The biology of locally advanced breast cancer: Inflammatory and non-inflammatory

Frédérique Penault-Llorca
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- **Personal financial interests:** Abbvie, Agendia, Astrazeneca, BMS, Genomic Health, Lilly, MERCK lifa, MSD, Myriad, Nanostring, Novartis, Pfizer, Roche

- **Institutional financial interests:** Astrazeneca, BMS, Genomic Health, MSD, Myriad, Nanostring, Roche

- **Non-financial interests:** Abbvie, Astrazeneca, BMS, MSD, Roche (Congress invitations)
Outlines

• Definition
• Diagnosis
• Biology
  – LABC
  – IBC
• Neoadjuvant evaluation
LOCALLY ADVANCED BREAST CANCER
LABC: TNM

- LABC corresponds either to
  - T4a extension to the chest wall,
  - T4B ulceration, ipsilateral satellite skin nodules or skin oedema (including peau d’orange)
  - or both (T4c)
Clarifications of the 7th AJCC

- **Skin involvement**
  - Satellite skin foci must be macroscopically identified and separate from the primary tumor (not contiguous).
  - Direct extension into skin and skin involvement only identified microscopically are NOT categorized as pT4b. Such tumors are categorized based on tumor size.
  - In the *absence of clinical findings of inflammatory carcinoma* (erythema and edema involving 1/3 of breast skin), *dermal lymphatic tumor emboli are NOT categorized as pT4d.*
We therefore propose a simple stratification for the prognostic grouping of patients with stage IV disease based on the presence of inflammatory criteria characteristic of IBC at diagnosis (Stage IVIBC). 

In preparing the next edition of the AJCC staging system, consideration should be given to incorporating an IBC as a prognostic factor within stage IV disease. This modification will allow the UICC/AJCC staging system to more accurately reflect the heterogeneous nature of metastatic breast cancer.
BIOLOGY OF LABC
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørli\textsuperscript{a,b,c}, Charles M. Perou\textsuperscript{a,d}, Robert Tibshirani\textsuperscript{a}, Turid Aas\textsuperscript{f}, Stephanie Geisler\textsuperscript{g}, Hilde Johnsen\textsuperscript{b}, Trevor Hastie\textsuperscript{a}, Michael B. Eisen\textsuperscript{h}, Matt van de Rijn\textsuperscript{i}, Stefanie S. Jeffrey\textsuperscript{j}, Thor Thorsen\textsuperscript{k}, Hanne Quist\textsuperscript{l}, John C. Matise\textsuperscript{e}, Patrick O. Brown\textsuperscript{m}, David Botstein\textsuperscript{n}, Per Eystein Lonning\textsuperscript{o}, and Anne-Lise Børresen-Dale\textsuperscript{b,n}

Departments of \textsuperscript{b}Genetics and \textsuperscript{c}Surgery, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway; \textsuperscript{d}Department of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; Departments of \textsuperscript{a}Health Research and Policy and Statistics, \textsuperscript{g}Genetics, \textsuperscript{i}Pathology, \textsuperscript{j}Surgery, and \textsuperscript{m}Biochemistry and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305; Departments of \textsuperscript{n}Medicine (Section of Oncology), \textsuperscript{k}Surgery, and \textsuperscript{h}Biochemical Endocrinology, Haukeland University Hospital, N-5021 Bergen, Norway; and \textsuperscript{l}Life Sciences Division, Lawrence Orlando Berkeley National Laboratories, and Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720

Contributed by David Botstein, July 17, 2001

Fifty-one of the patients were part of a prospective study on locally advanced breast cancer (T\textsubscript{3}/T\textsubscript{4} and/or N\textsubscript{2} tumors) treated with doxorubicin monotherapy before surgery followed
INFLAMMATORY BREAST CANCER
A RARE AND AGGRESSIVE VARIANT OF LABC
IBC: clinical presentation

- Redness
- Oedema
- Skin dimpling
- Tenderness

Morrow RJ et al Mediators of Inflammation 2017, doi.org/10.1155/2017/4754827
Inflammatory breast cancer

- T4d
- Erythema, “peau d’orange” aspect
- Swelling
- Rare (<5%) and aggressive
IBC: differential diagnosis

- This swollen and inflammatory aspect is also present in inflammatory lesions of the breast
  - Abcess
  - Mastitis
  - Galactophoritis
- Metastatic carcinoma to the breast may produce clinical signs mimicking IBC
  (metastatic from ovarian origin, gastric carcinoma, rarely from squamous cell carcinoma of the tonsil, and lung and pancreatic adenocarcinoma)
Primary versus secondary IBC

• “Primary IBC” = *de novo* development of IBC in a previously normal breast.
• “Secondary IBC” = development of inflammatory skin changes that mimic primary IBC either in a breast that already had cancer or on the chest wall after a mastectomy for non-IBC.
Figure 3: Proposed role of primed breast parenchyma in clinical presentations of breast cancer involving the skin.

T4d inflammatory breast cancer could occur when an inflammatory breast cancer-inducing mutation occurs in a primed inflammatory breast cancer breast (A). T4b could occur when an inflammatory breast cancer-inducing mutation occurs in an unprimed breast (B). Inflammatory recurrence after a non-inflammatory breast cancer could occur when a non-inflammatory breast cancer-inducing mutation occurs in a primed inflammatory breast cancer breast and then recurs as an inflammatory breast cancer mutation in this primed breast later (C). Reproduced by permission of the University of Texas MD Anderson Cancer Center.
Secondary IBC
Chest wall disease

An other biology, probably linked to inflammation, in particular to IL-6 pathways

Courtesy Dr Curigliano
IBC DIAGNOSIS
International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment

