Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Prognostic and Predictive Factors

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Prognostic and Predictive Factors

- **Versions 2002–2018:**
  Costa / Fasching / Fersis / Friedrichs / Gerber / Göhring / Harbeck / Janni / Kolberg-Liedtke / Loibl / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thomssen / Witzel / Wöckel
- **Version 2019:**
  Thill / Lück

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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”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

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 (LoEOx2001)“ 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**

[1] Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
[2] Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011
[3] McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

Category Element	A Prospective	B Prospective using archived samples	C Prospective/ observational	D Retrospective/ observational
Clinical trial	Prospective controlled trial (PCT) designed to address tumor marker	Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility Accommodation of predictive marker requires Prospective randomized controlled trial (PRCT)	Prospective observational registry, treatment and follow-up not dictated	No prospective aspect to study
Patients and patient data	Prospectively enrolled, treated, and followed in PCT	Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest	Prospectively enrolled in registry, but treatment and follow-up standard of care	No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review
Specimen collection, processing, and archival	Specimens collected, processed, and assayed for specific marker in real time	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed and archived with no prospective SOPs
Statistical design and analysis	Study powered to address tumor marker question	Study powered to address therapeutic question and underpowered to address tumor marker question Focused analysis plan for marker question developed before doing assays	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study Focused analysis plan for marker question developed before doing assays	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study No focused analysis plan for marker question developed before doing assays
Validation	Result unlikely to be play of chance Although preferred, validation not required	Result more likely to be play of chance that A but less likely than C Requires one or more validation studies	Result very likely to be play of chance Requires subsequent validation studies	Result very likely to be play of chance Requires subsequent validation

Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

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

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Level of Evidence	Category	Validation studies available
I	A	None required
I	B	One or more with consistent results
II	B	None or inconsistent results
II	C	2 or more with consistent results
III	C	None or 1 with consistent results or inconsistent results
IV–V	D	Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility

Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

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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

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Factor	Oxford LoE_{Ox2001}	GR	AGO
▪ Tumor size	1a	A	++
▪ Nodal status	1a	A	++
▪ Distant metastasis	1a	B	++
▪ Histological tumor type (colloid, mucinous, tubular etc.)	2b	B	++
▪ Grade (Elston & Ellis)	2a	B	++
▪ Age	2a	B	++
▪ Peritumoral lymphatic vessel and vascular invasion (L1 V1)	2b	B	+
▪ pCR after NACT* in (luminal-B-like, HER2+, TN)	1a	A	++
▪ Increased risk of recurrence in invas.-lob. subtype, cT3/4, N+	2a[a]	B	+/-
▪ Obesity (BMI > 30 kg/m²)	1b	B	+
▪ Margins (Resection status)	1a	A	+

* NACT = Neoadjuvant Chemotherapy

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)**

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 *

* Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446–1452, 2009

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Prognostic Factors II in Early Breast Cancer

Factor	Oxford LoE_{Ox2001}	GR	AGO
▪ ER / PgR	2a	B	+
▪ HER2 (IHC, FISH)	2b	B	+
▪ ER / PgR / HER2/ Ki-67 as surrogate markers for molecular subtypes	2b	B	+
▪ uPA / PAI (Femtelle® ELISA) § in N0	1a	A	+
▪ Proliferation markers			
▪ Ki-67 before, during or after treatment	1a	B	+

§ Validated clinical data only available for this assay

Commercially Available Molecular Tests

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

$ **Validated clinical data only available for this assay**

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Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $
Prognosis after 5 yrs (late recurrences)	not separately shown	yes	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes	not shown	not shown
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 **(14%)** NSABP B-20 **(28%)** ECOG 9127 SWOG 8814 **(40%)** ATAC **(30%)**	ABCSG 6 **(19%)** ABCSG 8 **(36%)** GEICAM-9906 **(45%)** ATAC **(10%)**	MA.12 **(59%)** MA.5 **(66%)** ABCSG 8 **(44%)** ATAC **(16%)**
Prospective evidence	MINDACT (N0, N1) (5-year DFS, OS)	TAILORx (9-year DFS, OS), N0, low-risk, S<11, intermediate risk RS ≤25, high risk RS ≥26) PlanB (N0, highrisk/N+) (5-year DFS, OS)	–	–

