Prognostische und prädiktive Faktoren
Prognostische und prädiktive Faktoren

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

- **Version 2018:**
  Fasching / Wöckel

Data bases screened

Guidelines screened


NCCN 2016: www.nccn.org


Definition

Ein **prognostischer Faktor** ist ein Parameter, der zu einem interessierenden Zeitpunkt z.B. bei Erstdiagnose vorliegt und, sofern keine weitere Therapie erfolgt, mit dem krankheitsfreien oder dem Gesamtüberleben d.h. mit dem natürlichen Krankheitsverlauf korreliert.

Ein **prädiktiver Faktor** ist ein Parameter, der das Ansprechen auf eine bestimmte Therapie definiert.

* Im Sinne dieser Leitlinie gemeint sind Faktoren, die mit einem Krankheitsrezidiv assoziiert sind.
“Low absolute risk implies low absolute benefit”


Qualitätskriterien

- Biologisches Modell
- Einfache und standardisierte Bestimmung, Qualitätssicherung des Tests
- Prospektive Planung der statistischen Auswertung (primäres Zielkriterium)
- Validierung der klinischen Bedeutung nach
  - „Oxford Level of Evidence (LoE, 2009)“-Kriterien und „Grades of Recommendation (GR)"
  - Modifizierte LOE Kriterien am archvierten Gewebe (LoE, 2009) und CTS-Kategorie
- Klinische Relevanz für Therapieentscheidung

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

<table>
<thead>
<tr>
<th>Category Element</th>
<th>A Prospective</th>
<th>B Prospective using archived samples</th>
<th>C Prospective/observational</th>
<th>D Retrospective/observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>Prospective controlled trial (PCT) designed to address tumor marker</td>
<td>Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility</td>
<td>Prospective observational registry, treatment and follow-up not dictated</td>
<td>No prospective aspect to study</td>
</tr>
<tr>
<td>Patients and patient data</td>
<td>Prospectively enrolled, treated, and followed in PCT</td>
<td>Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PCT addressing the treatment of interest</td>
<td>Prospectively enrolled in registry, but treatment and follow-up standard of care</td>
<td>No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review</td>
</tr>
<tr>
<td>Specimens 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 B</td>
<td>Result very likely to be play of chance</td>
<td>Result very likely to be play of chance</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.


**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% (PlanB, 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)


Es muss betont werden, dass die Levels of Evidence mittels Oxford- und CTS-Kriterien nicht direkt verglichen werden können.

Die prospektiv-geplante retrospektive Validierung von Biomarkern (CTS-Level 1) kann durch eine unzureichende Anzahl von Proben aus einer klinischen Studie verzerrt werden.

Diese Gewebesammlung könnte möglicherweise nicht das Ergebnis der Gesamtstudie repräsentieren. Ein optimaler Prozentsatz von Proben einer klinischen Studie für eine optimale Biomarker-Evaluierung ist bislang nicht etabliert.*


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**


## Prognosefaktoren II – Primäres Mammakarzinom

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoEOx2001</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER / PgR</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>HER2 (IHC, FISH)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>ER / PgR / HER2/Ki-67 als Surrogatmarker für molekulare Subtypen</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>uPA / PAI (Femtelle® ELISA)s in N0</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Proliferationsmarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 vor, während oder nach der Behandlung</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

*Validierte klinische Daten sind nur verfügbar für diesen Assay*

### ER/PR

### HER2

### Ki-67


Post-treatment Ki-67


uPA/PAI-1


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

Mammaprint

Onkotype DX

Several tests
### Prognosefaktoren III – Primäres Mammakarzinom

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminierte Tumorzellen (DTC, im Knochenmark)</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Zirkulierende Tumorzellen (CTC, im Blut, Cell Search&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>I</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>CTC vor NACT (in Bezug auf OS, DDFS, LRFI)</td>
<td>I&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Therapieentscheidungen basierend auf CTC-Phänotypen</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&lt;sup&gt;®&lt;/sup&gt; (N0-1, HR+, Her2 -)</td>
<td>I</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>Prosigna&lt;sup&gt;®&lt;/sup&gt; (N0-1, HR+, Her2 -)</td>
<td>I</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>MammaPrint&lt;sup&gt;®&lt;/sup&gt; (70 gene signature) (N0-1)</td>
<td>I</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>Oncotype DX&lt;sup&gt;®&lt;/sup&gt; (N0-1, HR+ HER2-, 5 Jahre)</td>
<td>I</td>
<td>A</td>
<td>+*</td>
</tr>
</tbody>
</table>