S. Dawood¹, S. D. Merajver², P. Viens³, P. B. Vermeulen⁴, S. M. Swain⁵, T. A. Buchholz⁶, L. Y. Dirix⁷, P. H. Levine⁸, A. Lucci⁹, S. Krishnamurthy¹⁰, F. M. Robertson¹¹, W. A. Woodward⁶, W. T. Yang¹², N. T. Ueno¹³ & M. Cristofanilli¹⁴*
- Vanishing of subcutaneous transparency
- Skin thickness
- Breast hyper density
Cutaneous biopsy

- By punch or scalpel (at least 2)
- Aiming to identify dermal embolism
• Presence of numerous dermal tumor emboli in the papillary and reticular dermis of the skin overlying the breast
• But
  – Absent in 25% of IBC (the diagnosis is clinical)
  – In the absence of a clinical presentation of inflammatory carcinoma (i.e. erythema and oedema invading 1/3 of breast skin), dermal tumor emboli ARE NOT CLASSIFIED as pT4d
BIOLOGY OF IBC
NORMAL BREAST PARENCHYMA AS A COMPLICIT PARTNER OR AN INNOCENT BYSTANDER?
Inflammatory breast cancer: unique biological and therapeutic considerations

Lancet Oncol 2015; 16: e568–76

Pattern of broad involvement throughout the breast, but not beyond, despite absence of a clear anatomical barrier

- Molecular signature of IBC are also present in a subset of non IBC (poorer prognosis)

- The unique presentation of IBC might require specific, identifiable changes in the breast parenchyma that occur before the tumour-initiating event (increased breast density, no breast feeding or interrupted BF, no involution...?) ➔ production of CD44+CD49f+CD133+ stem cells that are found in 100% of IBC with a unique distribution (IBC-promoting tissue) “Primed parenchyma”?

- Difference between a local skin limitation and the highly metastatic predisposition
IBC PATHOLOGY: SPECIFIC PROFILES?
Inflammatory Breast Cancer: A Distinct Clinicopathological Entity Transcending Histological Distinction

Lobular histology only in 4,5%.
Histology has no significant effect on survival outcomes in IBC patients, unlike in patients with non-inflammatory breast cancer (n-IBC), indicating the distinct biological behavior of the IBC phenotype.

<table>
<thead>
<tr>
<th></th>
<th>ILC 30 (4,6%)</th>
<th>Mixed 37 (5,6%)</th>
<th>IDC 592 (89,8%)</th>
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<tbody>
<tr>
<td>Age</td>
<td>53,5</td>
<td>52</td>
<td>49</td>
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<tr>
<td>Gr 3</td>
<td>60%</td>
<td>61%</td>
<td>78%</td>
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<td>Stage IV</td>
<td>47%</td>
<td>35%</td>
<td>23%</td>
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<td>Neoadj</td>
<td>57%</td>
<td>62%</td>
<td>76%</td>
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<tr>
<td>3yrs OS</td>
<td>68%</td>
<td>64%</td>
<td>62%</td>
</tr>
</tbody>
</table>

- **Lobular** histology only in 4,5%.
- **Histology has no significant effect on survival outcomes in IBC patients**, unlike in patients with non-inflammatory breast cancer (n-IBC), indicating the distinct biological behavior of the IBC phenotype.
IBC INTRINSIC CLASSIFICATION
Outcomes of patients with inflammatory breast cancer by hormone receptor- and HER2-defined molecular subtypes: A population-based study from the SEER program

Juanjuan Li¹,*, Yue Xia²,*, Qi Wu¹, Shan Zhu¹, Chuang Chen¹, Wen Yang¹, Wen Wei¹ and Shengrong Sun¹

• 403 pts extracted from 2010-2013
• HR+/HER2-: 36.5% - BCSM 16.3% - higher prob of bone mets
• HR+/HER2+: 20.5% - BCSM 9.8%  
• HR-/HER2+: 17% - BCSM 21.7%  
• TN: 26% - BCSM 30.5% - higher prob of lung mets

Multivariate analysis ➔ ER and HER2 positivity associated with better survival ➔ TN subtype: poorer OS and BCSM (p< 0.05).
75% of IBCs belonged to aggressive subtypes (basal-like, ErbB2e, claudin-low and luminal B), vs 53% of non-IBCs.

Luminal A subtype: 19% of IBCs vs 42% of non-IBCs

Differences in gene expression between IBC and non-IBC are dominated by the molecular subtype related differences.
IBC ACTIVATED PATHWAYS
Comprehensive genomic profiling of inflammatory breast cancer cases reveals a high frequency of clinically relevant genomic alterations

Jeffrey S. Ross¹,² · Siraj M. Ali¹ · Kai Wang¹ · Depinder Khaira¹ · Norma A. Palma¹ · Juliann Chmielecki¹ · Gary A. Palmer¹ · Deborah Morosini¹ · Julia A. Elvin¹ · Sandra V. Fernandez³ · Vincent A. Miller¹ · Philip J. Stephens¹ · Massimo Cristofanilli³

A genomically unstable disease with specific patterns of genomic abnormalities

TP53 (62%), MYC (32%), PIK3CA (28%), HER2 (26%), FGFR1 (17%), BRCA2 (15%), and PTEN (15%).

Fig. 1 Distribution of genomic alterations in 53 cases of inflammatory breast cancer

Fig. 2 Genomic alterations in 53 cases of inflammatory breast cancer grouped by biology pathways
High rates of activating HER3 point mutations

Infiltration by numerous CD8+/PD-L1+ lymphocytes

Immune infiltration correlated with an NGS-based estimate of neoantigen exposure (somatic mutation rate and mutant allele frequency) = iScore.