$ **Validated clinical data only available for this assay**

Prospective Randomized Trials

(Oncotype DX [TailorX, PlanB], MammaPrint [MINDACT])

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

	TailorX	PlanB	MINDACT
Follow-up period	Median 90 mo	5-yr-DFS	Median 60 mo
Proportion of low risk patients (study population suitable for chemotherapy)	16.7% (RS 0-10)	15.3% RS (0–11)	23.2% (high clinical and low genomic risk)
Test failure rate	n.r.	2.9%	26% (fresh frozen tissue)
Proportion of intermediate risk patients (applies only to Oncotype DX)	69.1% (RS 11–25)	60.4% (RS 12–25)	n.a.
Proportion of high risk patients (applies only to Oncotype DX)	14.3% (RS ≥ 26)	24.3% (RS ≥ 26)	27.0% (high clinical and high genomic risk)
10-yr-follow up	---	---	---

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

Sparano JA, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018

TAILORx

Defined cutoff for definitely determining chemotherapy benefit with Oncotype DX

Subgroup age >50 years

RS 0–10	RS 11–15	RS 16–20	RS 21–25	RS 26–100
Endocrine therapy alone	No CT benefit	No CT benefit	No CT benefit	chemotherapy

Subgroup age ≤50 years

RS 0–10	RS 11–15	RS 16–20	RS 21–25	RS 26–100
Endocrine therapy alone	No CT benefit	~1.6% CT benefit[1]	~6.5% CT benefit[1]	chemotherapy

[1]Benefit for DDFS, OS similar

Sparano JA, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018

Prognostic Factors III in Early Breast Cancer

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Faktor	LoE_{2009}	CTS	AGO
▪ Multigene assays			
▪ EndoPredict® (N0-1, HR+, HerER2 -)	I	B	+*
▪ Prosigna® (N0-1, HR+, HerER2 -)	I	B	+*
▪ MammaPrint® (70 gene signature) (N0-1)	I	A	+*
▪ Oncotype DX® (N0-1, HR+ HER2-)	I	A	+*
▪ Disseminated tumor cells (DTC, in bone marrow)	I	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®) $	I	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	I^a	B	+/-
▪ Therapy decisions based on CTC phenotypes	III	C	-
▪ Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)	I	B	+/-

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

Neoadjuvant Systemic Chemotherapy
Response Prediction I

Factor	CTS	LoE_{Ox2001}	GR	AGO
▪ Young age	B	1a	A	+
▪ cT1 / cT2 tumors o. N0 o. G3	B	1a	A	++
▪ Negative ER and PgR status	B	1a	A	++
▪ Triple negative breast cancer (TNBC)	B	1a	A	++
▪ Positive HER2 status	B	1a	A	++
▪ Non-lobular tumor type	B	1a	A	+
▪ Early clinical response	B	1b	A	+

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Neoadjuvant Systemic Chemotherapy Response Prediction II

Factor	LoE_{2009}	CTS	AGO
▪ Multigene signature (Mammaprint, Endopredict Oncotyp Dx,PAM50 Prosigna$^{\$}$)	II	C	+/-
▪ Ki-67	I	B	+
▪ Tumor infiltrating lymphocytes*	I	B	+
▪ *PIK3CA* mutation	I	B	+/-
▪ gBRCA in TNBC	II	B	+

$ 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)