<sup>a</sup> Sollte nur bei ausgewählten Patientinnen angewandt werden, wenn alle anderen Kriterien keine Therapieentscheidung zulassen

<sup>®</sup> Validierte klinische Daten nur verfügbar für diesen Assay

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### DTC


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### 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


### Faktor

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigensignatur (Mammaprint, Endopredict, Oncotype Dx, Prosigna&lt;sup&gt;5&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 bei TNBC</td>
<td>II</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>5</sup> Validierte klinische Daten nur verfügbar für diesen Assay

* Definiert als dichte lymphozytäre Infiltration des inneren peritumoralen Stromas außerhalb der Invasionsfront (Stroma besteht mit > 50% aus Lymphozyten)

### TIL

7. Denkert et al, SABCS 2016
PIK3CA


### Prädiktive Faktoren – Endokrine Therapie

<table>
<thead>
<tr>
<th>Faktor</th>
<th>Oxford</th>
<th>LoE O2001</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endokrine Therapie</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ER/PgR Status</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>2. IHC Färbeintensität (ER/PgR)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. CYP2D6 Polymorphism</td>
<td>2b</td>
<td>D</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Ovarielle Ablation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Menopausenstatus</td>
<td>1c</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Aromataseinhibitoren vs. Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Menopausenstatus</td>
<td>1c</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>2. ER / PgR / HER2 als Einzelmarker</td>
<td>1c</td>
<td>A</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3. Lobulärer Subtyp</td>
<td>2b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4. Ki-67 hoch</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>5. Übergewicht (BMI &gt; 30 kg/m²)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>


Prädiktive Faktoren
HER2 gezielte Therapie / Adjuvante Chemotherapie

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE&lt;sub&gt;Dx2001&lt;/sub&gt; (§ LoEO&lt;sub&gt;x2009&lt;/sub&gt;)</th>
<th>GR (§ CTS)</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HER2-Therapie</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvante Chemotherapie</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-Gen-Recurrence-Score (Oncotype DX&lt;sup&gt;®&lt;/sup&gt;) §</td>
<td>1 §</td>
<td>B&lt;sup&gt;®&lt;/sup&gt;</td>
<td>+/-</td>
</tr>
</tbody>
</table>

§ Validierte klinische Daten nur verfügbar für diesen Assay.

Onkotype


uPA/PAI-1


Prognosefaktoren – Metastasiertes Mammakarzinom

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE2009</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zirkulierende Tumorzellen (CTC im Blut, Cell Search®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognose</td>
<td>I</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Frühes Therapieansprechen (3 Wo.)</td>
<td>I</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Therapieentscheidungen basiert auf CTC-Anzahl oder CTC-Phänotypen</td>
<td>I</td>
<td>A</td>
<td>-*</td>
</tr>
</tbody>
</table>

* Studienteilnahme empfohlen


CTC

# Exome/Whole Gene Testing of Panel Genes or the Whole Genome (Genomic Profile Tests)

<table>
<thead>
<tr>
<th>Provider</th>
<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>Number of Genes</td>
<td>Ca. 25- ca. 150</td>
<td>&gt;300</td>
<td>&gt;600</td>
<td>39</td>
<td>whole genome</td>
</tr>
<tr>
<td>Central lab</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes/no</td>
<td>yes</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>
<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>
<td>CLIA certified CAP accredited</td>
</tr>
<tr>
<td>Implementati on Status</td>
<td>part of clinical routine care</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)

### Commercially Available Comprehensive Molecular Profiling Tests

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


10. Tutt APE, Kilburn L, Gilett C, et 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: 10.1158/1538-7445SABCS14-S3-01 Published May 2015 2015.