DNA mismatch repair alterations (43%) correlated with high TILS.
IMPLICATION FOR TREATMENT
Classical activated pathways

- Angiogenesis ➔ no benefit of bevacizumab, deceptive results with pazopanib (HER2+)
- HER2 ➔ better survival of HER2+ IBC, HER3 potential target
- EGFR ➔ potential target (7/16 IBC TNBC with pCR)
- mTOR/AKT ➔ potential target
- JAK/STAT (activation of transcription) ➔ potential target
- RHOC GTPASE (motility) ➔ potential target
- Cell cycle/MYC ➔ CD4/6 inhibitors?
- PD-L1 activation ➔ immunotherapy
CONCLUSION
Conclusion

• LABC reflect all the subtypes
• IBC is a rare and aggressive form of breast cancer that remains poorly understood (role of normal breast ? Specific genes ?).
• Low representation of lobular cancer
• More aggressive phenotypes (TNBC 26%, HER2+ 37,5%, 43% HR-)
• Standard tt is neoadjuvant approach
Conclusion ..

- Discriminator genes (IBC vs non IBC) are associated with cell motility, adhesion and angiogenesis
- Activated pathways in IBC tumor tissues can provide potential therapeutic targets in HER/PI3K/mTOR signaling
- Neoadjuvant treatment is the standard/radiation therapy is important
- Potential candidate for immunotherapy
PREDICTION OF RESPONSE TO NEOADJUVANT TREATMENT
Neoadjuvant treatment

Initial concept

- Early introduction of a systemic treatment
  - Locally advanced BC
  - Survival benefit?
  - Conservative surgery
- Meta-analysis NACT vs adjuvant CT
  - No difference in OS/DFS
  - Augmentation of breast conservation rate

Evolution of the concept

- Clinical situation allowing in vivo analysis of tumor response
- Prognosis of pCR in HER2 and TNBC
- Dynamic evaluation
- Treatment adjustment
Different Goals

Before

Prediction of response to NACT

After

Prognosis
Prediction of response to different drugs

During

Treatment adaption
Prediction of response to NACT

Before

Prediction of response to NACT

Histologic subtype
Tumor grade
HR status
HER2 status
SBR grade, proliferation
Intrinsic classification
High TILs
Predictive factors of response to NACT classical biomarkers

Original article

Clinical implications of the intrinsic molecular subtypes of breast cancer

Aleix Aranzabal, Ana A.

pCR TNBC~HER2+ 37-34%
pCR HR+/HER2- 12%

Table 4 Association of the intrinsic subtypes with chemotherapy response across the various pathology-based groups

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2-enriched</th>
<th>Basal-like</th>
<th>P value*</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
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<tr>
<td>All subgroups</td>
<td>838</td>
<td>23 %</td>
<td>281</td>
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<td>168</td>
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</tr>
<tr>
<td>HR+/HER2-</td>
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<td>19</td>
<td>26 %</td>
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P value* = Likelihood ratio tests: adjusting clinical features: age, clinical stage, clinical nodal status and study cohort. Hormone receptors status and HER2 status were also included in “all subgroups.”
Predictive factors of response to NACT intrinsic molecular subtypes by PAM50


Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

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*Likelihood ratio tests: adjusting clinical features: age, clinical stage, clinical nodal status and study cohort. Hormone receptors status and HER2 status were also included in “all subgroups”

pCR basal like ~HER2e 38-37%

pCR lum B 16% > lum A 6%
Predicting outcome: pCR rates based on intrinsic biology following chemotherapy (N=838)

### ALL PATIENTS

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
<th>pCR rate</th>
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</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>293</td>
<td>6%</td>
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<tr>
<td>Luminal B</td>
<td>174</td>
<td>16%</td>
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<tr>
<td>Basal-like</td>
<td>313</td>
<td>37%</td>
</tr>
<tr>
<td>HER2-E</td>
<td>99</td>
<td>38%</td>
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### HR+/HER2-negative (N=451)

<table>
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<th>Subtype</th>
<th>N</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>239</td>
<td>5%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>143</td>
<td>15%</td>
</tr>
<tr>
<td>Basal-like</td>
<td>44</td>
<td>36%</td>
</tr>
<tr>
<td>HER2-E</td>
<td>25</td>
<td>16%</td>
</tr>
</tbody>
</table>

Prat et al. BMC Medicine
2016
PAM50: PAMELA (SOLTI, HER2+)

- pCRB to dual HER2 blockade with lapatinib and trastuzumab in all patients, at the time of surgery, **predicted by PAM50 HER2-E subtype**
- Comparison between the PAM50 HER2-E versus non HER2-E cases to achieve pCRB from dual HER2 blockade with lapatinib and trastuzumab at the time of surgery

Prosigna Breast Cancer Prognostic Gene Signature Assay for use on the nCounter Dx Analysis System is 510(k) cleared and CE-marked for in vitro diagnostic use in the United States and EU, respectively. See territory-specific Package Insert in www.prosigna.com for details. EU label provided in this presentation.
Intrinsic subtype at baseline vs. pCR

Baseline samples (N=151)

pCR

- HER2-E
- Others

Δ=30.6% Δ=24.7%

pCR rate

- HER2-E (n=101)
- LumA (n=22)
- LumB (n=16)
- Basal-like (n=9)
- Normal-like (n=3)

pCR breast: 66.7%

pCR breast/axilla: 40.6%, 10.0%

Prosigna Breast Cancer Prognostic Gene Signature Assay for use on the nCounter Dx Analysis System is 510(k) cleared and CE-marked for in vitro diagnostic use in the United States and EU, respectively. See territory-specific Package Insert in www.prosigna.com for details. EU label provided in this presentation.
Original article

Tumor infiltrating lymphocytes in early breast cancer

Giancarlo Pruneri, MD a,b, *, 1, Andrea Vingiani, MD a, 1, Carsten Denkert, MD c


Clinical Validity and Utility of Tumor-Infiltrating Lymphocytes in Routine Clinical Practice for Breast Cancer Patients: Current and Future Directions

Lironne Wein 1, Peter Savas 1, Stephen J. Luen 1, Balaji Virassamy 1, Roberto Salgado 1,2 and Sherene Loi 1,3, *

