Placebo: 85
- Tamoxifen: 69

High Risk (RS≥31)
- Placebo: 99
- Tamoxifen: 79

Interaction P = 0.06

1 The results should not be used to conclude that tamoxifen should not be given to the high-risk group

B-14 Benefit of Tamoxifen
By Recurrence Score Risk Category

Low Risk (RS<18)

- Placebo: 171
- Tamoxifen: 142

High Risk (RS≥31)

- Placebo: 99
- Tamoxifen: 79

Interaction $P = 0.06$

1 The results should not be used to conclude that tamoxifen should not be given to the high-risk group.

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 Ulleval, 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 (IRR) 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.
Prognostic value of PAM50 and risk of recurrence score in patients with early stage breast cancer with long-term follow-up

Observational Oslo1 study (1995–1998)

Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up

Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones
- Prediction of response to chemotherapy
Prognostication and prediction are linked in ER+/HER2- breast cancer
Chemotherapy Benefit and Onco\emph{type} DX®

NSABP B-20

Paik et al. \emph{J Clin Oncol.} 2006;24:3726-3734.
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>
Pathologic complete response to neoadjuvant chemotherapy differs by subtype

<table>
<thead>
<tr>
<th></th>
<th>T-FAC$^1$ (N=82)</th>
<th>AC-T$^2$ (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A/B</td>
<td>2/30 (7%)</td>
<td>4/62 (7%)</td>
</tr>
<tr>
<td>Normal-like</td>
<td>0/10 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>9/20 (45%)</td>
<td>4/11 (36%)</td>
</tr>
<tr>
<td>Basal-like</td>
<td>10/22 (45%)</td>
<td>9/34 (26%)</td>
</tr>
</tbody>
</table>

P<0.001

P=0.003

Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones
- Prediction of response to chemotherapy
- Prediction of response to targeted therapies
- Prediction of response to specific CT drugs
Responsiveness of Intrinsic Subtypes to Adjuvant Anthracycline Substitution in the NCIC.CTG MA.5 Randomized Trial

Responsiveness of Intrinsic Subtypes to Adjuvant Anthracycline Substitution in the NCIC.CTG MA.5 Randomized Trial

Premenopausal N+ (n=710)

CMFx6

CEFx6

Respuesta a quimioterapia neoadyuvante con docetaxel+carboplatino en cáncer de mama triple negativo (n=96)

**Distribución subtipo intrínseco**
- Basal: 83%
- HER2E: 3%
- LumB: 13%
- Normal: 1%

**Respuesta global (Symmans)**
- pCR: 44.7%
- RCB-I: 12.8%
- RCB-II: 30.9%
- RCB-III: 11.7%
Respuesta a quimioterapia neoadyuvante con docetaxel+carboplatino en cáncer de mama triple negativo

Distribución subtipo intrínseco

Respuesta global (Symmans)

Basal  No-basal

p=0,007

Isabel Echavarría, Tesis Doctoral, UCM 2017
Genomic platforms: potential clinical applications in breast cancer

- Prognostication
- Prediction of response to hormones
- Prediction of response to chemotherapy
- Prediction of response to specific CT drugs
- Prediction of response to targeted therapies