Predictive Factors – Endocrine Therapy

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Factor	Oxford LoE_{Ox2001}	GR	AGO
▪ **Endocrine therapy**			
▪ ER/PgR status	1a	A	++
▪ IHC staining intensity (ER/PgR)	1a	A	+
▪ **Tamoxifen**			
▪ CYP2D6 polymorphism	2b	D	-
▪ **Ovarian ablation**			
▪ Menopausal status	1c	A	++
▪ **Aromatase inhibitors vs. Tamoxifen**			
▪ Menopausal status	1c	A	++
▪ ER/PgR/HER2 as single markers	1c	A	-
▪ Lobular subtype	2b	B	+
▪ Ki-67 high (published cutoffs > 11% and > 14%)	2b	B	+/-
▪ Obesity (BMI > 30 kg/m²)	2b	B	+/-

Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

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Factor	LoE$_{Ox2001}$ [§] (LoEO$_{x2009}$)	GR ([§] CTS)	AGO
Anti-HER2-Therapy			
HER2	1a	A	++
Adjuvant Chemotherapy			
uPA / PAI1 (Femtelle®) ELISA [$]	1a	A	+
21 gene recurrence score (Oncotype DX®) [$]	I [§]	B [§]	+/-

[$] Validated clinical data only available for this assay

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Prognostic Factors – Metastatic Breast Cancer

Factor	LoE_{2009}	CTS	AGO
▪ Circulating tumor cells (CTC in blood, Cell Search®)			
▪ Prognosis at baseline	I	A	+
▪ Early response assessment (3w)	I	B	+
▪ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	I	A	-*
▪ Cell-free DNA (cfDNA in blood)	I	A	+/-

* Study participation recommended

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Treatment of Metastatic Breast Cancer
Predictive Factors

Therapy	Factor	Oxford LoE	Oxford GR	AGO
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	previous response	2b	B	++
Chemotherapy	previous response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better metastasis)	1a	A	++
Checkpoint-Inhibitors (Atezolizumab)	PD-L1 IC# Positivity in TNBC	1b	B	+
PARP-Inhibitors	gBRCA1/2-Mutation	1a	A	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*

* Within clinical trials

≥ 1% on immune cells (IC) (see chapter „pathology“)

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

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	Local Pathology based*, **, ***	Foundation one*	Molecular Health Guide*	NeoSelect*	GPS Cancer*
Provider	Local Pathologist	Roche	Molecular Health	Siemens Healthineers	NantHealth
Number of Genes	Ca. 25- ca. 150	>300	>600	39	Whole genome
Central lab	No	yes	yes	Yes/no	yes
Indication and population studied	Not yet defined	Not yet defined	Not yet defined	Not yet defined	Not yet defined
Registration / QM	Local QC Standards, Analyse „CE konform“	FDA Approved	ISO13485	„CE-konform“	CLIA Certified CAP accredited
Implementation Status	Part of clinical routine care	External Service Providers			

* **Interpretation of genomic alterations with regard to resistance or efficacy of therapies, eligibility for clinical trails 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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Actionable genomic alterations

Factor*	Outcome	LoE_{2009}	CTS	AGO
Evidence from studies with breast cancer patients				
▪ sPIK3CA Mutation	Efficacy of anti-HER2 therapies	I	B	+/-**
▪ sPIK3CA Mutation	Efficacy of endocrine therapy	I	B	+/-**
▪ sESR1 Mutation	Efficacy of endocrine therapy	II	B	+/-**
▪ sHER2 Mutation	Efficacy of anti-HER2 therapies	II	B	+/-**
▪ sBRCA1/2 or gBRCA1/2	Efficacy of platinum chemotherapy	II	B	+/-**
▪ sBRCA1/2 or gBRCA1/2	Efficacy of chemotherapy	II	B	+/-**
▪ or gBRCA1/2	Efficacy of PARP Inhibitors	I	A	+**
Evidence from studies with other cancer patients				
▪ Companion Diagnostics for therapies of other tumor entities (z.B. BRAF, FGFR1, …)	Efficacy of diverse therapies	IV	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, Lokale „hand selected„ Panels)	Efficacy of diverse therapies, Prognosis	III	C	+/-**

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

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