Tumor-infiltrating lymphocytes in patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy plus trastuzumab, lapatinib or their combination: A meta-analysis of randomized controlled trials

C. Solinas et al. / Cancer Treatment Reviews 57 (2017) 8–15

C. Solinas a, M. Ceppi b, M. Lambertini c,*, M. Scartozzi d, L. Buisseret a,c,e, S. Garaud a, D. Fumagalli f, E. de Azambuja e, R. Salgado c,g, C. Sotiriou c,e, K. Willard-Gallo a,1, M. Ignatiadis e,1
TILs assessment requires standardized approaches
Lymphocyte predominant breast cancer can be used as a descriptive term for tumors that contain “more lymphocytes than tumor cells.” However, the thresholds vary between 50% and 60% stromal lymphocytes.
# TILs as Predictive factors of response of NACT

**Table 2**

Neoadjuvant trials in which TILs have been assessed and their prognostic values. Adapted from Savas et al. [114].

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatments</th>
<th>Subtypes</th>
<th>n</th>
<th>Outcome</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td>GeparDuo [65]</td>
<td>Doxorubicin</td>
<td>All</td>
<td>218</td>
<td>&gt;60% sTILs: pCR 41.7% &lt;60% sTILs: pCR 9.3%</td>
<td>OR 1.38 of pCR per 10% iTILs (95% CI 1.08—1.78, P = 0.012)</td>
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<tr>
<td></td>
<td>Docetaxel</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<tr>
<td>GeparTrio [65]</td>
<td>Doxorubicin</td>
<td>All</td>
<td>840</td>
<td>&gt;60% sTILs: pCR 40% &lt;60% sTILs: pCR 13.9%</td>
<td>OR 1.21 of pCR per 10% iTILs (95% CI 1.08—1.35, P = 0.001)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
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<td>Cyclophosphamide</td>
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<td></td>
<td>Vinorelbine</td>
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<td></td>
<td>Capcitabine</td>
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<tr>
<td>GeparQuattro [70]</td>
<td>Epirubicin</td>
<td>HER2+</td>
<td>156</td>
<td>&gt;50% sTILs: pCR 47.4% &lt;50% sTILs: pCR 31.7%</td>
<td>OR 1.16 of pCR per 10% sTILs (95% CI 1.01—1.32, P = 0.038)</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<td></td>
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<td>Capcitabine</td>
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<td>Trastuzumab</td>
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<tr>
<td>GeparQuinto [67]</td>
<td>Epirubicin</td>
<td>ER+ and TNBC</td>
<td>313</td>
<td>&gt;60% sTILs: pCR 36.6% &lt;60% sTILs: pCR 14.3% (P &lt; 0.001)</td>
<td>OR 1.2 of pCR per 10% sTILs (95% CI 1.0—1.3, P = 0.01)</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<td>Everolimus</td>
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<tr>
<td>GeparSixto [66]</td>
<td>Paclitaxel</td>
<td>HER2+ and TNBC</td>
<td>580</td>
<td>&gt;60% sTILs: pCR 59.9% &lt;60% sTILs: pCR 33.8% (P &lt; 0.001)</td>
<td>OR 1.2 of pCR per 10% sTILs increase (95% CI 1.11—1.29, P &lt; 0.001)</td>
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<tr>
<td></td>
<td>Liposomal</td>
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<td>Paclitaxel Liposomal</td>
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<td></td>
<td>Paclitaxel Carboplatin</td>
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<td>Bevacizumab</td>
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<td></td>
<td>Trastuzumab</td>
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<tr>
<td>EORTC 10994 and BIG 00—01 [68]</td>
<td>Paclitaxel</td>
<td>ER−</td>
<td>111</td>
<td>High gTILs: pCR 74.2% Low gTILs: pCR 31.3%</td>
<td>OR 6.42 of pCR for high versus low gTILs (95% CI 2.08—19.83, P = 0.001)</td>
</tr>
<tr>
<td>CHER-LOB [69]</td>
<td>Docetaxel</td>
<td>HER2+</td>
<td>105</td>
<td>&gt;60% sTILs: pCR 59% &lt;60% sTILs: pCR 27% (P &lt; 0.015)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; gTIL, gene-expression surrogate TIL; H&E, haematoxylin and eosin; iTIL, intratumoural TIL; OR, odds ratio; pCR, pathological complete response; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte.

**Table 2**

Neoadjuvant trials in which TILs have been assessed and their prognostic values. Adapted from Savas et al. [114].

