Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Prognostic and Predictive Factors
Data bases screened

Guidelines screened
3. 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”


Quality Criteria

- Biological hypothesis
- Simple and standardized assessment method, quality assurance (QA) of the test
- Prospectively planned statistical evaluation (primary goal)
- Validation of clinical significance according to
  - „Oxford Level of Evidence (LoE2001)” criteria and „Grades of Recommendation (GR)”
  - „Grades of Recommendation (GR)” as well as modified LoE criteria for the use in archived specimen (LoE2009) and category of tumor marker study (CTS)
- Clinical relevance for treatment decisions


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<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>


**Statement: Obesity**


pCR after NACT


2013, 31(31):3997-4013.
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


**uPA/PAI-1**


## Prognostic Factors II in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Oxford LoE</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 as surrogate markers for molecular subtypes</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>uPA / PAI (Femtelle® ELISA)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Proliferation markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ki-67 before, during or after treatment</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

1. Validated clinical data only available for this assay

### ER/PR


### HER2

Ki-67


Post-treatment Ki-67


uPA/PAI-1


Endopredict


Mammaprint


Oncotype


Prosigna (ROR / PAM50)


Multiple assays

Endopredict


**MammaPrint**


415, 530–536. doi:10.1038/415530a.


**Oncotype**


Prosigna (ROR / PAM50)


Multiple assays

Mammaprint

Oncotype DX
Several tests

### TAILORx trial

**Total patient number N = 10,273, main analysis N = 9,719**

- Endocrine therapy (RS ≤ 10) in 1,629 patients
- Endocrine therapy (RS 11–25) in 3,458 patients
- Chemoendocrine therapy (RS 11–25) in 3,449 patients
- Chemoendocrine therapy (RS ≥ 26) in 1,389 patients

**median follow-up 7.5 years RS 11–25**

**Absolute 9-year data:**

- IDFS: 83.3% in the endocrine-therapy group (ET) vs. 84.3% in the chemo-endocrine-therapy group (C-ET)
- DDFS: 94.5% (ET) vs. 95% (C-ET)
- OS: 93.9% (ET) vs. 93.8% (C-ET)

**Note:** 72% in the intermediate risk group (RS 11–25) have been clinically low risk


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**Oncotype DX**

**Oncotype DX**

Prognostic Factors III in Early Breast Cancer

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE2009</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multigene assays</strong></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-)</td>
<td>I</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>- Disseminated tumor cells (DTC, in bone marrow)</td>
<td>I</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>- Circulating tumor cells (CTC, in blood, Cell Search®) $^5$</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>- Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making

$^5$ Validated clinical data only available for this assay

# Cuzick et al., J Clin Oncol 29: 4273-4278, 2011

DTC

DTC and radiation

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
Mammaprint


Lobular cancer
1. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular...
### Neoadjuvant Systemic Chemotherapy Response Prediction II

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene signature (MammaPrint, Endopredict Oncotype Dx, PAM50 Prosigna)</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>

* validated clinical data only available for this assay

* defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up >50% of stroma area)

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**TIL**


7. Denkert et al, SABCS 2016

PIK3CA


**CYP2D6**


Oncotype DX


uPA/PAI-1


CTC


Cell-free DNA


CTC monitoring


PARP-Inhibitoren


Checkpoint-Inhibitoren
### 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></td>
<td>Local Pathologist</td>
<td>Roche</td>
<td>Molecular Health</td>
<td>Siemens Healthineers</td>
<td>NanHealth</td>
</tr>
<tr>
<td>Number of Genes</td>
<td>Ca. 25–ca. 150</td>
<td>&gt;500</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 conform“</td>
<td>FDA Approved</td>
<td>ISO13485</td>
<td>„CE-conform“</td>
<td>CUA Certified CAP accredited</td>
</tr>
<tr>
<td>Implementation Status</td>
<td>Part of clinical routine care</td>
<td></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)

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**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: 101158/1538-7445SABCS14-S3-01 Published May 2015 2015.


PIK3CA


