Prognostic and Predictive Factors
Prognostic and Predictive Factors

- **Versions 2002–2017:**
  Costa / Fersis / Friedrichs / Gerber / Göhring / Harbeck / Janni / Liedtke / Loibl / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiß / Simon / Solomayer / Thomssen / Witzel / Harbeck / Rody

- **Version 2018:**
  Fasching / Wöckel

**Data bases screened**

**Guidelines screened**


NCCN 2016: www.nccn.org


Definition

A **Prognostic Factor** is any parameter available at the time of interest (e.g. primary diagnosis) that correlates with disease-free or overall survival, in the absence of any therapy and, as a result, is able to correlate with the natural history of the disease.

A **Predictive Factor** is any parameter associated with response to a given therapy.

* As mentioned in this context represent markers of BC recurrence
“Low absolute risk implies low absolute benefit”


Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Category</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>Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility</td>
</tr>
</tbody>
</table>


Requirements for a Marker-Based Test to Reach Level IB Evidence

- 1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial ... for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.
- 2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.
- 3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.
- 4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.

McShane & Hayes, J Clin Oncol 30: 4223-4232, 2012

**Prognostic Factors I in Early Breast Cancer**

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Nodal status</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Histological tumor type (colloid, mucinous, tubular etc.)</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Grade (Elston &amp; Ellis)</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Age</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Peritumoral lymphatic vessel and vascular invasion (L1 V1)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>pCR after NACT* in (HR+/G3, HER2+, TN)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Margins (Resection status)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>

* NACT = Neoadjuvant Chemotherapy


**Statement: Obesity**

3. Houssami, N., et al., The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving
Reproducibility

- ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)
- Grading: concordance central vs local is 68% (Plan B, JCO 2016)
- HER2: frequency of false-positive test results 6% (ASCO/CAP JCO 2013)
- Impact of routine pathologic review in N0 BC: 20% changes: grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)
- pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)
- Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)


Critical Issues Regarding LoEs for Biomarkers

It needs to be emphasized that the *levels of evidence* obtained by Oxford-criteria and CTS-criteria cannot be directly compared.

The prospectively-planned retrospective validation of a biomarker (CTS level 1) may be biased by an insufficient number of clinical trial samples used for the biomarker analysis.

This sample collection may not represent the reported outcome of the clinical trial. An optimal percentage of sample needed from clinical trials needed for optimal biomarker validation has not yet been established *

---

**ER/PR**


**HER2**


**Ki-67**


Post-treatment Ki-67:


labeling index after short-term presurgical tamoxifen in women with ER-positive breast cancer. Annals of Oncology, 2010

**uPA/PAI-1**


Prognostic Factors II in Early Breast Cancer

**ER/PR**

**HER2**

**Ki-67**


uPA/PAI-1


## Commercially Available Molecular Tests

<table>
<thead>
<tr>
<th>Provider</th>
<th>70 gene signature (MammaPrint®)</th>
<th>21 gene Recurrence score (Oncotype DX®)</th>
<th>8 gene signature (Endopredict®)</th>
<th>PAM 50 (Prosigna®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of assay</td>
<td>fresh frozen</td>
<td>21-gene recurrence score</td>
<td>11-gene assay</td>
<td>50-gene assay</td>
</tr>
<tr>
<td>Type of tissue</td>
<td>(technical validation for FFPE available)</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td>Technique</td>
<td>Microarrays for RNA</td>
<td>qRT-PCR</td>
<td>q-RT-PCR</td>
<td>Direct hybridization</td>
</tr>
<tr>
<td>Central lab</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Indication and population studied</td>
<td>prognostic N-/+, &lt; 70 Jahre</td>
<td>prognostic N-/+, ER+, endocrine treated</td>
<td>prognostic (pre-) postmenopausal N-/+, ER+, HER2-, endocrine treated</td>
<td>prognostic postmenopausal N-/+, ER+, HER2-, endocrine treated</td>
</tr>
<tr>
<td>Clinical Validation</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Registration</td>
<td>FDA clearance as <strong>In Vitro Diagnostic Multivariate Index Assay (IVDxIA)</strong> CE-Mark (fresh tissue and FFPE)</td>
<td>Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab</td>
<td>CE-Mark</td>
<td>CE-Mark FDA 510(k) Clearance</td>
</tr>
</tbody>
</table>