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatments</th>
<th>Subtypes</th>
<th>n</th>
<th>Outcome</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparDuo [65]</td>
<td>Doxorubicin</td>
<td>All</td>
<td>218</td>
<td>&gt;60% sTILs: pCR 41.7%</td>
<td>OR 1.38 of pCR per 10% iTILs (95% CI 1.08–1.78, (P = 0.012))</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td></td>
<td></td>
<td>&lt;60% sTILs: pCR 9.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GeparTrio [65]</td>
<td>Doxorubicin</td>
<td>All</td>
<td>840</td>
<td>&gt;60% sTILs: pCR 40%</td>
<td>OR 1.16 of pCR per 10% sTILs (95% CI 1.01–1.32, (P = 0.038))</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td></td>
<td></td>
<td>&lt;60% sTILs: pCR 13.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GeparQuattro [70]</td>
<td>Epirubicin</td>
<td>HER2+</td>
<td>156</td>
<td>&gt;50% sTILs: pCR 36.6%</td>
<td>OR 1.2 of pCR per 10% sTILs (95% CI 1.0–1.3, (P = 0.01))</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td>&lt;50% sTILs: pCR 14.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GeparQuinto [67]</td>
<td>Epirubicin</td>
<td>ER+ and TNBC</td>
<td>136</td>
<td>&gt;50% sTILs: pCR 23.6%</td>
<td>OR 1.2 of pCR per 10% sTILs increase (95% CI 1.11–1.29, (P &lt; 0.001))</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td>&lt;50% sTILs: pCR 14.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taxane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Everolimus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GeparSixto [66]</td>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td></td>
<td>OR 1.2 of pCR for &gt;60% sTILs         (95% CI 1.76–4.02, (P &lt; 0.001))</td>
</tr>
<tr>
<td></td>
<td>Liposomal</td>
<td></td>
<td></td>
<td></td>
<td>Significant test for interaction</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td></td>
<td>between increased TILs and</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td></td>
<td></td>
<td></td>
<td>response to carboplatin therapy</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td></td>
<td>OR 2.66 of pCR for &gt;60% sTILs       (95% CI 2.08–19.83, (P = 0.001))</td>
</tr>
<tr>
<td>EORTC 10994 and</td>
<td>FEC</td>
<td>ER−</td>
<td>111</td>
<td>High gTILs: pCR 74.2%</td>
<td>OR 6.42 of pCR for high versus low gTILs</td>
</tr>
<tr>
<td>BIG 00–01 [68]</td>
<td>Docetaxel</td>
<td></td>
<td></td>
<td>Low gTILs: pCR 31.3%</td>
<td>(95% CI 2.08–19.83, (P = 0.001))</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>HER2+</td>
<td>105</td>
<td>&gt;60% sTILs: pCR 59%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td>&lt;60% sTILs: pCR 27%</td>
<td></td>
</tr>
</tbody>
</table>

ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; gTIL, gene-expression surrogate TIL; H&E, haematoxylin and eosin; iTIL, intratumoural TIL; OR, odds ratio; pCR, pathological complete response; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte.

High TILs is a reliable biomarker of pathological complete response across ALL BC subtypes.
Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer


Table 1. HR deficiency status and association with response to platinum-containing therapy

<table>
<thead>
<tr>
<th>Responder</th>
<th>Deficient number (% response)</th>
<th>Nondeficient number (% response)</th>
<th>OR (95% CI) Reference = nondeficient</th>
<th>Logistic P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCB 0/1 = No</td>
<td>16 (66%)</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCB 0/1 = Yes</td>
<td>34 (68%)</td>
<td>6 (30%)</td>
<td>4.96 (1.61-15.3)</td>
<td>0.0036</td>
</tr>
<tr>
<td>pCR = No</td>
<td>29</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCR = Yes</td>
<td>21 (42%)</td>
<td>2 (10%)</td>
<td>6.52 (1.36-31.2)</td>
<td>0.0058</td>
</tr>
</tbody>
</table>

Cisplatin Trials Cohort (N = 50)

<table>
<thead>
<tr>
<th>Responder</th>
<th>Deficient number (% response)</th>
<th>Nondeficient number (% response)</th>
<th>OR (95% CI) Reference = nondeficient</th>
<th>Logistic P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCB 0/1 = No</td>
<td>14</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCB 0/1 = Yes</td>
<td>15 (51.7%)</td>
<td>2 (9.5%)</td>
<td>10.18 (2.00-51.89)</td>
<td>0.0011</td>
</tr>
<tr>
<td>pCR = No</td>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCR = Yes</td>
<td>8 (27.5%)</td>
<td>0 (0%)</td>
<td>17.00 (1.91-2,249)</td>
<td>0.0066</td>
</tr>
</tbody>
</table>

*Based on Firth's penalized profile likelihood.

Clin Cancer Res 2016; 22 (15), 3764
Post treatment specimen

- a standardized procedure of gross handling will be provided to the local pathologist (sampling will depend on the presence or not of a lesion and on the size of the specimen)

- a standardized histologic report will be provided to the pathologists (presence or not of tumor cells)

- inking of the tumors’ margins is mandatory
Different patterns of pathological response

- Complete pathological response
- Concentric shrinking
  - Same cellularity
- Heterogeneity
- Decrease in cellularity
- Tumor fragmentation

No change resistance
Residual Breast Cancer Burden:
The Pathological Variables Included Bidimensional Diameters of the Primary Tumor Bed (d1, d2), the Proportion of Primary Tumor Area Containing Invasive Carcinoma (finv), the Number of Positive Lymph Nodes (LN), and the Diameter of the Largest Nodal Metastasis

\[ RCB = 1.4 \left( f_{inv} d_{prim} \right)^{0.17} + \left[ 4 \left( 1 - 0.75^{LN} \right) d_{met} \right]^{0.17} \]

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Symmans W F et al. JCO 2007;25:4414-4422
Residual Cancer Burden

http://www.mdanderson.org/breastcancer_RCB.

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

- Primary Tumor Bed Area: \[ \square (\text{mm}) \times \square (\text{mm}) \]
- Overall Cancer Cellularity (as percentage of area): \[ \square (\%) \]
- Percentage of Cancer That Is \textit{in situ} Disease: \[ \square (\%) \]

(2) Lymph Nodes

- Number of Positive Lymph Nodes: \[ \square \]
- Diameter of Largest Metastasis: \[ \square (\text{mm}) \]

Residual Cancer Burden: \[ \square \]
Residual Cancer Burden Class: \[ \square \]
Survival according to the Residual Cancer Burden
When we don’t have a ypT0/is ypN0

Before

After
Biomarkers of residual disease after neoadjuvant therapy for breast cancer

Frederique Penault-Llorca¹,² and Nina Radosevic-Robin¹,²

BIOMARKERS AFTER (PROGNOSTIC AND PREDICTIVE)
### Table 6: Most promising biomarkers assessed on post-NAT residual tissue

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Biomarker</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+</td>
<td>Ki67 index</td>
<td>Prognosis&lt;sup&gt;58,59,63&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PEPI score</td>
<td>Prognosis&lt;sup&gt;60&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Loss of ER positivity&lt;sup&gt;70,73,79&lt;/sup&gt;</td>
<td>Prognosis/Treatment adaptation</td>
</tr>
<tr>
<td>HER2+</td>
<td>Loss of HER2 positivity&lt;sup&gt;72,74&lt;/sup&gt;</td>
<td>Treatment adaptation</td>
</tr>
<tr>
<td></td>
<td>Gain of ER positivity&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Treatment adaptation</td>
</tr>
<tr>
<td></td>
<td>TIL quantity/profile</td>
<td>Prognosis&lt;sup&gt;108&lt;/sup&gt;</td>
</tr>
<tr>
<td>TNBC</td>
<td>Gene mutations</td>
<td>Treatment adaptation</td>
</tr>
<tr>
<td></td>
<td>TIL quantity/profile</td>
<td>Prognosis&lt;sup&gt;120&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor; HER2+, HER2-positive; HR+, hormone receptor-positive; NAT, neoadjuvant therapy; PEPI, preoperative endocrine prognostic index; TIL, tumour-infiltrating lymphocytes; TNBC, triple negative breast cancer.
# ER+/HER2- BC: the PEPI score

**Outcome Prediction for Estrogen Receptor–Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics**

Matthew J. Ellis, Yu Tao, Jingqin Luc, Roger A’Hern, Dean B. Evans, Ajay S. Bhatnagar, Hilary A. Chaudri Ross, Alexander von Kameke, William R. Miller, Ian Smith, Wolfgang Eiermann, Mitch Dowsett

---

## Table 4. The preoperative endocrine prognostic index

<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS</th>
<th>BCSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>T3/4</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Positive</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Ki67 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%–2.7% (0–1†)</td>
<td>1.7</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt;2.7%–7.3% (1–2†)</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt;7.3%–19.7% (2–3†)</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>&gt;19.7%–53.1% (3–4†)</td>
<td>2.9</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;53.1% (&gt;4†)</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>ER status, Allred score</td>
<td>2.8</td>
<td>7.0</td>
</tr>
<tr>
<td>0–2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3–8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
IF I HAVE 5 MINUTES....
ER+, HER2- EBC: Yes, we have molecular biology!
4 signatures, 4 different worlds

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Oncotype DX</th>
<th>MammaPrint</th>
<th>Prosigna</th>
<th>EndoPredict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre or postmenopausal HR+, HER2</td>
<td>Pre or postmenopausal ER+/- Node -/+ (1-3) early stage</td>
<td>Postmenopausal HR+, HER2- Node -/+ (1-3) tumor &lt;5cm</td>
<td>Postmenopausal HR+, HER2- Node -/+</td>
<td></td>
</tr>
<tr>
<td>Pre or postmenopausal ER+/- Node -/+ early stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Gene number**: 16 + 5 reference
- **Patient Type**
  - Pre or postmenopausal HR+, HER2
  - Node -/+ (1-3) early stage
- **Individual Risk**: Yes
- **Classification**: Continuous score 0-100; reports individualised
- **Prognostic**: Yes level 1A
- **Predictive of chemotherapy benefit**: Yes level 1A
- **Technology**: Quantitative RT-PCR

**Gene number**: 70

**Patient Type**
- Pre or postmenopausal HR+, HER2
- Node -/+ (1-3) early stage
- **Individual Risk**: No
- **Classification**: Low, High
- **Prognostic**: Yes level 1A
- **Predictive of chemotherapy benefit**: No clinical evidence
- **Technology**: Microarray

**Gene number**: 50 + 8 reference

**Patient Type**
- Postmenopausal HR+, HER2- Node -/+ (1-3) Stage I to IIIA BC
- **Individual Risk**: Yes
- **Classification**: Continuous score reported as Low, Inter, High
- **Prognostic**: Yes level 1B
- **Predictive of chemotherapy benefit**: No clinical evidence
- **Technology**: direct mRNA hybridization

**Gene number**: 8 + 3 reference

**Patient Type**
- Postmenopausal HR+, HER2- Node -/+ (1-3) early stage
- **Individual Risk**: Yes
- **Classification**: Low, High
- **Prognostic**: Yes level 1B
- **Predictive of chemotherapy benefit**: No clinical evidence
- **Technology**: Quantitative RT-PCR

References:
Centralized tests
MammaPrint
(Agendia, NL)

HR+ ET HR- / HER2-, T < 5cm, N ≤ 3

Fresh frozen=> FFPE DNA array
70 GENES
CELL CYCLE/ PROLIFERATION SIGNAL TRANSUDUCTION INVASION, METASTASIS, ANGIOGENESIS

« CENTRALIZED » TEST

RECENTLY ADAPTATED TO FFPE

Group of genes (« signatures »)
EARLY RECURRENCE (Dg < 5 ans) PROGNOSTIC
GOOD SIGNATURE :
LOW RISK
POOR SIGNATURE :
HIGH RISK
• Level of Evidence 1A for the clinical utility of MammaPrint® in the c-High group
• C-High / g-Low (including 48% N +) have a 5-year survival (DMFS)> 94% (with or without CT)
• In the whole population: 14% reduction in CT prescription
• In the c-High population: 46% CT reduction
OncotypeDX (Genomic Health, USA)

**HR+ / HER2- , T1-3, N-/N+ FFPE specimens**

**qRT-PCR**

**21 GENES**

PROLIFERATION, OESTROGENE, HER2, INVASION (16 GENES) + REFS (5 GENES)

« CENTRALIZED » TEST

(recurrence score) RS

Late recurrence (10 years)