### Endopredict


**MammaPrint**


10. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to
Oncotype


Prosigna (ROR / PAM50)

Multiple assays
signatures for breast cancer in TransATAC. SABCS 2016: S6-05
Endopredict


MammaPrint


Prosigna (ROR / PAM50)


Multiple assays


### Prognosis in the low-risk group is for both tests favorable (94% 5-Jahres DFS with adjuvant endocrine therapy only)

<table>
<thead>
<tr>
<th></th>
<th>TailorX</th>
<th>PlanB</th>
<th>MINDACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period</td>
<td>Median 69 mo</td>
<td>5-yr-DFS</td>
<td>Median 60 mo</td>
</tr>
<tr>
<td>Proportion of low risk patients</td>
<td>16%</td>
<td>15.3%</td>
<td>23.2% (high clinical and low genomic risk)</td>
</tr>
<tr>
<td>(study population suitable for chemotherapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test failure rate</td>
<td>n.r.</td>
<td>2.9%</td>
<td>26% (fresh frozen tissue)</td>
</tr>
<tr>
<td>Proportion of intermediate risk patients (applies only to OncotypeDX)</td>
<td>67.3%</td>
<td>60.4%</td>
<td>n.a.</td>
</tr>
<tr>
<td>10-yr-follow up</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

---

**Mammaprint**


**Onkotype DX**


**Several tests**

**Prognostic Factors III in Early Breast Cancer**

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE$_{2009}$</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tumor cells (DTC, in bone marrow)</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Circulating tumor cells (CTC, in blood, Cell Search®)</td>
<td>I</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>CTC before NACT (regarding OS, DDFS, LRFI)</td>
<td>I$^a$</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Therapy decisions based on CTC phenotypes</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Multigene assays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EndoPredict® (N0-1, HR+, Her2 -)</td>
<td>I</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>Prosigna® (N0-1, HR+, Her2 -)</td>
<td>I</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>MammaPrint® (70 gene signature) (N0-1)</td>
<td>I</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>Oncotype DX® (N0-1, HR+ HER2-, 5 years)</td>
<td>I</td>
<td>A</td>
<td>+*</td>
</tr>
</tbody>
</table>

* Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making
$^a$ Validated clinical data only available for this assay
$^b$ Cuzick et al., J Clin Oncol 29: 4273-4278, 2011

**DTC**


**CTC**


**Oncotype**


Endopredict


6. Dubsky, San Antonio 2017


Prosigna (ROR, PAM50)
10. Sestak I, Cuzick J, Dowsett M, et al. Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen

Mammaprint
Neoadjuvant Systemic Chemotherapy Response Prediction I

<table>
<thead>
<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE&lt;sub&gt;2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative ER and PgR status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>B</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>B</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>

**TIL**


7. Denkert et al, SABCS 2016

---

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene signature (Mammaprint, Endopredict Oncotyp, Dx,PAM50 Prosigna&lt;sup&gt;§&lt;/sup&gt;)</td>
<td>II</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Tumor infiltrating lymphocytes*</td>
<td>I</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>gBRCA in TNBC</td>
<td>II</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>§</sup> validated clinical data only available for this assay  
<sup>*</sup> defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up >50% of stroma area)
PIK3CA


Predictive Factors – Endocrine Therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Oxford LoE</th>
<th>ORC</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>  ER/PgR status</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>  IHC staining intensity (ER/PgR)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>  CYP2D6 polymorphism</td>
<td>2b</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ovarian ablation</strong></td>
<td>1c</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>  Menopausal status</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors vs. Tamoxifen</strong></td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>  Menopausal status</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>  ER/PgR/HER2 as single markers</td>
<td>1c</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>  Lobular subtype</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>  Ki-67 high (published cutoffs &gt; 11% and &gt;14%)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>  Obesity (BMI &gt;30 kg/m²)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>


## Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;Dx2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LoE&lt;sub&gt;Meta2009&lt;/sub&gt;</td>
<td>(&lt;sup&gt;5&lt;/sup&gt; CTS)</td>
<td></td>
</tr>
<tr>
<td>Anti-HER2-Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uPA / PAI-1 (Femtelle&lt;sup&gt;®&lt;/sup&gt;) ELISA</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>21 gene recurrence score (Oncotype DX&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>1&lt;sup&gt;5&lt;/sup&gt;</td>
<td>B&lt;sup&gt;®&lt;/sup&gt;</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<sup>5</sup> Validated clinical data only available for this assay

### Onkotype


### uPA/PAI-1


Prognostic Factors – Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating tumor cells (CTC in blood, Cell Search®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis at baseline</td>
<td>I</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early response assessment (3w)</td>
<td>I</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype</td>
<td>I</td>
<td>A</td>
<td>-*</td>
</tr>
</tbody>
</table>

* Study participation recommended


CTC
# Exome/whole Gene testing of Panel Genes or the whole Genome (Genomic Profile Tests)

<table>
<thead>
<tr>
<th>Local Pathology based*, **, ***</th>
<th>Foundation one*</th>
<th>Molecular Health Guide*</th>
<th>NeoSelect*</th>
<th>GPS Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider</td>
<td>Local Pathologist</td>
<td>Roche</td>
<td>Molecular Health</td>
<td>Siemens Healthineers</td>
</tr>
<tr>
<td>Number of Genes</td>
<td>Ca. 25- ca. 150</td>
<td>&gt;300</td>
<td>&gt;600</td>
<td>39</td>
</tr>
<tr>
<td>Central lab</td>
<td>No</td>
<td>yes</td>
<td>yes</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Indication and population studied</td>
<td>Not yet defined</td>
<td>Not yet defined</td>
<td>Not yet defined</td>
<td>Not yet defined</td>
</tr>
<tr>
<td>Registration / QM</td>
<td>Local QC Standards, Analyse „CE konform“</td>
<td>FDA Approved</td>
<td>ISO13485</td>
<td>„CE-konform“</td>
</tr>
<tr>
<td>Implementation Status</td>
<td>Part of clinical routine care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>External Service Providers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Interpretation of genomic alterations with regard to resistance or efficacy of therapies, eligibility for clinical trials etc. by bioinformatic, automated, quality controlled algorithms (e.g. OncoKb.org)
** Implemented in molecular tumor boards as part of clinical routine
*** some of which are professionalized like MSK-IMPACT (FDA authorized)

3. [https://www.foundationmedicine.com/genomic-testing/foundation-one](https://www.foundationmedicine.com/genomic-testing/foundation-one)
### Actionable genomic alterations

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Outcome</th>
<th>LoE</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPI3K Mutation</td>
<td>Efficacy of anti-HER2 therapies</td>
<td>I</td>
<td>B</td>
<td>+**</td>
</tr>
<tr>
<td>sESR1 Mutation</td>
<td>Efficacy of endocrine therapy</td>
<td>II</td>
<td>B</td>
<td>+/-**</td>
</tr>
<tr>
<td>sHER2 Mutation</td>
<td>Efficacy of anti-HER2 therapies</td>
<td>II</td>
<td>B</td>
<td>+/-**</td>
</tr>
<tr>
<td>sBRCA1/2 or gBRCA1/2</td>
<td>Efficacy of platinum chemotherapy</td>
<td>II</td>
<td>B</td>
<td>+/-**</td>
</tr>
<tr>
<td>sBRCA1/2 or gBRCA1/2</td>
<td>Efficacy of chemotherapy</td>
<td>II</td>
<td>B</td>
<td>+/-**</td>
</tr>
<tr>
<td>sBRCA1/2 or gBRCA1/2</td>
<td>Efficacy of PARP Inhibitors</td>
<td>I</td>
<td>A</td>
<td>+**</td>
</tr>
</tbody>
</table>

#### Evidence from studies with breast cancer patients
- Companion Diagnostics for therapies of other tumor entities (z.B. BRAF, FGFR1, ...)
- Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, Lokale „hand selected“ Panels)

* Assessment method of somatic mutations is not taken into consideration for LoE

** Participation in clinical trials or structured registries recommended / s=somatic / g = germline

---


10. Tutt APE, Kilburn L, Gilett C, al. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). DOI: 101158/1538-7445SABCS14-S3-01 Published May 2015