Benefit from adjuvant TT

PROGNOSTIC AND PREDICTIVE

**LOW RISK :**

+ HORMONOTHERAPY / - CHEMOTHERAPY

**INTERMEDIATE RISK :**

DISCUSSION

**HIGH RISK :**

+ HORMONOTHERAPY / + CHEMOTHERAPY
# OncotypeDX Summary

## PROGNOSTIC

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-B14</td>
<td>ER+, pN-, Tam alone</td>
<td>Paik, NEJM 2004</td>
</tr>
<tr>
<td>NSABP-B20</td>
<td>ER+, pN-, Tam alone</td>
<td>Mamounas, JCO 2010</td>
</tr>
<tr>
<td>ATAC</td>
<td>ER+, pN- &amp; pN+, Tam or anast</td>
<td>Dowsett, JCO 2010</td>
</tr>
<tr>
<td>ECOG2197</td>
<td>ER+, pN+, AC or AT</td>
<td>Goldstein, JCO 2008</td>
</tr>
<tr>
<td>PACS 01</td>
<td>HR+, pN+, Chemo &amp; HT</td>
<td>Penault-Llorca, ASCO 2014</td>
</tr>
<tr>
<td>TAILORx</td>
<td>ER+, pN0, HT, or HT CT non inferiority</td>
<td>Sparano; NEJM 2018</td>
</tr>
</tbody>
</table>

- Level of evidence Ia for prognosis and prediction of benefit from hormonal treatment for RS<26

## PREDICTION

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-B20</td>
<td>ER+, pN-, Tam alone or TAM+ CT</td>
<td>Paik, JCO 2006</td>
</tr>
<tr>
<td>SWOG-8814</td>
<td>ER+, pN+, Tam + CT</td>
<td>Albain, JCO 2010</td>
</tr>
<tr>
<td>First generation signatures</td>
<td>Prognostic</td>
<td>Predictive</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>MammaPrint®</strong>&lt;br&gt;All BC, N0-N1-3&lt;br&gt;70 genes signature&lt;br&gt;2 categories (low &amp; high risk)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Oncotype Dx®</strong>&lt;br&gt;ER+, HER2- BC, N0-N1-3&lt;br&gt;21 genes signature&lt;br&gt;Recurrence score RS&lt;br&gt;3 categories</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Clinical validation**

**MammaPrint®**: LOEIA Prospective validation for **prognostic** value of low genetic in clinically high risk: 5yrs DMFS >94% (48%N+)<br>14% reduction in CT prescription up to 46% in high clinical risk

**Oncotype Dx®**: LOEIA prospective validation for RS <26 **prognosis**

LO1B validated retrospectively in prospective clinical trials (prediction chemotherapy benefit), prospective clinical validation ongoing for prediction.
Decentralized tests
Include T & N
EndoPredict
(Sividon, GE)

HR+ / HER2-, T1-2, N0

FFPE
qRT-PCR
8 GENES SIGNATURE
PROLIFERATION, OESTROGENES

« LOCAL » TEST
(SPECIAL EQUIPMENT IS REQUIRED)

SCORE OF RECURRENCE EP SCORE
LATE AND EARLY RECURRENTS
(5 & 10 YEARS)
PROGNOSIS
LOW RISK
HIGH RISK

UBE2C
BIRC5
DHCR7

STC2
AZGP1
IL65T
RBBP8
MGP
## Endopredict summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROGNOSTIC</strong></td>
<td>more than 2000 patients</td>
<td></td>
</tr>
<tr>
<td>ABCSG 06 et 08</td>
<td>ER+, HER2-, pN- or pN+</td>
<td>Filipits, CCR 2011</td>
</tr>
<tr>
<td></td>
<td>Tam 5 yrs or Sequential 5 yrs</td>
<td></td>
</tr>
<tr>
<td>ABCSG 06 et 08</td>
<td>Idem</td>
<td>Dubsky, BJC 2013</td>
</tr>
<tr>
<td></td>
<td>but focus on late recurrences</td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>ER+, HER2-, pN- or pN+, menop</td>
<td>Sestak, JNCI 2013</td>
</tr>
<tr>
<td></td>
<td>Tam 5 yrs or AA 5 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focus on late recurrence</td>
<td>Buus, JNCI 2016</td>
</tr>
<tr>
<td>GEICAM 9906</td>
<td>ER+, HER2 -, menop or not</td>
<td>Martin, BCR 2014</td>
</tr>
<tr>
<td></td>
<td>6 FEC or 4 FEC then 6 hebdo P</td>
<td></td>
</tr>
<tr>
<td><strong>PREDICTION</strong></td>
<td></td>
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<tr>
<td></td>
<td>No studies...</td>
<td></td>
</tr>
</tbody>
</table>

Retrospective studies from prospective trials LOE Ib
Prosigna (PAM50)  
(NanoString Technology, USA)  

**IDENTIFICATION OF « MOLECULAR3 SUBTYPES »**  
(LumA, LumB, HER2-enrichi, Basal)  

**FFPE DNA ARRAY WITH BARCODES**  
(1 gene = 1 barcode)  

**50 GENES**  

**« LOCAL » TEST**  
(SPECIAL EQUIPMENT IS REQUIRED)  

**LATE AND EARLY RECURRENCES**  
(5 & 10 YEARS)  

**PROGNOSIS**  

- **LOW RISK (ROR)**  
- Intermediate risk  
- **HIGH RISK (ROR)**  

Two risk scales  
N0  
N 1-3  

Tumor size  
\( \leq 2\text{cm} \)  
\( >2\text{cm} \)  

Subtypes have distinct gene expression.
## PROSIGNA Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROGNOSTIC près de 2000 patientes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>ER+, HER2-, pN- or pN+, menop</td>
<td>Sestak, JNCI 2013</td>
</tr>
<tr>
<td></td>
<td>Tam 5 yrs or AA 5 yrs</td>
<td></td>
</tr>
<tr>
<td>ABCSG 08</td>
<td>ER+, HER2-, pN- or pN+, menop receiving HormonoT</td>
<td>Filipits, CCR 2014</td>
</tr>
<tr>
<td>Pooled Analysis</td>
<td>Idem pN- &amp; pN+</td>
<td>Sestak, JCO 2014</td>
</tr>
<tr>
<td><strong>PREDICTION</strong></td>
<td><strong>No studies ...</strong></td>
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</table>

Retrospective studies from prospective trials LOE Ib
<table>
<thead>
<tr>
<th>Second generation signatures</th>
<th>Prognostic</th>
<th>Predictive</th>
<th>Technical validation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prosigna®</strong>&lt;br&gt;ER+, HER2- BC, N0-N1-3 50 genes signature&lt;br&gt;Includes size and N</td>
<td>++</td>
<td>++</td>
<td>YES N-Counter® technology Dedicated instrument</td>
</tr>
<tr>
<td><strong>Endopredict®</strong>&lt;br&gt;ER+, HER2- BC, N0-N1-3 8 genes signature&lt;br&gt;Includes size and N</td>
<td>++</td>
<td>++</td>
<td>YES RT-PCR Dedicated instrument</td>
</tr>
</tbody>
</table>

**Clinical validation**

**Prosigna®:** LOE1B Validated retrospectively in prospective clinical trials of HT<br>Prognosis<br>Late recurrences (after 5 years)

**Endopredict®:** LOE1B Validated retrospectively in prospective clinical trials of HT<br>Prognosis<br>Late recurrences (after 5 years)
NEW AJCC TNM AND SIGNATURES
8th Edition – “Genomic panels...have become as or more important than the anatomic extent of disease to define prognosis”*

2010-

*AJCC 8th Edition, pgs 617, 621, 624

2018 and
Oncotype DX Breast Recurrence Score® result <11 may result in lower stage than would be recorded using biologic and anatomic factors alone.

### Stage IB
- T1, Gr 1, PR-, N0, M0, ER+, HER2-
- T1, Gr 3, PR+, N0, M0, ER+, HER2-
- T2, Gr 1-2, PR+, N0, M0, ER+, HER2-

### Stage IIA
- T1, Gr 3, PR-, N0, M0, ER+, HER2-
- T2, Gr 1, PR-, N0, M0, ER+, HER2-
- T2, Gr 3, PR+, N0, M0, ER+, HER2-

### Stage IIB
- T2, Gr 2, PR-, N0, M0, ER+, HER2-

### Stage IIIA
- T2, Gr 3, PR-, N0, M0, ER+, HER2-

8th ed. Prognostic Stage using T,N,M, grade, ER, PR, HER2

If Recurrence Score result <11, all of these patients are classified as Stage IA.
Breast Cancer classification in practice

**ER+**
- **Luminal A**
  - ER $\geq 10\%$
  - Ki67 $\leq 14\%$
  - PR $\geq 20\%$
  - HER2 -
  - Tubular, Cribriform, IDC grade 1, Mucinous, ILC grade 1

- **Luminal B**
  - ER $\geq 10\%$
  - Ki67 $> 14\%$
  - PR $< 20\%$
  - HER2 + possible
  - Micropapillary, ILC grade 2 & 3, IDC grade 2 et3, Mucinous type B, Neuroendocrine

- **HER2**
  - ER $< 10\%$
  - PR $< 10\%$
  - HER2 3+
  - High Grade
  - CCI grade 2 & 3, Micropapillaire

- **Molecular apocrine**
  - AR +
  - EGFR+/-
  - HER2 +/-
  - Apocrine, CCI grade 3

- **Triple-negative**
  - ER$<10\%$
  - PR$<10\%$
  - HER2-
  - Ki67 $> 14\%$
  - High grade
  - Medullairy, Métaplasique, CCI & CLI grade 3

**ER-**
- **Low frequency of mutations**
- **Mutation in numerous genes**
- **Most frequently mutated genes:**
  - *PIK3CA*, *MAP3K1*, *MAP2K4*

**TILs**
- Proliferation
  - Mutations of *TP53* or *PIK3CA*
  - Genomic instability
  - Intratumor heterogeneity
  - BRCAAness

**Translocations**
- *(ETV6; NTRK3)*
- *(MYB; NF1B)*
- Mutations *IDH2*

References:
Clinical implications of the intrinsic molecular subtypes of breast cancer

Aleix Prat a,b, c, *, Estela Pineda a, b, Barbara Adamo a, b, Patricia Galván a, c, Aranzazu Fernández a, b, Lydia Gaba a, b, Marc Díez a, b, Margarita Viladot a, b, Ana Arance a, b, Montserrat Muñoz a, b

a Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
b Medical Oncology Department, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain
c Translational Genomics Group, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

• **ER+, HER2- EBC:** Luminal A and B subtypes predict 10-year outcome regardless of previous systemic treatment as well as residual risk of distant recurrence after 5 years of endocrine therapy.

• **HER2+:** the 4 main intrinsic subtypes can be found
  - HER2+/HER2-enriched benefit the most from neoadjuvant trastuzumab, or dual HER2 blockade with trastuzumab/lapatinib, in combination with CT
  - HER2+/Luminal A disease have a relative better outcome compared to the other subtypes.
Clinical implications of the intrinsic molecular subtypes of breast cancer

Aleix Prat a,b,c, Estela Pineda a,b, Barbara Adamo a,b, Patricia Galván a,c, Aranzazu Fernández a,b, Lydia Gaba a,b, Marc Díez a,b, Margarita Viladot a,b, Ana Arance a,b, Montserrat Muñoz a,b

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- **triple-negative breast cancer** (TNBC), of 70-80%
  Basal-like ➔ from a biological perspective, should be considered a cancer-type by itself.
- Distinction between **Basal-like** versus **non-Basal-like** within TNBC predict
  - survival following (neo)adjuvant multi-agent chemotherapy,
  - bevacizumab benefit in the neoadjuvant setting (CALGB40603)
  - docetaxel vs. carboplatin benefit in first-line metastatic disease (TNT study).